Background Document for Joint Meeting of Advisory Committee for Reproductive Health Drugs and the Drug Safety and Risk Management Advisory Committee

December 8, 2011

NDA 21-098 Yasmin
(3 mg drospirenone/0.03 mg ethinyl estradiol)

NDA 21-676 YAZ
(3 mg drospirenone/0.02 mg ethinyl estradiol)

NDA 22-532 Beyaz
(3 mg drospirenone/0.02 mg ethinyl estradiol/0.451 mg levomefolate calcium)

NDA 22-574 Safyral
(3 mg drospirenone/0.03 mg ethinyl estradiol/0.451 mg levomefolate calcium)

Bayer HealthCare Pharmaceuticals, Inc.

Primary Indication:

Prevention of Pregnancy

Dosing regimen:

Oral tablet taken once daily

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Food and Drug Administration
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AMI	Acute myocardial infarction
AT	As-treated
ATE(s)	Arterial thrombotic event(s)
BMI	Body mass index
CHC(s)	Combination hormonal contraceptive(s): includes oral and non-oral products
CI	Confidence interval
COC(s)	Combination oral contraceptive(s)
DRSP	Drospirenone
DVT	Deep vein thrombosis
EE	Ethinyl estradiol
EMA	European Medicines Agency
GPRD	General Practice Research Database
HMO	Health maintenance organization
HR	Hazard ratio
IRR	Incidence rate ratio
IS	Ischemic stroke
ITT	Intent-to-treat
LNG	Levonorgestrel
MEB	Medicines Evaluation Board
MEGA	Multiple Environmental and Genetic Assessment
MI	Myocardial infarction
NETA	Norethindrone acetate
NGM	Norgestimate
NOHC	Non-oral hormonal contraceptive
OR	Odds ratio
OSE	Office of Surveillance and Epidemiology
PCOS	Polycystic ovary syndrome
PE	Pulmonary embolus
PhVWP	Pharmacovigilance Working Party
PMDD	Premenstrual dysphoric disorder
PY	Person-years
RDD	Random digit dialing
RR	Rate ratio or relative risk depending on context
TTE	Thrombotic and thromboembolic events: includes both VTE and ATE
UHC	UnitedHealthCare
VTE(s)	Venous thrombotic and thromboembolic event(s): includes both DVT and PE

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committees. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought questions concerning the risk/benefit profile of drospirenone-containing oral contraceptive pills to these two Advisory Committees in order to gain the Committees' insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committees. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee meeting has been considered. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

1. BACKGROUND

1.1 Objective of Meeting

The purpose of this Advisory Committee meeting is to review and discuss the overall risk/benefit profile of oral contraceptives that contain the progestin drospirenone (DRSP). These products are used for the prevention of pregnancy; several of them also have additional secondary indications that include a) treatment of moderate acne, b) treatment of symptoms of premenstrual dysphoric disorder (PMDD), and c) to raise folate levels. Like all combination oral contraceptives (COC), these DRSP-containing COCs are associated with an increased risk of venous thrombotic and thromboembolic events (VTEs) as compared to nonuse of hormonal contraception. The presentations at the meeting will discuss the conflicting data comparing the risk of VTE among COCs containing DRSP vs. COCs containing other progestins. Some of the epidemiologic studies report that there is a greater increase in VTE risk with use of DRSP-containing COCs than with the use of other COCs that contain the progestin levonorgestrel (LNG), while other studies report no increase in VTE risk.

1.2 Product

Combination oral contraceptives contain both an estrogen and progestin. Ethinyl estradiol (EE) is by far the principal synthetic estrogen utilized in COCs today. Mestranol was used in early pill formulations; recently a new COC containing estradiol valerate has been approved in the US. The estrogenic component of the COC contributes to the contraceptive efficacy by suppressing follicle-stimulating hormone and potentiating the action of the progestin. The estrogenic component also provides some stability to the endometrium to minimize breakthrough bleeding.

As compared to the relatively few different types of estrogens in COCs, there are a relatively large number of different progestins that are used in currently marketed COCs. Progestins in general aid contraception by suppressing luteinizing hormone secretion and thereby preventing ovulation from occurring. Progestins additionally produce an unreceptive endometrial lining and thickened cervical mucus that impedes sperm transport.

Many authors have characterized the progestins based on when they were developed and have labeled them as first generation, second generation, etc. DRSP has been characterized by some

as being a fourth generation progestin. Much of the comparative safety data that will be discussed at this meeting will focus on DRSP as compared to LNG, one of the second generation progestins.

Drospirenone is an analog of spironolactone. As such, it exhibits anti-mineralocorticoid effects. Labeling for DRSP-containing COCs includes Warnings and Contraindications that address potential risks of hyperkalemia relating to these effects.

Yasmin, which was approved in the US in May 2001, was the first DRSP-containing COC to be approved for the US market. Subsequent to this approval, YAZ (with a lower dose of EE [20 µg EE vs. 30 µg EE] and a 24-day dosing regimen) was approved for prevention of pregnancy in March 2006. Secondary indications for YAZ (acne and PMDD) were both approved within one year after the original approval. Beyaz and Safyral are newer products that have EE and DRSP doses comparable to YAZ and Yasmin, respectively, but in addition contain levomefolate. Both of these folate-containing products were approved in 2010 and include a secondary indication to raise folate levels. The dose of DRSP and EE in each active tablet of the aforementioned products is shown in Table 1.

Table 1 Quantity of Drospirenone, Ethinyl Estradiol, and Levomefolate in Drospirenone-Containing Combination Oral Contraceptives Approved in the US

Product	DRSP	EE	Levomefolate
Yasmin	3 mg	30 µg	0
YAZ	3 mg	20 µg	0
Beyaz	3 mg	20 µg	0.451 mg
Safyral	3 mg	30 µg	0.451 mg

DRSP = drospirenone; EE = ethinyl estradiol

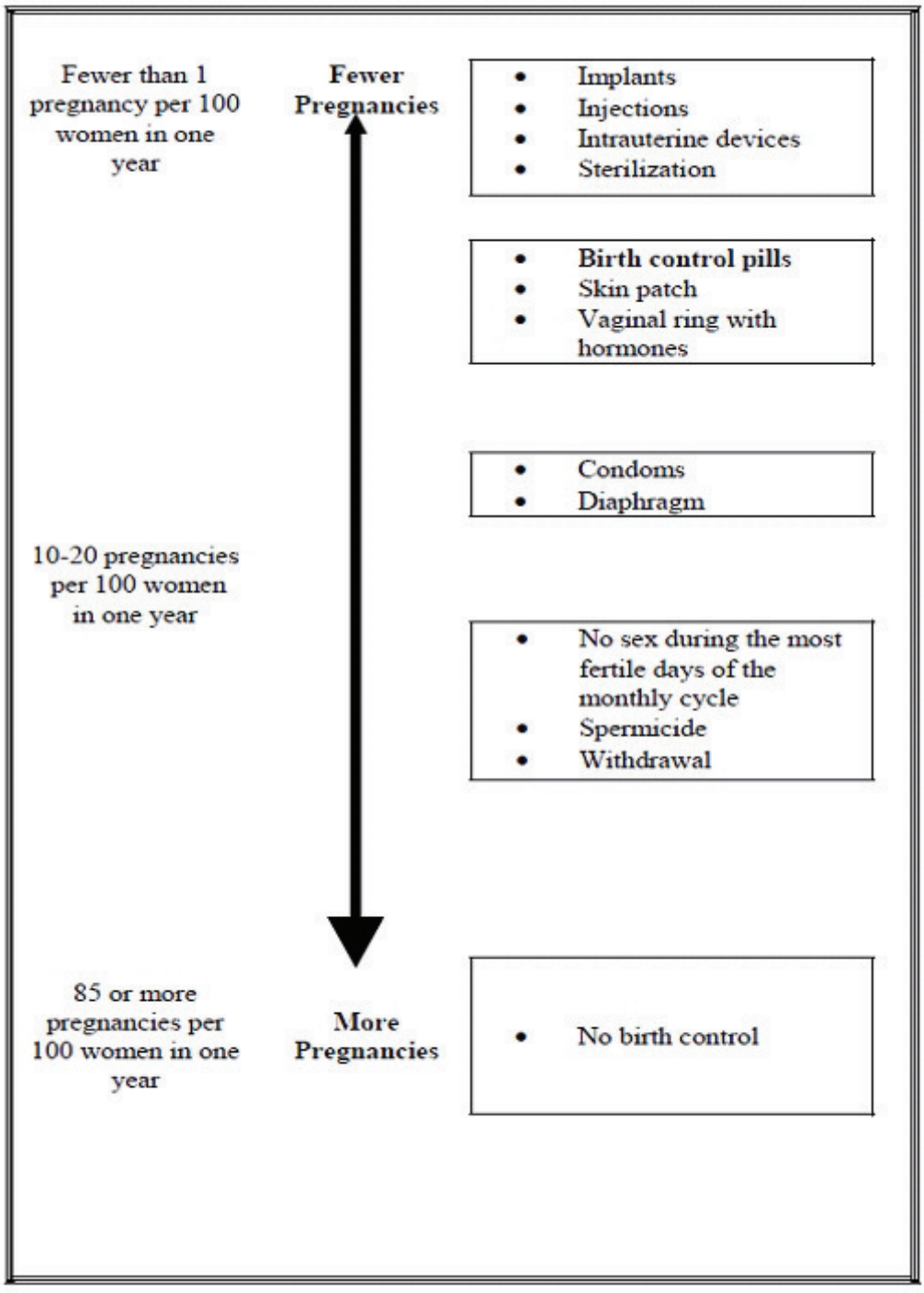
1.3 Effectiveness of Contraceptives in Prevention of Pregnancy

1.3.1 Overview of Effectiveness

A variety of products are indicated for the prevention of pregnancy. Prescription-only products include non-hormonal or hormonal contraceptives. Hormonal products include oral contraceptives, intrauterine devices, implants, injections, and vaginal rings. Most hormonal contraceptives combine a progestin with an estrogen; however, progestin-only products are also available with oral, intrauterine, implant, and injectable routes of administration. Non-hormonal prescription-only products include devices such as diaphragms and some intrauterine devices (IUDs), while male or female condoms, sponges, and spermicides are available over-the-counter without a prescription.

The relative effectiveness of various contraceptive products in shown Figure 1, which is included in current patient labeling for CHCs.

Figure 1 Contraceptive Effectiveness of Different Methods



1.3.2 Combination Oral Contraceptives

The evaluation of COC efficacy during preapproval review of a new contraceptive product is based on the number of unplanned pregnancies observed in clinical trials. The Division specifically looks at the number of pregnancies occurring in women 35 years and younger in cycles in which no back-up contraception was used.

The pregnancy rate, expressed as the Pearl Index in product labeling, is computed as:

$$\text{Pearl Index} = \frac{\text{(number of “on-treatment” pregnancies) x 13 cycles/year}}{\text{(total number of completed 28-day treatment cycles)}} \times 100$$

As an example for the DRSP-containing contraceptives, YAZ had a Pearl Index of 1.41 (95% confidence interval [CI] 0.73-2.47) per 100 woman-years of use based on 12 on-treatment pregnancies in a one year clinical trial.

1.3.3 Secondary Indications for DRSP-Containing Oral Contraceptives

The DRSP-containing COCs all have a primary indication of prevention of pregnancy. In addition, some of these products have additional secondary indications (shown in Table 2).

Table 2 Secondary Indications for Drospirenone-Containing COCs

Product	Secondary indications
Yasmin	None
YAZ	• Treat symptoms of premenstrual dysphoric disorder (PMDD) for women who choose to use an oral contraceptive for contraception • Treat moderate acne for women at least 14 years old only if the patient desires an oral contraceptive for birth control
Beyaz	• Treat symptoms of premenstrual dysphoric disorder (PMDD) for women who choose to use an oral contraceptive for contraception • Treat moderate acne for women at least 14 years old only if the patient desires an oral contraceptive for birth control • Raise folate levels in women who choose to use an oral contraceptive for contraception
Safyral	• Raise folate levels in women who choose to use an oral contraceptive for contraception

1.4 Cardiovascular and Thrombotic Risk Associated with the Use of COCs

Combined estrogen/progestin contraceptives, including those containing DRSP as the progestin, are associated with a number of well-recognized safety concerns, in particular, VTEs. Product labeling for all COCs have a boxed warning about the risk of serious cardiovascular events in women over age 35 who smoke, and warnings regarding the risk of thromboembolic and other vascular events.

The cardiovascular risks of COCs as a drug class have been extensively evaluated in the 50 years since their introduction as a contraceptive method. Thrombotic and thromboembolic events, both venous and arterial, are observed more commonly in users of COCs than in non-users. The rate for these events, however, is lower than the rate of these events in pregnancy, especially the post-partum period. Much of the cardiovascular risk was initially attributed to the effect of the estrogenic component of the COC. In the 1990s, attention was also focused on the possible role of the progestin component with respect to VTE risk, especially third generation progestins (e.g., desogestrel and gestodene). Table 3 lists important cardiovascular safety findings related to COCs in the first 15 years following their initial approval in the US.

Table 3 Key Dates in the Early Assessment of Cardiovascular Safety of COCs

Year	Action
1960	First approval of a COC in the US (9.85 mg norethynodrel and 150 µg of mestranol).
1963	First case report linking a myocardial infarction in a 32-year-old woman to a combination hormonal product.
1967	Surveys by the Medical Research Council, the Royal College of General Practitioners, and the Committee on Safety of Drugs reviewed by the British Medical Journal (1967) confirmed that the administration of estrogen and progestin mixtures for contraceptive purposes increases the risk of thromboembolism.
1970	Vessey article[1] in the British Medical Journal that found a positive correlation between the dose of estrogen in oral contraceptives and the risk for pulmonary embolism, deep vein thrombosis, cerebral thrombosis, and coronary thrombosis in the United Kingdom.
1973	The Collaborative Group for the Study of Stroke in Young Women[2] reported an increase in both thrombotic and hemorrhagic stroke for women using oral contraceptives.
1975	Mann et al[3] reported an increased risk for myocardial infarction for current users of oral contraceptives.

1.4.1 Overview of VTE Risk in Women

The incidence of VTE in the general population was reported in a study by Silverstein et al in 1998.[4] The study was an inception cohort design that looked at 2,218 individuals during a 25-year period from 1966 through 1990 in Olmstead County, Minnesota. The annual incidence per 10,000 person-years (PY) for reproductive-age women in this study is shown in Table 4.

Table 4 Incidence of VTE (Events per 10,000 Person Years)* in Reproductive-Age Women (1966-1990 in Olmstead County, Minnesota)

Age Group	DVT only	PE ± DVT	All VTEs
15-19	1.8	0.8	2.7
20-24	4.1	1.0	5.1
25-29	5.1	2.1	7.2
30-34	4.6	2.9	7.5
35-39	3.5	4.0	7.4
40-44	4.7	3.7	8.4
45-49	5.1	4.5	9.6

* Rates include pregnant women and women taking COCs
DVT = deep vein thrombosis; PE = pulmonary embolism
Source: Derived from Table 1 in Reference #4

Additional data from Olmstead County (1966 through 1995)[5] analyzed the incidence of VTE during pregnancy and the postpartum period. The results for all VTEs (converted to a rate per 10,000 PY) are shown in Table 5.

Table 5 Incidence of VTE (Events per 10,000 Person-Years) during Pregnancy and Postpartum (1966-1995 in Olmstead County, Minnesota)

Age Group	Pregnancy	Postpartum	Total	Not Pregnant or Postpartum
15-19	24.0	24.1	24.0	1.7
20-24	7.1	49.0	17.6	3.5
25-29	5.6	54.8	17.9	4.7
30-34	13.1	42.9	20.6	5.7
≥ 35	14.9	89.8	33.7	6.2
All ages	9.5	51.1	20.0	4.6

Source: Derived from Table 1 in reference #5

As shown in the preceding table, the incidence of VTE is highest in the postpartum period. It should be noted that in the early part of the era being analyzed in this study, women were in the hospital for longer periods of time with the potential for less early ambulation.

1.4.2 Comparative VTE risk: COC Users vs. Non-users

There have been a number of comparative studies focusing on the incidence rates of VTE for current users of COCs vs. non-users. The following table presents VTE incidence rates in selected studies over the last 40 years. It is noteworthy that the exclusion criteria used to define "idiopathic cases" have not been standardized, and therefore it is difficult to compare the rates in these studies.

Table 6 Incidence Rates for VTE in Users and Non-users of COCs (per 10,000 Person-Years)

Author Year	Incidence rate for COC current users Per 10,000 Person-Years	Incidence rate for COC "non-users" Per 10,000 Person-Years
BCDSP * 1973[6]	Phlebitis, thrombophlebitis and/or PE (age 20-44, idiopathic) = **6.6**	Non-users Phlebitis, thrombophlebitis and/or PE (age 20-44, idiopathic) = **0.6**
RCGP ** 1978[7]	DVT of leg (idiopathic) = **8.2** PE (idiopathic) = **1.9**	Never users DVT of leg (idiopathic) = **2.0** PE (idiopathic) = **0.8** Past users DVT of leg (idiopathic) = **1.5** PE (idiopathic) = **0.8**
Stadel 1981[8]	VTE (averaging of cited references) = **11.0**	VTE (averaging of cited references) = **3.0**
Vessey 1986[1]	VTE (DVT or PE, certain or probable cases unassociated with surgery, adjusted for age, smoking and history of varicose veins) = **4.7**	VTE (DVT or PE, certain or probable cases unassociated with surgery, adjusted for age, smoking and history of varicose veins) = **0.6**
Jick 1995[9]	VTE for levonorgestrel (idiopathic) = **1.6**	VTE (estimated idiopathic) = **0.4**
Dinger 2007[10]	VTE (crude incidence) = **8.0-9.9**	VTE (no-use) = **4.7**
Lidegaard 2009[11]	VTE (crude incidence) = **6.3**	VTE (never or past use, crude incidence) = **3.0**

BCDSP = Boston Collaborative Drug Surveillance Program

RCGP = Royal College of General Practitioners

VTE = venous thromboembolism; DVT = deep vein thrombosis; PE = pulmonary embolism

Note: Non-users is further characterized as never users or past users, if known

* Exclusions included past history of phlebitis, diabetes, cardiovascular disease, pregnancy, menopause, extreme obesity, chronic debilitating disease

** Exclusions included malignant or unspecified neoplasms, endocrine disorders, blood disorders, central neurological disorders, circulatory disorders, liver disorders, chronic renal disorders, recent surgery, pregnancy, and all hospitalizations for medical treatment other than cerebrovascular and venous thromboembolic disorders

Although a recent review of the literature reports the increased risk for VTE with current COC use vs. non-use to be three- to four-fold, the preceding table illustrates a wider range that extends from approximately two-fold in recent publications to approximately ten-fold with the earliest studies. The higher numbers for the earliest studies may reflect the inclusion of superficial thrombophlebitis in the case definition and the use of COCs with much higher EE doses.

1.4.3 COC-Associated Risk of Stroke and Myocardial Infarction

An increased risk for stroke was reported with early studies of higher dose COCs. More recent studies have varied in their risk assessment by stroke type (thrombotic vs. hemorrhagic).[12] Smoking, hypertension, and a history of migraine with aura are separate risk factors for stroke that may further raise safety concerns for COC users.

An increased risk of myocardial infarction has been attributed to COC use. This risk is primarily found in smokers aged 35 years or older, or women with underlying risk factors for coronary-artery disease (hypertension, hypercholesterolemia, morbid obesity, and diabetes).

1.5 Chronology of Approvals, Postmarketing Safety Studies and Labeling Changes for Yasmin and other DRSP-containing COCs

A chronology of approvals, postmarketing safety studies, and labeling changes for Yasmin and other DRSP-containing COCs are shown in Table 7.

Table 7 Major Events Related to Approvals or Safety Issues for Drospirenone-containing COCs

2000	Approval of Yasmin in Europe
2001	
May	Yasmin (NDA 21-098) approved in US
2006	
March	YAZ (NDA 21-676) approved (contraceptive indication)
October	YAZ (NDA 21-873) approved (PMDD secondary indication)
2007	
January	YAZ (NDA 22-045) approved (acne secondary indication)
May	Publication of the EURAS study in the journal *Contraception*[10]
September	Publication of the Ingenix study in the journal *Obstetrics & Gynecology*[13]
2009	
August	Publication of two studies in the *British Medical Journal* related to VTE risk of Yasmin (van Hylckama Vlieg[14] and Lidegaard[11]) compared to other COCs, including levonorgestrel-containing COCs
2010	
April	Labeling change in US is approved for Yasmin and YAZ that discusses VTE risk in light of two prospective studies (EURAS and Ingenix) and two epidemiologic studies in BMJ (van Hylckama Vlieg and Lidegaard)
September	Beyaz (NDA 22-532) approved (contraception and secondary indications for PMDD, acne and raising folate levels)
December	Safyral (NDA 22-574) approved (contraception and secondary indication for raising folate levels)
2011	
March	Labeling change is approved in US for YAZ that states that the risk for VTE is greatest in the first 6 months of use and is present after initially starting a COC or restarting (following a 4-week or greater pill-free interval) the same or a different COC. This labeling change was based on preliminary data from an extension of the EURAS Study (LASS)
April	Publication of two additional epidemiologic studies regarding VTE risk for Yasmin compared to levonorgestrel-containing COCs in *British Medical Journal* (Parkin et al[15] and Jick et al[16])
May	In a Drug Safety Communication, the FDA alerts the public to the April 21, 2011 *British Medical Journa*l articles and states that these studies are under review
September	In a Drug Safety Communication, the FDA announces preliminary findings from FDA-funded study and that an Advisory Committee meeting to discuss the risks and benefits of DRSP-COCs will be held in December 2011
October	FDA-funded study report is posted on FDA Web site

1.6 New FDA Epidemiology data

The FDA recently sponsored a large retrospective cohort study to evaluate use of contraceptive products in a population of prevalent and new users and their risk for a venous or arterial thromboembolic event or death. Details and results of the study are presented in Section 2.3 and Appendix A.

1.7 Issues for Committee Consideration

The issues for Committee consideration include the following:

A. How do you view the impact of differences between studies, particularly those that provide differing results? How do different study designs, study populations, comparator groups, and handling of potential confounding factors affect the outcomes of the various studies? Are there other important confounding variables that need to be addressed?

B. What do you believe are the strongest studies/findings?

C. Based on your interpretation of the available epidemiologic studies, do you believe that users of DRSP-containing COCs are at an increased risk of VTE compared to users of COCs that contain other progestins?

D. Do you believe that the benefits of the DRSP-containing oral contraceptives for prevention of pregnancy outweigh their risks?

E. Do you believe the current DRSP labels adequately reflect the risk/benefit profile for these products?

   If not, in general terms, how would you recommend revising the label, for example,

   a. provide descriptive data about risk,
   b. interpret the findings of the epidemiologic data,
   c. discuss subpopulations of women who might or might not be appropriate users of the products.

F. Are there different studies or re-analyses of existing data that might be conducted that would help to clarify the thrombotic/thromboembolic risk for users of DRSP-containing COCs?

2. OVERVIEW OF THE POST MARKETING SAFETY DATA FOR YASMIN

2.1 Introduction and Background

Drospirenone is a derivative of spironolactone and has anti-mineralocorticoid activity in addition to progestational activity. Because of its spironolactone-like properties, there was concern at the time of approval of Yasmin about the potential of DRSP to increase potassium levels.

Two prospective observational studies were funded by the Sponsor at the time of approval of Yasmin in 2000 (Europe) and 2001 (US). The study requested by the FDA was designed primarily to monitor for adverse events that might be associated with hyperkalemia. Specifically, the Sponsor was asked to "Use a database to evaluate all patients prescribed Yasmin® for the subsequent outcomes of death, hospitalization, syncope, arrhythmia, hyperkalemia, electrolyte disturbances, dialysis, etc." The study requested by European regulators was designed primarily to assess the cardiovascular and other risks associated with the

use of DRSP. Early monitoring of the safety of Yasmin was also reported in a United Kingdom Prescription Monitoring Event (PEM) study.[17]

After approval, additional concerns surfaced about a possible increased frequency of thrombotic and thromboembolic events (TTEs) among women using Yasmin. TTE comprises both VTE and arterial thrombotic events (ATE). Spontaneous or voluntary reports of TTE submitted to the FDA were adjudicated by FDA. Based on these adjudicated cases, reporting rates for TTE in women using Yasmin were compared to rates for other (some newly approved) combined hormonal contraceptives (CHCs). These comparisons suggested similar or slightly higher TTE risks for users of Yasmin during the first three years of marketing.

TTE reporting rates for Yasmin were 1.4 per 10,000 person-years (PY) in 2003[18] and 1.2 per 10,000 PY in 2004.[19] TTE reporting rates for several older contraceptives in their first years of marketing ranged from 0.2 to 0.7 per 10,000 PY. Mortality reporting rates were also higher for Yasmin (0.8 per 100,000 PY) than for the other older products (0.0 to 0.4 per 100,000 PY). Comparing Yasmin with the newly approved transdermal contraceptive patch, however, showed no difference in risk, as both newly approved products had similar reporting rates for TTE. Because of the observed reporting rates for TTE in users of Yasmin, the Sponsor-funded US study for Yasmin, which was initially designed to identify adverse events potentially associated with hyperkalemia, was modified at the request of the FDA to address the issue of a possible increased risk of TTE in women using Yasmin.

As early as 2004, it was noted that differences in risk between the newer combined hormonal contraceptives (CHCs) compared to older CHCs consistently depended on which CHC was selected as the comparator and how the CHC was being prescribed, especially for off-label use. Consequently, the Office of Surveillance and Epidemiology (OSE, then known as the Office of Drug Safety) considered funding a study to explore the population and prescriber characteristics affecting use and TTE risk.

It needs to be emphasized that all published epidemiologic studies to date have included only Yasmin or its equivalent (3 mg DRSP, 30 μg EE) as the DRSP-containing COC. The 20 μg EE DRSP-containing product YAZ has not been evaluated in the epidemiologic studies reviewed in this document.

2.2 Sponsor-funded Epidemiologic Studies

At the request of regulatory agencies, the Sponsor conducted two epidemiologic studies that assessed the TTE risk associated with the use of DRSP-containing COCs. The postmarketing study requested by European regulators was called the European Active Surveillance (EURAS) Study[20] and included users of a DRSP-containing COC, which also contained 30 μg EE, and two groups of comparators: LNG-containing COCs and other contraceptives. The study requested by FDA was a US-based study conducted by i3 Ingenix.[13, 21] This study identified initiators of Yasmin quarterly for the first year beginning June 11, 2001 and then semi-annually through June 30, 2004 and matched each woman on propensity scores to two initiators of other contraceptives. These studies capture the experience of contraceptive users who very likely had comparable baseline characteristics and, in the EURAS study, were likely using these products mainly for contraception.

2.2.1 EURAS Study

The EURAS Study was conducted entirely in Europe.[20] According to the published manuscript, the study was initiated in 2000 and completed in 2004. Clinical prescribers recruited women who received a prescription for a hormonal contraceptive. Once enlisted, each woman was contacted every six months during the study period to obtain information on adverse events and changes in contraceptive use. The study implemented an aggressive loss-to-follow-up protocol.

All women who were starters or switchers and who were willing to participate in the study were enrolled. The study participants were given a baseline interview and, when contacted every six months during the study period, provided information on adverse events and changes in contraceptive use. The study was conducted to compare risks of adverse cardiovascular and other events associated with the use of the DRSP-containing COC compared to those in users of LNG-containing COCs and other CHCs. TTE data capture was included in the list of monitored events in the original study.

All study participants, including women who became pregnant during the study, were included in follow-up until the end of the study, unless they withdrew their informed consent. TTE risks among DRSP users were compared to the risks in users of LNG-containing COCs and other contraceptives.

The interim results of the EURAS Study were based on intention-to-treat (ITT) analyses. That is, all data from an individual patient were assigned to the treatment she used at study entry. The final analyses included both (1) an as-treated (AT) or current use analysis and (2) an ITT analysis. Conclusions based on the initial ITT results for this study did not differ from the conclusions based on the AT results because, as noted by the investigators, the ITT analysis was completed within six months of initiation of CHCs.

Based on the published manuscript, 58,674 women were enrolled by 1,113 study centers in seven European countries and followed for 142,475 PY of observation. Loss to follow-up was 2.4%.

The EURAS Study showed no increased risk of VTE, ATE, or mortality for users of the DRSP-containing COC when compared to users of LNG-containing COCs or the other CHCs. Hazard ratios (HRs) for VTE, crude or adjusted for age, body mass index (BMI), duration of use and VTE history, showed no difference in risk between use of the DRSP-containing COC and LNG or the DRSP-containing COC and other CHCs. Similarly, HRs for ATE (which consisted of acute myocardial infarction [AMI] and ischemic stroke [IS]), crude or adjusted for age, BMI, smoking, and hypertension showed no difference in risk between the DRSP-containing COC and LNG or the DRSP-containing COC and other CHCs.

Cox regression analysis of cardiovascular outcomes yielded the following HRs for DRSP-containing vs. LNG-containing COCs and other CHCs (see Table 8).

Table 8 Hazard Ratios (HR) for VTE and ATE: DRSP-containing COC vs. LNG-containing COCs and other CHCs (EURAS Study)

Comparison	HR	95% CI
VTE		
DRSP vs. LNG	1.0	0.6-1.8
DRSP vs. CHC	0.8	0.5-1.3
ATE		
DRSP vs. LNG	0.3	0.1-1.2
DRSP vs. CHC	0.3	0.1-1.5

Source: Modified from Table 3 in Reference #10

VTE incidence rates for the DRSP-containing COC were similar to the rates for LNG-containing COCs and those for other CHCs. However, for ATE, the LNG incidence rate per 10,000 PY (2.9; 95% CI 1.3-5.4) was higher than that for DRSP (0.7; 95% CI 0.1-2.5). The same trend was observed for mortality, with incidence rates per 10,000 PY of (2.5; 95% CI 1.1-5.0) for LNG compared to (1.4; 95% CI 0.4-3.6) for DRSP, but the number of cases was very small. In addition, risks of cardiovascular and other serious events in users of DRSP were similar to those associated with the use of other CHCs.

2.2.2 Long-term Active Surveillance Study for Oral Contraceptives (LASS)

The LASS was designed as a continuation of the EURAS study. Based on the LASS report,[22] the EURAS Study was initiated in 2000 and completed in 2005 (this differs from what was reported in the EURAS publication, which stated that the EURAS Study was completed in 2004). EURAS included 59,510 (or 58,674*) women followed for 142,475 PY. Loss to follow-up was 2.4% at the end of the EURAS Study and 2.9% at the end of LASS. LASS included five additional years of follow-up for 47,799 users who were still in the EURAS study at the end of 2005. LASS added another 176,309 PY of observation and 103,379 PY of exposure for a total of 318,784 PY of observation and 216,038 PY of exposure. LASS also added two additional cohorts of users: women who stopped using oral contraceptives and switched to another form of contraception (non-oral hormonal contraceptives or NOHC) and women who stopped using any form of contraception (non-users). Overall, the study participants were divided into five cohorts for the analysis:

- four user cohorts
  - DRSP
  - LNG
  - Other oral contraceptives
  - Non-oral hormonal contraception
- One nonuser cohort

VTE incidence rates for DRSP users were similar to those for LNG users and other CHC users.

* *The Final Report notes 59,510 enrollees with 836 refusals yielding 58,674 women in the study.*

In LASS, incidence rates for ATE were again higher in the LNG group (2.3; 95% CI 1.2-3.9) compared to rates in the DRSP group (1.3; 95% CI 0.5-2.8) but similar to rates in the other contraceptives group (3.2; 95% CI 2.2-4.5). Mortality rates were also higher for the LNG group (2.3; 95% CI 1.2-3.9) compared to the DRSP group (1.3; 95% CI 0.5-2.8) and the other contraceptives group (1.8; 95% CI 1.1-2.8). The adjusted hazard ratios, however, did not show any difference in TTE, VTE, or ATE risk across the different groups.

Comment

It is likely that the EURAS study represents the experience of European women who use hormonal contraceptives primarily for contraceptive purposes because both the prescribers and the study subjects needed to provide consent to participate. The EURAS study also reflects the experience of European contraceptive users because women were recruited only from seven European countries: Austria, Belgium, Denmark, France, Germany, the Netherlands, and the United Kingdom. Baseline demographic information for the women participating in the EURAS study also was similar to the demographic information provided in case reports for non-US users of DRSP-containing COCs that were submitted to the FDA's Adverse Event Reporting System (AERS). Other than contraception, no information was provided in the study report on gynecologic disorders that women may have had. Despite the thoroughness of recruitment, case validation, and analyses by the investigators, this study design is subject to selection and recall bias because it depends greatly on the willingness and availability of clinical providers and study subjects to participate in the study.

2.2.3 i3 Ingenix Study

The other Sponsor-funded study (i3 Ingenix Study) was US-based.[13, 21] This study was initially designed to identify all instances of death, hospitalization, syncope, arrhythmia, hyperkalemia, and other clinically apparent electrolyte disturbances, dialysis, and MI among DRSP (Yasmin) initiators. Assessments for the risk of VTE and ATE were added after the study had been initiated, as previously described. Using the UnitedHealthCare database, the study identified DRSP initiators age 10 to 59 years during every quarter for the first year beginning in 2001 and semiannually for the remainder of the 3-year study, which ended in June 2004. Each three or six months, the investigators matched each DRSP initiator to two other contraceptive initiators based on their respective propensity scores (i.e., their probability of being prescribed DRSP) using information from the prior six months. Propensity scores were estimated using logistic regression, with the outcome being initiation of DRSP or another COC and predictors being derived from a woman's history of claims prior to initiating contraceptive use. Some of the variables included in the propensity score were specified in the study protocol based on expected association with DRSP and others were added later, as newly recognized differences between DRSP and other COC initiators were noted.

This study also analyzed the information using an "as matched" (or ITT analysis) as well as using an "as treated" (AT) analysis. Follow-up continued and person-time accrued for each woman beginning with entry into the cohorts until the earliest of the following: end of enrollment in the health plan, end of follow-up on June 30, 2004, or 180 days after the last use of the initial COC. Insurance claims were searched for data on the cohort members during follow-up to identify study diagnoses, procedures, and drugs possibly related to VTE. Medical records were sought for all patients whose insurance claims were possibly consistent with the occurrence of VTE. Proportional hazards models were used to provide estimates of the relative incidence of TTEs in the compared groups

Of the initial 22,887 DRSP initiators who qualified for the study, 22,429 were matched 1:2 using propensity scores to 44,858 other COC initiators and were followed for an average of 7.6 months. There were 18 cases of VTE in DRSP initiators and 39 in the comparators, providing an incidence rate per 10,000 PY of 13.0 (95% CI 8.0-20.0) for DRSP and 14.0 (95% CI 10.0-19.0) for the comparators, yielding an incidence rate ratio (IRR) of 0.9 (95% CI 0.5–1.6) (see Table 9). Results of the AT analysis were similar to those of the ITT analysis (IRR 1.0; 95% CI 0.5-1.9).

Table 9 VTE Incidence Rates (IR) in Initiators of Yasmin or Other Combination Oral Contraceptives and Rate Ratios (RR)

Yasmin Initiators			Other COC Initiators				
N=22,429	PY=14,081		N=44,858	PY=27,575			
No. of VTEs *	**IR‡**	95% CI	No. of VTEs *	**IR‡**	95% CI	**RR§**	95% CI
18	13.0	8.0-20.0	39	14.0	10.0-19.0	0.9	0.5-1.6

N: number of subjects; PY: person-years; IR: incidence rate; CI: confidence interval
* Some of these outcomes may be “continuations” of preexisting conditions
‡ Incidence rates expressed as events per 10,000 person-years
§ From a proportional hazards model
Source: Modified from Table 3 in Seeger 2007, Reference # 13

The Poisson regression analysis identified age 40 years and above and aggregated preexisting chronic medical conditions (diabetes, hypertension, history of MI, and arrhythmia), as well as prior VTE, as being associated with elevated incidence rates of thromboembolism during follow-up, but suggested no difference in incidence of VTE between users of DRSP and the other COCs.

The investigators also noted that a separate analysis of incidence rates and rate ratios stratified by duration of follow-up yielded essentially the same results, indicating that there was no association at different stages of follow-up (no exposure by time interaction).

Comment
This Sponsor-funded study used propensity scores to match patient characteristics of DRSP users to those of the other COC users. Consequently, DRSP users were very comparable to controls on their baseline risk, as captured in the claims data. This study also includes use of COC comparators other than LNG, the use of which is more representative of the US market. Nonetheless, matching was unsuccessful for 458 DRSP initiators, women that are likely included in the more recent claims-based studies if not excluded for other health conditions.

2.3 FDA-funded Epidemiologic Study

The FDA also funded a separate CHC study, led by Kaiser Permanente of California, which also included data from Tennessee Medicaid (through Vanderbilt University) and Washington State Medicaid (through the University of Washington). The objectives of the Sponsor-funded studies were primarily to assess TTE risks for users of a DRSP-containing COC compared to risks associated with other COCs, including LNG-containing COCs that are perceived by some to be associated with a lower risk for VTE. The objectives of the FDA-funded study, however, were to identify TTE risks, and if any were identified, then to explore the population and prescriber characteristics of use that might have resulted in these increased risks.

The FDA-funded study was conducted at two HMO sites (Kaiser Permanente Northern and Southern California) and two state Medicaid programs (Tennessee and Washington) each associated with an academic institution. In addition to having access to data from a large group of young women of reproductive age, reasons for selecting study sites included: 1) the ability of the investigators to validate study outcomes with medical records; 2) the ability of the sites to link to state vital status files to identify deaths quickly; and 3) the ability of the sites to facilitate physician and patient contact if and when needed. Diversity of populations was favored over similarity to maximize capture of possible reasons for an increased risk, if observed. A detailed review of this study was completed by FDA's OSE, Division of Epidemiology II (DEPI II) in 2011[23] and is provided in Appendix A.

The FDA-funded study was designed as a retrospective cohort study of women age 10 to 55 years who were current users of DRSP-containing COCs and other CHCs from January 1, 2001 to December 31, 2007. Two exposure cohorts, one of current users and the other of new users, were created for evaluation. For each study contraceptive in the primary analysis, the comparison group included a composite of frequently prescribed products that contained the progestins LNG, norethindrone acetate (NETA), or norgestimate (NGM) combined with 20 μg to 35 μg of EE (this comparator group was referred to as "COMP"). As a secondary analysis following recent published studies, comparisons of the risk for TTEs were also made for each study contraceptive with COCs containing LNG and 30 μg EE (referred to as the "LNG2" comparator group).

The FDA-funded CHC study did not match on age but rather adjusted for age in the analyses. The effect of age, therefore, could be evaluated. Investigators in the CHC study chose not to pre-specify the age relationship. Instead, the Cox models were stratified by 5-year age intervals with the exact age included as a continuous covariate in the regression model to provide additional control for potential residual confounding within the age strata. This provided tight control for age, freed the investigators from having to pre-specify the form of the relationship between age and outcomes in the regression models, while allowing for the independent evaluation of the effect of age.

The findings for the DRSP group (Yasmin) relative to the COMP and LNG groups reported by the FDA-funded study are provided in Table 10. The risk of VTE in DRSP users is increased for All Users and New Users, particularly in Users younger than 35 years of age. The risk of ATE is increased for New Users, particularly in those 35 years and older.

Table 10 Relative Hazard* for DRSP (Yasmin) Users for VTE, ATE, and Total Mortality Relative to the Combined (COMP) and LNG-only Groups ** (FDA-funded Study)

	VTE	ATE***	Total mortality
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**
All Users			
DRSP vs. COMP	**1.7 (1.4-2.1)**	1.0 (0.6-1.7)	0.9 (0.6-1.2)
DRSP vs. LNG	**1.5 (1.2-1.8)**	0.8 (0.5-1.4)	0.7 (0.5-1.0)
Ages 10-34 years ‡	**1.9 (1.4-2.5)**	0.5 (0.2-1.3)	0.8 (0.5 1.2)
Ages 35-55 years ‡	1.4 (1.0-1.8)	1.1 (0.6-2.1)	0.7 (0.3-1.6)
New Users			
DRSP vs. COMP	**1.8 (1.3-2.4)**	**2.0 (1.1-3.8)**	0.9 (0.5-1.5)
DRSP vs. LNG	**1.6 (1.1-2.2)**	1.6 (0.8-3.4)	0.6 (0.3-1.0)
Ages 10-34 years ‡	**2.1 (1.4-3.2)**	0.6 (0.2-2.3)	0.7 (0.4-1.3)
Ages 35-55 years ‡	1.2 (0.8-1.8)	**2.6 (1.3-5.4)**	1.5 (0.5-4.2)

*Estimates from Cox proportional hazards models. All models adjusted for age, site, and year of entry into study.
** The "COMP" group includes COCs containing the progestins LNG, NETA, and NGM with doses of EE ranging from 20 to 35 µg. The LNG group includes only COCs containing LNG and EE 30 µg
*** ATE models are further adjusted for hypertension, hyperlipidemia, and diabetes
‡ Age-specific models are adjusted for site, age (5 year age groups), and year of entry into the study; Reference = COMP
Source: Modified from Tables 12 and 14 of the Report for the FDA-funded study[27]

2.4 Other Published Studies Regarding the Risk of VTE in Women using DRSP-containing COCs

Several additional studies that limited risk assessment only to VTE, the most common of the TTEs, have been published.

2.4.1 The Prescription-Event Monitoring (PEM) Study

One of the earliest attempts to monitor the VTE risk associated with a DRSP-containing COC was through the UK's Prescription-Event Monitoring (PEM) System. The PEM is a well-established postmarketing surveillance technique in the United Kingdom designed to monitor the overall safety of newly marketed products as used in clinical practice. This is usually done when the marketed product is projected to have been used in at least 10,000 patients. At the time of marketing approval, DRSP (Yasmin) was subject to a PEM study designed to evaluate cases of DVT and PE.[17] Women who were prescribed DRSP in the UK between May 2002 and December 2002 were asked to complete a simple questionnaire (green form) which was returned to their prescribing general practitioner (GP) 6 to 12 months after the first prescription. GPs

were then asked to report any health-related events that had occurred since DRSP was prescribed. All potential VTE events were reviewed and validated by Drug Safety Research Unit physicians.

A total of 30,797 patients prescribed DRSP were sent green forms to complete. Of these, 17,877 (58.0%) were returned. Only 15,645 women prescribed DRSP had forms containing clinical information. Of these, 13 VTE cases (five DVT; eight PE) were identified. The crude incidence rate was estimated as 13.7 cases per 10,000 PY (95% CI 7.3-23.4). The investigators concluded that DRSP was associated with an increased incidence of VTE, but cautioned about the interpretability of the results.

Comment

Although an incidence rate was calculated, the investigators interpreted (and we agree) that the results are possibly subject to bias and should be interpreted with caution due to the large proportion of non-responders, missing information, and the lack of an internal comparator group. The calculated incidence rate for VTE in DRSP users in the UK (13.7 cases per 10,000 PY), however, is similar to, although slightly higher than the age-adjusted incidence rate reported in the FDA-funded study (10.3 per 10,000 PY) and similar to the incidence rates reported for the i3 Ingenix study (13.0 per 10,000 PY).

2.4.2 Lidegaard Epidemiologic Studies – 2009 and 2011

Both the Lidegaard[24] and the van Hylckama Vlieg[14] studies were designed to assess the VTE risk in users of COCs compared to non-users with a focus on estrogen dose and type of progestin. Lidegaard also focused on dose regimen and route of administration. The two studies were recently reviewed by OSE/DEPI II and results are summarized in this Background Document.

The Danish study (Lidegaard's) was a population-based cohort study with linkage across four national registries:

1. The National Registry of Medicinal Products Statistics
2. The National Registry of Patients (discharge diagnoses, and surgical codes that includes births and abortions)
3. Statistics of Denmark, which includes information on education
4. Central Person Registry, which includes a 10-digit personal ID given at birth or immigration, provides information on current address and vital status

Non-pregnant women with no evidence of cancer or cardiovascular disease who were between 15 and 49 years of age from January 1, 1995 to December 31, 2005 were identified for the study.

The main objective of the 2009 Lidegaard cohort study was to compare VTE risks of CHC users to non-users. The investigators, however, also compared VTE risks between users of DRSP- and LNG-containing COCs that contained the same dose of estrogen. The rate ratio for VTE for DRSP users compared to LNG users was 1.6 (95% CI 1.3 to 2.1). Compared to non-users, the VTE risk was highest in the first year of exposure for all study CHCs except LNG. The unexpected finding for LNG raised concern about the study methodology with the European regulators, who later requested a reanalysis of the data.[25, 26]

2.4.3 Lidegaard Reanalysis

Shortly after Lidegaard reported an increased VTE risk for DRSP compared to LNG in his 2009 manuscript,[24] the Medicines Evaluation Board (MEB) on behalf of the Pharmacovigilance Working Party (PhVWP) of the European Medicines Agency (EMA) requested him to reanalyze

the Danish data to address 1) left truncation effects perceived potentially to lead to survivor bias and 2) to focus on the time period between 2001 and 2005, the first 4-5 years that DRSP was available in the Danish market. The left truncation effect is the effect on risk estimates introduced by women who may have started any COC use months or years prior to enrollment in the study cohorts, thus creating cohorts of "survivors" or women at lower VTE risk. The re-analysis was supervised by a Steering Committee. Some results of the reanalysis were published in 2011.[25] In this later analysis, Lidegaard reported a two-fold increased VTE risk for first-ever DRSP users compared to first-ever users of LNG-containing COCs with 30 to 40 μg of EE, after adjusting for length of use of confirmed cases (RR 2.1; 95% CI 1.6-2.8).

The design for both the 2009 publication and the re-analysis was based on identifying a historical cohort of all Danish women 15 to 49 years of age from 1995 onwards. Data for both analyses were obtained from the *Statistics of Denmark, the National Registry of Patients*, the *Abortion and Birth Registry*, and the *National Registry of Medicinal Products*. Differences in the analyses focused mostly on study time periods and exposure definitions with some changes imposed on eligibility in the re-analysis. The re-analysis also included outcome validation with medical records; these were referred to in the manuscript as confirmed events or confirmed cases.

Comment

The Danish investigators agreed to re-analyze their data at the request of the EMA, although the objectives of their original 2009 analysis were very different from those requested by the EMA. In the 2009 analysis, the objective was to assess the risk of VTE in current users compared to non-users for different types of CHCs, focusing on regimen, estrogen dose, type of progestin, and route of administration. Nonetheless, the investigators extended their conclusions beyond user/non-user comparisons to include comparisons of different CHCs with LNG-containing COCs. The EMA-requested objectives proposed to assess the comparative risk of developing first time VTE among users of DRSP compared to users of LNG. The exclusions, re-definition criteria, and the time period restrictions imposed in the re-analyses changed the actual relative risks, sometimes dramatically (Table 11).[26] In no instance, however, did the increase in VTE risk associated with use of DRSP disappear completely or appear reversed. And, unlike the 2009 analysis, the increased VTE risk was higher during the first year compared to subsequent years of use for both DRSP and LNG.

Table 11 The Significance of Specific Methodological Rules Applied in the Re-analysis Compared with the Primary Publication in BMJ for the Relative Risk (RR) of VTE in Users of LNG-containing and DRSP-containing COCs Compared with Non-users

LNG vs. no use	<1 year			1-4 years			>4 years		
Criteria effected	**RR**	**Low**	**High**	**RR**	**Low**	**High**	**RR**	**Low**	**High**
No new criteria in effect, 1995-2005[1]	**2.0**	1.4	3.0	**2.1**	1.7	2.6	**2.0**	1.6	2.4
No new criteria in effect, 2001-2005[1]	**5.2**	2.2	12.6	**2.3**	1.3	3.9	**1.9**	1.5	2.4
Extension of use with 4 weeks[2]	**6.1**	2.7	13.6	**2.3**	1.3	3.9	**2.1**	1.6	2.6
Exclusion of 4 weeks after switch[3]	**6.2**	2.8	13.8	**2.3**	1.3	4.0	**2.1**	1.6	2.6
Change in duration of use definition[4]	**3.2**	2.2	4.5	**1.8**	1.2	2.7	**2.0**	1.4	2.7
Restriction to confirmed events[5]	**4.3**	2.9	6.3	**2.3**	1.5	3.6	**2.6**	1.8	3.8
Introduction of wash out period[6]	**4.3**	2.5	7.4	**2.3**	0.9	5.5	**-**	-	-
DRSP vs. no use	**<1 year**			**1-4 years**			**>4 years**		
Criteria effected	**RR**	**Low**	**High**	**RR**	**Low**	**High**	**RR**	**Low**	**High**
No new criteria in effect, 2001-2005[1]	**8.5**	6.0	11.9	**3.3**	2.4	4.6	**3.0**	2.2	4.1
Extension of use with 4 weeks[2]	**9.8**	7.1	13.5	**3.6**	2.6	4.9	**3.1**	2.2	4.2
Exclusion of 4 weeks after switch[3]	**10.0**	7.3	13.9	**3.6**	2.6	5.0	**3.1**	2.3	4.3
Change in duration of use definition[4]	**5.6**	4.4	7.1	**3.3**	2.3	4.6	**2.4**	1.2	5.1
Restriction to confirmed events[5]	**7.4**	5.5	9.9	**5.4**	3.7	7.8	**3.8**	1.7	8.7
Introduction of wash out period[6]	**7.5**	5.6	10.2	**5.1**	3.3	7.9	**-**	-	-

Low and High refer to the lower and upper bounds of the 95% confidence interval around the RR

[1] *Baseline: Period 2001-2005, Duration defined as in BMJ 2009 paper, no extension of strings (restrictions), no exclusions after switch, all events included, no wash out period*

[2] *Extension of current use by four weeks after the expiration of prescription period (cases included during the extension)*

[3] *Exclusion of time at risk and VTE events during first four weeks after switch*

[4] *Change from definition in BMJ paper (sum of all COC prescriptions) to definition in EMA analysis (sum of prescriptions beginning no earlier than 2001)*

[5] *Only confirmed events included*

[6] *Restriction to starters and new users = at least 12 weeks of non-use before current use = "wash out"*

Source: Data abridged and rounded to 1 decimal place from Table14, pg. 12462 in Reference # 26

The ratio between the relative risks for DRSP-containing COCs compared to LNG-containing COCs also remained the same (Table 12), except where left truncation effects among treatment groups were suspected. Higher risk ratios were seen in women using DRSP when compared to LNG in the 1 to 4 year follow-up group when the analyses were restricted to confirmed cases and to first time users (new users and re-starters with >12 weeks gap). The restrictions seemed to have affected the number of new users and re-starters in the LNG user group more than in the DRSP user group. After the new restrictions were implemented, only 29% of the LNG cohort remained, whereas 78% of the DRSP cohort remained under observation.

Table 12 Ratios of Relative Risks (RR) for VTE: DRSP–containing COCs Compared to LNG-containing COCs

	DRSP/LNG RR Ratios		
	< 1 Year	**1-4 Years**	**> 4 Years**
No new criteria in effect, 2001-2005[1]	1.6	1.4	1.6
Extension of use with 4 weeks[2]	1.6	1.6	1.5
Exclusion of 4 weeks after switch[3]	1.6	1.6	1.5
Change in duration of use definition[4]	1.8	1.8	1.2
Restriction to confirmed events[5]	1.7	2.3	1.5
Introduction of wash out period[6]	1.7	2.2	

[1] Baseline criteria: Period 2001-2005, Duration defined as in BMJ 2009 paper, no extension of strings (additional restrictions), no exclusions after switch, all events included, no wash out period
[2] Extension of current use by four weeks after expiration of prescription
[3] Exclusion of time at risk and VTE events during first four weeks after switch
[4] Change from definition in BMJ paper (sum of all COC prescriptions) to definition in EMA analysis (sum of prescriptions beginning no earlier than 2001)
[5] Only confirmed events included
[6] Restriction to starters and new users = at least 12 weeks of non use before current use ="wash out"

Source: Derived from data in Table 11 of this Background Document

Comment

The one- to four-year time period of use is the one least affected by varying risks among users (naïve users, switchers, re-starters) associated with new use and is probably the best time period to assess specific risks between the oral contraceptives.

In the new user analysis, neither DRSP nor LNG users had sufficient follow-up time to identify long-term risk (more than 4 years). Even when the follow-up was extended to 2009, the number of LNG users was too small for accurate measurement.

2.4.4 Van Hylckama Vlieg Epidemiologic Study – 2009

Van Hylckama Vlieg's study was a population-based case-control study of non-pregnant, pre-menopausal women 18 to 50 years of age who attended six participating clinics in the Netherlands (Amersfoort, Amsterdam, The Hague, Leiden, Rotterdam, and Utrecht) between March 1999 and September 2004 as part of the Multiple Environmental and Genetic Assessment (MEGA) study (a large, population-based, case-control study designed to assess risk factors for VTE in both men and women less than 70 years of age).[14] Patients with severe psychiatric problems and those who could not speak Dutch were excluded. Refusals, cases with no matched control, and deaths prior to the interview were additional reasons why only 46.2% of the identified eligible study subjects participated in the MEGA study. Cases were individuals

diagnosed with DVT. Controls included an identified partner of patients, supplemented with subjects recruited via random-digit-dialing (RDD) between January 2002 and September 2004. Information for this study was obtained during clinic visits or by telephone interview.

Although the MEGA study included males and females, for the published analysis, only female cases aged 15 to 50 years of age were included. Women who were postmenopausal, pregnant, within 4 weeks postpartum at the time of the thrombotic event or index date, or using non-oral hormonal contraceptives (NOHCs) were excluded from the analysis. There were 1,524 female cases identified, 712 female partner controls, and 1,048 RDD controls. Partners and RDD controls were pooled in the analyses that were adjusted for inclusion date.

For this case-control study, the main analysis was to assess risk in COC users compared to non-users. The VTE odds ratio (OR) for LNG users to non-users was 3.6 (95% CI 2.9-4.6). For DRSP users compared to non-users, the OR was 6.3 (95% CI 2.9-13.7), suggesting a higher risk in DRSP users than LNG users, although the CI for DRSP users is much wider. The investigators also noted that VTE risk was positively associated with estrogen dose.

Summary Comments regarding 2009 Studies

Although different in design (population-based cohort study vs. population-based case-control study) and populations (Denmark vs. Netherlands), both studies confirmed already published results that the incidence or risk for VTE

- **Is greater among hormonal contraceptive users compared to non-users**
- **Increases with age**
- **Increases with increasing estrogen dose regardless of which progestin is used and**
- **Is highest in the first months of use**

In addition, Lidegaard's population-based cohort study also showed that VTE incidence

- **Was inversely proportional to education levels and**
- **Had been increasing by calendar year**

Although both studies showed an increased risk for DRSP when controlling for estrogen content and time of use, DRSP risk estimates had confidence intervals that overlapped with those for LNG, which suggests similar risks. In addition, the number of cases in the case-control study and the number of users in the cohort study exposed to DRSP was very small compared to the number of users of LNG, yielding greater instability as seen by the wider confidence intervals for the DRSP risk estimate. A larger DRSP-exposed population would be needed to provide more stable risk estimates.

The DRSP-containing COC in both studies contained 30 µg of EE. This is equivalent to the EE content of the US product Yasmin. Consequently, neither study provided information on VTE events associated with the use of YAZ, the DRSP-containing COC that contains 20 µg EE. Both studies confirmed a decreasing risk of VTE with decreasing estrogen levels and, therefore, it is possible that YAZ might have a lower risk of VTE than Yasmin. However, the lower dose estrogen pills in YAZ are taken over 24 days instead of the usual 21 days for Yasmin. The effect of this difference (lower dose of EE but more days of exposure to DRSP and EE) on VTE risk has not been evaluated.

Finally, we would like to emphasize Dr. Lidegaard's cautionary note[24] that, when comparing products by progestin type, the arterial effects of these products should also be assessed before making clinical recommendations. Some studies suggest a higher ATE risk for products that are shown to have a lower VTE risk. The LNG users in the EURAS[20] and the FDA-funded studies had higher ATE and mortality incidence rates than DRSP users[23, 27] (Table 13).

Table 13 ATE and Mortality Rates in EURAS and FDA-funded Studies

	ATE Incidence Rate (IR) Rate per 100,000 PY				Mortality Rate (MR) Rate per 100,000 PY			
	DRSP		LNG		DRSP		LNG	
Study	**IR**	**95% CI**	**IR**	**95% CI**	**MR**	**95% CI**	**MR**	**95% CI**
EURAS[20]	7.0	1.0–25.0	29.0	13.0–54.0	14.0	4.0–36.0	25.0	11.0–50.0
FDA Study[27]	11.3	--	16.2	--	24.7	--	45.0	--

This increase could be related to providers channeling higher risk women toward LNG-containing COCs because LNG may have been perceived as a safer product. The findings could also represent a real risk of ATE associated with LNG.

2.4.5 Jick and Parkin Epidemiologic Studies – 2011

In 2011, two additional published studies[15, 16] assessed VTE risk among DRSP users compared to LNG users. OSE/DEPI II also reviewed and commented on these manuscripts.[28]

Although using two different databases, the basic design of these two studies was generally the same, with some notable differences. The study by Parkin et al used an electronic medical record database (General Practice Research Database or GPRD), which represents a sample of British women receiving care from their GPs. The study by Jick et al used a de-identified US-based database (PharMetrics) that captures claims submitted for reimbursement by managed care and other health plans. The objective for both studies was to evaluate the risk of non-fatal, idiopathic VTE among users of DRSP-containing COCs compared to users of LNG-containing COCs with 30 μg EE. The Jick study also compared the risk of DRSP-containing COCs to the LNG-containing COCs with 20 μg of EE. The time period is longer for the Parkin study but both time periods overlap the years 2003 to 2008; the Parkin study covers the time period from May 1, 2002 though September 2009 and the Jick study covers the period from January 1, 2002 through December 31, 2008. Both studies exclude women at high risk of VTE and those who had a history of cancer, renal failure, chronic cardiovascular disease, and inflammatory or autoimmune disease. Both studies included women who were current users of the study contraceptives on the index date.

The main outcome for both studies is a first time diagnosis of a DVT or PE (definition included hospital admission and/or emergency room visit for PharMetrics-based cases) followed by treatment with anticoagulants, and no evidence of continued contraceptive use after diagnosis. Finally, cases with evidence of other risk factors for VTE, such as trauma and pregnancy (present in the 90 days before the index date for Jick study subjects) were excluded from analysis. More information was available in GPRD, and therefore more criteria relating to VTE risk factors were used to exclude cases. Only non-fatal idiopathic cases who were current users of the study contraceptives were included for analysis.

To take account of the matching, a conditional logistic regression model was used as the primary analysis for both studies. Secondary analyses included stratification with matching variable adjustment and an assessment of interaction (effect modification) terms.

Comment

The design for both studies is stated by the investigators to be a nested case-control study, but because there was no apparent creation of an exposure cohort, the design more appropriately reflects that of a *population-based* case-control study of women 15 to 44 years of age who ever used a study contraceptive.

Despite the many similarities, the two studies differed significantly in the criteria used for matching cases and controls, in the number and type of covariates and confounders available for analysis, and in selections of exposure criteria used for study. These differences were mostly dictated by the database used.

Jick reported a two-fold increased VTE risk for DRSP users when compared to LNG users (OR 2.3; 95% CI 1.6-3.2). The incidence rate per 10,000 PY for DRSP users was 3.1 (95% CI 2.6-3.7), and for LNG users the rate was 1.3 (95% CI 1.0-1.6). The age-adjusted IRR for DRSP, using LNG as reference, was 2.8 (95% CI 2.1-3.8).

Parkin reported a three-fold higher risk of non-fatal idiopathic VTE when compared to LNG: (OR 3.3; 95% CI 1.4-7.6). The crude incidence rate per 10,000 PY was 2.3 (95% CI 1.3-3.7) for current users of DRSP and 0.9 (95% CI 0.7-1.2) per 10,000 PY for current users of LNG. The age-adjusted IRR was 2.7 (95% CI 1.5-4.7).

Comment

These two BMJ studies raise questions about the reliability of the reported increased VTE risks associated with the use of DRSP-containing COCs when compared to LNG-containing COCs. Concerns have been raised that the reported increased VTE risks may be due to the inappropriateness of the databases used[28], the epidemiologic methods employed (cohort vs. case-control), and the fact that the investigators reported exclusively on "idiopathic" cases with no clinical record validation. There are also concerns about the statistical approach used. These methodological issues by themselves may introduce bias, but if they apply consistently to both cases and controls, they should not introduce imbalance in the DRSP and LNG comparisons and would not necessarily explain the increased risk reported by these studies compared to the negative findings in the Sponsor-funded studies.

Of greater concern are questions about the appropriateness of the LNG comparator, because LNG use in the US represents less than 5% of the total market. Furthermore, the lack of specificity in the published manuscripts on exactly how exposure was defined for each study could mask possible imbalance across the treatment groups and across studies being compared. For example, it is unclear whether the look-back period in the Parkin study included all years of data available for cases, although cases were matched to controls on length of available data. But some case-control matched units could differ in available information. Therefore, results reported by these studies may apply only to a very limited subset of DRSP and LNG users.

2.4.6 Dinger Epidemiologic Study – 2010

A case-control study published in 2010[29] by the same investigators who conducted the EURAS and LASS studies reported no increased VTE risk for DRSP uses when compared to low EE dose LNG-containing COCs (crude OR 1.0; 95% CI 0.6-1.6 and adjusted OR 1.0; 95% CI 0.5-1.8).

This study was a German community-based, case-control study. A randomly selected sample of 250 clinical providers were contacted and asked to identify VTE cases. Eligible cases were women aged 15–49 years with a VTE between January 2002 and February 2008. Four community-based controls (women without a confirmed or potential VTE before the index date) were matched by age and region to each case. Medical information relevant to VTE was abstracted from patient charts. Data on personal characteristics of the patients (age, past and current use of hormonal contraception, body weight and height, smoking habits, personal and family history of VTE, varicose veins, recent immobilization, pregnancy, surgery and accidents, and genetic risk factors as well as chronic diseases, concomitant medication, socioeconomic and

lifestyle indicators) were collected via self-administered questionnaires. At the end of the study, a blinded adjudication of the reported VTEs was conducted. Conditional logistic regression techniques were used, adjusting for nine potential confounders, including personal history of VTE, family history of VTE, BMI, duration of current COC use and smoking.

This case-control study found no increased VTE risk for DRSP users when compared to LNG users. The crude OR for VTE among CHC users compared to women who were non-users before the index date was 1.9 (95% CI 1.5-2.5). The crude OR for DRSP users compared to LNG users was 1.0 (95% CI 0.6-1.6), and the adjusted OR for DRSP users compared to LNG users was 1.0 (95% CI 0.6-1.8).

Comment

Other than confirming VTEs by medical record review, most of the other information obtained in this study was reported by the women themselves. This allows capture of more historical information including family and personal history of VTE, but it is also subject to recall bias. Although 650 medical providers were targeted, the manuscript does not report on the proportion responding to the survey. Those that did respond reported 879 potential cases. Furthermore, respondents were more likely to participate if they perceive a personal benefit. Despite the thoroughness of recruitment, case validation and analyses by the investigators in this study, this study design is subject to selection and recall bias because it depends greatly on the willingness and availability of clinical providers and study subjects to participate in the study.

3. Discussion

Of particular interest is the difference in findings between the Sponsor-funded studies and the Dinger case-control study, and other studies described in this Background Document. The Sponsor-funded prospective studies and the Dinger study showed no increased VTE risk when comparing DRSP-containing COCs with LNG-containing COCs or other CHCs, whereas the other published retrospective studies and the results of the FDA-funded study all showed a consistent increased VTE risk associated with DRSP-containing COCs.

These studies differ from each other in many ways. A more detailed discussion of the Agency's thoughts can be found in the FDA-funded study review[23] but some of the highlights will be addressed in this Background Document. Although it is tempting to find flaws in these studies because all studies have limitations as well as strengths, each study, despite its limitations, contributes specific information to the overall body of knowledge.

The studies consistently report that VTE risk:

- Is higher among CHC users compared to non-users
- Increases with age
- Is highest in the first months of use whether this is defined as 3 months, 6 months, or first year.

Many, but not all, of the studies have evaluated the risk of ATE and death as well as VTE. Many of the studies are based on a cohort design; others use a case-control design. Results, however, seem to depend more on the choice of study populations, exposure definitions, and the study's ability to adjust for known confounders (either those that can be measured or those typically unmeasured).

3.1 Population Sources/Databases

Each study presents results from different populations and, based on published and unpublished comments, one might assume that product-related VTE risks are the same in each population studied. But as can be seen in Table 14, only three of the eight studies listed used a US population (i3 Ingenix, Jick, and FDA study). The age distributions also differed, although all studies included women 18 to 44 years. The mean age, when available, however, differed across studies. The effect of age has been discussed in greater detail in FDA's review of the FDA-funded study[23].

Population differences in risk can be seen clearly in the FDA-funded study, where two different populations were included. The interaction term for site or study population was significant. The FDA-funded study included Medicaid and health maintenance organization (HMO) users. Medicaid users were on average 4.5 years younger than HMO users. The differences in use across CHC types at both sites also suggested that use of only one specific CHC comparator might be misleading when evaluating VTE risk in multiple population sources. Type of CHC use varies by populations studied, as demonstrated in this study, and may be affected by differential prescribing, insurance formularies, and site-specific preferences. A detailed discussion can be found in the FDA review of the study (see Appendix A). Another question of interest, however, is whether prescription fill trends differ by CHC type over the study period (see Section 3.1.1).

An overview of all the studies reviewed here is provided in Table 14.

Table 14 Summary of Study Populations, Inclusion, and Exclusion Criteria

Author Study time period	Population	Case Validation	Design CHC	Mean Age	Exclusions	Selection Criteria
EURAS 2007[10] 2000-2005	European countries: Austria, Belgium Denmark France Germany Netherlands UK	Yes	Prospective Cohort: DRSP LNG Other	Age: all ages DRSP: 25.9 LNG: 25.1 Other: 24.8	Refused participation	Network of physicians offered participation to CHC starters and switchers who consented
I3 Ingenix 2007[13] 2001- 2004	US - UHC	Yes	Prospective Cohort: DRSP Other	Age: 10-59 DRSP: 28.4 Other: 28.4	Initiators with no matching on propensity score; < 6 mos enrollment	Initiators
Lidegaard 2009[24] 1995-2005	Denmark	No	Population cohort: DRSP LNG Others No use	Age 15-49	Malignant disease CVD Pregnancy	Cohort assembled during study period and use classified as current, former, or no use at the time of hospitalization
Vlieg 2009[14] 1999-2004	Netherland clinics	Yes	Case-control DRSP No use	Age 18-50 years Cases: 37.1 Controls: 37.4	Pregnancy IUD & depot use NOHCs	First episode of DVT or PE with clinical evidence in clinics
Dinger 2010[29] 2007-2008	Germany	Yes	Case-control DRSP LNG	Age 15-44 years	No informed consent Language barrier	Clinic referrals Community controls
Jick 2011[16] 2002-2008	US claims	No	Case-control (nested) DRSP LNG	Age 15 – 44 years	< 6 mos enrollment Lower limb injury Major surgery Severe trauma Pregnancy	First diagnosis Current use (DRSP and LNG)
Parkin 2011[15] 2002-2009	United Kingdom	E-records	Cohort & Case-control (nested) DRSP LNG	Age 15 – 44 years Cases: 32.2 Controls: 31.8	History of VTE Cancer Renal failure CVD Contraindications to CHC use.	First VTE diagnosis Current use (DRSP and LNG)

Author Study time period	Population	Case Validation	Design CHC	Mean Age	Exclusions	Selection Criteria
FDA Study 2011[27] 2001-2007	US HMO, Medicaid	Yes	Cohort DRSP LNG Other CHCs	Age 10-55 years DRSP: 25.9 LNG: 27.9 Other: 27.7	< 6 mos enrollment Serious or life threatening illness History of VTE, CVD Pregnancy	Any user New user with no prior CHC exposure in look back period
Lidegaard 2011[25, 26] 2001-2009	Denmark	Yes	Population cohort DRSP LNG Other CHCs No use	Age 15-49 years	Prior event between 1999 and 2000 Malignant disease, cancer of abdominal organs, breast, lung, or blood. Gynecological surgery	First event

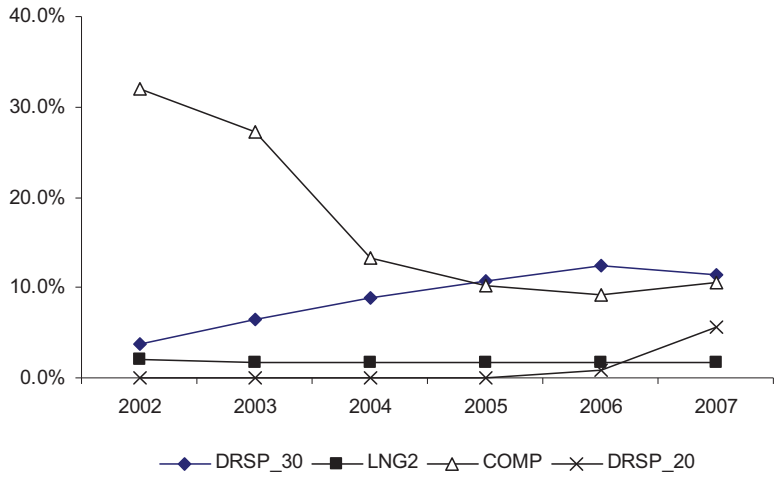
DRSP – drospirenone-containing contraceptive; LNG – levonorgestrel-containing contraceptive; CHC – combined hormonal contraceptive
UHC - UnitedHealthCare; IUD – intrauterine device; NOHCs – non-oral hormonal contraceptive
CVD – cardiovascular disease, VTE – venous thrombotic event; DVT – deep vein thrombosis; PE – pulmonary embolism

3.1.1 Trends in Prescription Fills

All studies compared users of DRSP between the years 2001 to as late as 2010, but most, including the US-based studies, evaluated the period between 2001 and 2008. It is unclear whether differences in risks reported across studies could be a reflection of differences in patterns of use for the products being compared over time, although most studies either adjusted for calendar time or matched on index date. Trends in prescriptions filled for the contraceptives included in the FDA-funded study are shown in Figure 2 for the years 2002 through 2007. During this time period, "DRSP_30" prescriptions (Yasmin or its generic equivalent) increased though 2006, then a decrease was evident for DRSP_30. The decline was not necessarily related to safety concerns, but rather to the introduction of the DRSP product containing 20 μg EE (YAZ) on the US market. During the same time period, prescription fills for the "COMP" products (COCs containing LNG, NETA, or NGM) were decreasing through 2005 but were greater than prescription fills for DRSP. Prescription fills for LNG-containing COCs remained relatively constant during the study period, but use was much lower than for the other COCs. Clearly, use over time differs across products. (More information about drug use over time is provided in Appendix B). This observation of differences in prescription patterns raises the question of whether these differences in prescribing patterns are also reflective of differences in the population of users over time.

Taken together, DRSP and LNG, as used in the FDA-funded study, represented less than 20% of hormonal contraceptives used in the marketplace according to the projected numbers obtained from *SDI Vector One*® databases. However, the trends do show that beginning in 2004, the level of DRSP use, whether DRSP_30 or DRSP with 20 μg EE, is about equal to that of the COMP, the combined comparator group in the FDA-funded study, which included NGM-, NETA- and LNG-containing COCs with 20 to 35 μg EE. COMP included more prescription fills for the NGM-containing COCs between 2002 and 2004. These nationally projected trends reflect aggregation of many health plans and cash payers; these trends may look very different, however, for specific providers or payers with strict formularies, such as HMOs or Medicaid programs.

Figure 2 Total Prescriptions for Selected Contraceptives as a Proportion of the Total Market, 2002-2007



DRSP_30 = Drospirenone-containing contraceptive with 30 µg ethinyl estradiol;
LNG = levonorgestrel-containing contraceptive; COMP = includes norgestimate-, norethindrone acetate- and levonorgestrel-containing contraceptives
Source: SDI Vector One®: National, Years 2002-2010 Data Extracted September 2011

Differences in VTE risks are not likely due only to the effect of secular trends within studies, because risk estimates for most studies were adjusted for calendar time or matched on index year and age. The same cannot be said when comparing across studies, particularly when these studies include users from different countries. In addition, differences seen in risk estimates may be related more specifically to the differences in populations of users over time, which may differ by type of CHC.

3.1.2 Exclusions

Published studies differed as to which women were included in the study (Table 14). The two Sponsor-funded studies[13, 10] and a case-control study[29] did not exclude women for any reason from the study. The only women excluded from the EURAS Study were those who refused participation. The i3 Ingenix study matched each DRSP initiator to two other non-DRSP initiators using propensity probabilities. It should be noted that, in the i3 Ingenix Study, there were 428 DRSP initiators (2%) who could not be matched and were therefore excluded from the cohort analysis. Other studies excluded users who were pregnant or had serious health conditions such as cancer, history of cardiovascular disease, and renal failure prior to cohort assembly or case-control selection. Some studies limited evaluation only to users who had no known condition associated with a high risk of VTE and used only non-fatal, idiopathic VTE cases for analysis. These exclusions, if applied equally to each treatment group within a study, do not necessarily bias the study results, but may affect the interpretation when results are compared across studies if studies being compared apply different exclusion criteria.

3.2 Exposure Definitions

Exposure definitions in the published studies referenced in this Background Document (Table 15) usually included a first new prescription fill for the CHC of interest during the

study period, with only some studies imposing a new user or initiator design. The new user definitions may have included a **study**-contraceptive-free period (or gap) during the specified look-back period, but most allowed use of non-study CHCs. Only three studies required the look-back period to exclude study and non-study CHCs, two of these studies evaluated only DRSP.[15, 25] The third was the FDA-funded study, which evaluated both DRSP and other products. Another study[16] analyzed the data differently, stratifying on new use with and without prior CHC.

The FDA-funded study also evaluated the effect of two exposure definitions; one definition basically not imposing any prior use restrictions; the other, using a much stricter new user definition, excluded women with any CHC use (not just use of the study CHCs) in the prior six months. These two extreme exposure definitions using the same design allowed for a better assessment of the impact of using different exposure definitions.

In the FDA-funded study, incidence rates for New Users were higher than those for All Users, but not for analyses adjusting for age, site, and calendar year with the time-dependent Cox Proportional Hazards models. The FDA-funded study clearly showed an interaction with age and study population. Lidegaard, in his unpublished 2011 reanalysis,[26] also reported the VTE rate ratio (RR) for DRSP vs. LNG among Starters (no history of CHC use before the current prescription) and All Users. The adjusted RR for Starters (like New Users in the FDA study) was slightly higher (RR 2.7; 95% CI 1.7-4.1) than for All Users (RR 2.0; 95% CI 1.6-2.4). The CIs, however, overlapped and were tighter for All Users, likely due to the larger number of users in this group. If risk estimates vary within studies based on different exposure definitions, it is likely that different exposure definitions across studies would explain some of the differences seen in the risk estimates.

Table 15 Summary of Exposure Definitions, Analyses, and Study Results

Author Study time period	Design CHCs Compared	Exposure Criteria	Analysis	Events	Included covariates	Results (95% CI)
EURAS 2007[10] 2000-2005	Prospective Cohort: DRSP LNG Other	First ever users of new study CHC Switchers Starters	ITT interim AT final Cox PH for HR; Poisson for IR Non-inferiority	TEE VTE ATE Death	BMI, smoking, past history VTE assumed	Adjusted HR DRSP vs. LNG VTE: 1.0 (0.6-1.8) ATE: 0.3 (0.1-1.2) Death:0.5 (0.2-1.7)
I3 Ingenix 2007[13] 2001- 2004	Prospective Cohort: DRSP Other	Initiators, new study CHC in prior 6 months; comparator matched on propensity score	ITT and AT Poisson Cox PH	TEE VTE ATE Death	Age, calendar time, hx of CHC use, health plan, chronic disease, use of health services	IRR DRSP vs. Other TTE: 0.9 (0.5–1.) Current: 1.0 (0.5-1.9)
Lidegaard 2009[11] 1995-2005	Population cohort DRSP LNG Others No use	Current use at time of event	Poisson	TEE VTE	Age Calendar year Education	IRR: Use vs. no use VTE LNG: 2.0 (1.8-2.3) DRSP: 4.0 (3.3-4.9) Current: 2.8 (2.7 - 3.0)
Vlieg 2009[14] 1999-2004	Case-control DRSP Any use vs. No use	Current OC use DRSP, LNG, others	Logistic regression	TEE VTE	Age & period of inclusion. Information on + family hx, BMI, and smoking available but not entered in model.	OR – Use vs. No use ref VTE LNG: 3.6 (2.9-4.6) DRSP: 6.3 (2.9-13.7)
Dinger 2010[29] 2007-2008	Case-control DRSP LNG	Current users of study CHCs at index date DRSP & LNG others	Conditional logistic regression	VTE	Matched on age & region Personal & family of VTE; BMI, duration of current use, smoking	OR (adjusted) Use vs. no use:: 2.4 (1.8-3.2) DRSP vs. LNG: 1.0 (0.5-1.8)
Jick 2011[16] 2002-2008	Case-control (nested) DRSP LNG	Current users of study CHCs: DRSP & LNG Overall, New use New with no previous episode	Conditional logistic regression	First diagnosis VTE non-fatal, idiopathic	Matched on age, index year, duration of use, other comorbidities, and use of health services. 10% change in risk estimate rule	OR (adjusted) Overall 2.2 (1.5-3.4) New use: 2.7 (1.7-4.1) New use with no previous episode: 2.8 (1.5-5.2)

Author Study time period	Design CHCs Compared	Exposure Criteria	Analysis	Events	Included covariates	Results (95% CI)
Parkin 2011[15] 2002-2009	Cohort & case-control (nested) DRSP LNG	Current NEW users of study CHCs: DRSP & LNG Exclude use of any prior CHC in past year	Conditional logistic regression Poisson for Incidence	First diagnosis VTE non-fatal, idiopathic	Matched on age, duration of recorded information, & general practice	OR matched & imputed DRSP vs. LNG OR: 3.3 (1.4-7.6) Complete case analysis OR: 2.9 (1.1-74)
FDA Study 2011[27] 2001-2007	Cohort DRSP LNG Others	Any use New user (no CHC in prior 6 months)	Cox PH Poisson for incidence	New diagnosis VTE, ATE, Death	Age, site, calendar year. Hypertension, hyperlipidemia and diabetes in ATE model	VTE **All Users vs. LNG** HR: 1.5 (1.2-1.8) **All Users vs. COMP** HR: 1.7 (1.4-2.3 **VTE New User vs. LNG** HR: 1.6 (1.1-2.2) **New Users vs. COMP** HR: 1.8 (1.3-2.4)
Lidegaard 2011[25, 26] 2001-2009	Population cohort DRSP LNG Others No use	New Users DRSP LNG Others Non-users	Poisson regression model	First diagnosis VTE	Duration of use Calendar time to control for obesity	Use vs. no use DRSP: 4.5 (3.9-5.1) LNG: 2.2 (1.7-2.8) Use vs. LNG with 30 μg EE DRSP vs. LNG confirmed RR adj 2.1 (1.7-2.7)

DRSP – drospirenone-containing contraceptive; LNG – levonorgestrel-containing contraceptive; CHC combined hormonal contraceptive; IUD –intrauterine device
HR – hazard ratio; OR – odds ratio; CI–confidence Intervals; RR – Rate Ratio; adj – adjusted; COMP – comparator group (includes LNG-, NGM-, and NETA-containing COCs with 20-35 μg EE
ITT – intent to treat analysis; AT – as treated analysis; TTE – thrombotic and thromboembolic events

All studies, whether designed as cohort or case-control, evaluated current use of the CHCs (Table 15). Many also considered past use or duration of current use separately. The EURAS,[20] Dinger,[29] and Vlieg[14] studies were the only ones that could consider lifetime use, because that information can only be obtained by personal interview.

The Sponsor-funded cohort studies[20, 13] recruited first-ever users or switchers to any new study CHC product, with one of these studies[13] also requiring no previous dispensing of the study CHCs in the previous 6 months. Lidegaard's 2009 study[24] identified a cohort of contraceptive users with exposure defined as current, previous, or never (included former) use. Duration of use, however, included use of any past CHC, not just the study CHC. Lidegaard's reanalysis,[25, 26] however, included a sub-analysis of new users having no CHC use in the previous 12 weeks (the gap analysis).

The 2010 case-control study[29] showed no increased risk of VTE with DRSP. This study, however, also interviewed cases and community controls to obtain CHC exposure information (current, past, or never use) at the index date. Therefore, differences in VTE risk may depend more on study investigators' methods and their ability to capture unmeasured confounders.

Variations in exposure definitions alone, whether it be utilizing a new user or initiator definition (whether referring to use of study CHCs only or all CHCs) or whether an exposure gap is imposed, make a difference in VTE risk estimates for users of DRSP-containing COCs, but not in the risk ratios for the products being compared, provided that study restrictions are applied equally to all exposure groups being compared and that the restrictions do not affect one treatment group more than the other. This is demonstrated clearly in Lidegaard's reanalysis[26] (Table 11 and Table 12 in this review). Although the relative risk estimates of users compared to non-users differed based on the restrictions applied (the relative risk estimates ranged from 2.0 to 6.1 for LNG users and from 5.6 to 10.0 for DRSP users in the first year of exposure), the ratio of the relative risks for DRSP users compared to LNG users remained around 1.6 with two exceptions. The risk ratio increased to 2.2 and to 2.3 with the inclusion only of confirmed events or the imposition of a CHC-free gap, suggesting possible differences between users in the two treatment groups (channeling bias). Again, caution should be exercised when comparing rates and relative risks across studies.

Three studies[10, 13, 27] listed in Table 15 were exposure cohorts from which cases were identified during current use. These studies show no risk or smaller risk estimates compared to those from the case-control studies or cohort studies that identify cases prior to determining exposure. It may be that the case-control studies underestimate the exposure experience of women who do not develop VTE.

3.3 Unmeasured Confounders

Population characteristics that are usually available for evaluation include age and some variables that measures year of entry or index date and in the study,[10, 29] family history of thrombosis was available because the investigators hypothesized that a positive family history could lead to preferential prescribing of specific types of COCs. The effect has been extensively discussed in the FDA review of the FDA-funded study.[23] Other covariates and

prescribing patterns in different countries, however, may also be important contributors to differences in reported risks.

3.3.1 Other Covariates

Covariates known to predict VTE risk in users compared to non-users were tested individually for possible inclusion in the VTE analytical models in many studies, including the FDA-funded study. Invariably, in the studies that used stepwise modeling to identify covariates, none of the preselected covariates made a predictable difference (e.g., a 10% or greater change) in the risk estimates modeled and none were included in the final analyses. Although none of the covariates contributed to a predicted change in the analytical models for the entire study cohort, some covariates in the FDA-funded study (Table 16) such as acne, premenstrual tension, and use of potassium-sparing diuretics were present more frequently in DRSP users, including those younger than 35 years of age. In the FDA-funded study, this was the group with the higher VTE risk, suggesting possible channeling (selective prescribing) of DRSP-containing COCs in this group.

Table 16 Proportion (%) of Study CHC Users with Select Covariates by Age Groups and Study Contraceptives, All Sites 2001-2007 (FDA-funded study)

Covariates	Products Studied	All ages		Age 10-34	Age 35-55
		New Users	All Users	New Users	New Users
Acne	DRSP	4.2	4.3	4.6	1.9
	COMP *	2.1	2.5	2.5	0.8
Premenstrual Tension	DRSP	0.2	0.2	0.1	0.7
	COMP	0.1	0.1	0.1	0.3
Potassium-sparing Diuretic	DRSP	0.9	1.2	0.7	2.0
	COMP	0.8	1.2	0.4	2.2
Polycystic ovarian syndrome (PCOS)	DRSP	0.0	0.0	0.0	0.0
	COMP	0.0	0.0	0.0	0.0

* COMP: Comparator group that included COCs containing the progestins LNG, NETA, or NGM) and EE ranging from 20 to 35 µg per tablet

3.3.2 Prescribing Patterns

The Society of Obstetrics and Gynecology of Canada (SGOC) Clinical Practice Gynecology Committee (whose guidelines were approved by the Executive and Council of the SGOC)[30] suggested that, because newer products tend to be prescribed to women who already have VTE and ATE risk factors, occurrence of outcomes may be selectively biased towards certain products, giving a misleading impression of risk. If this statement is true for many prescribers of CHCs, any resulting epidemiologic analyses should seriously consider and adjust for potential channeling bias. This statement is also consistent with the observation that the products that were newer at the time of study initiation, at least in the more recent published studies and the FDA-funded study, were nearly always associated with an increased risk of VTE when compared to older products. The FDA-funded study was initiated to begin a deeper examination of these concerns.

The literature assessing prescribing patterns, however, is overwhelmingly European and describes prescribing patterns of European clinicians, who may have different prescribing patterns than US clinicians. Nonetheless, the findings by Bitzer[31] and colleagues are worth

considering. The authors note that Swiss gynecologists and GPs use indirect markers for differential prescribing. The most relevant criteria were family history of VTE, headache, smoking, stability of the menstrual cycle, breast tenderness, BMI, irregular bleeding, age > 35 years, and acne. The 20 µg EE dose products were preferred for women older than 35 years, those smoking more than 15 cigarettes per day, those with a family history of VTE, and those complaining of breast tenderness or headache. The 30 µg EE dose products were preferred for patients with a history of irregular bleeding, a family history of osteoporosis, expected poor compliance, and acne. It is unclear whether similar prescribing patterns exist in the US.

With the exception of the Dinger and the van Hylckama Vlieg studies, where investigators were able to interview the women, all other studies (including the FDA-funded study) rely on information captured in claims or electronic databases. Therefore, information on family history of VTE, headache, smoking, stability of the menstrual cycle, breast tenderness, BMI, and irregular bleeding is not readily available or available only for hospitalized cases. Information on poor compliance, acne, and other diagnosed conditions may be available, but most often is not captured.

3.3.3 Unmeasured Covariates

Serious consideration needs to be given to the possibility of channeling bias when comparing progestin types. The 2004 European Society of Human Reproduction and Embryology (ESHRE) Workgroup,[32] the 2010 American College of Obstetricians and Gynecologists (ACOG) Guidelines,[33] and the SGOC guidelines[30] address the non-contraceptive benefits of hormonal contraceptive use, summarize scientific studies that support these benefits, and provide prescribing recommendations. The potential benefits of interest that may influence the results of epidemiologic studies include use of hormonal contraceptives to treat menorrhagia (heavy menstrual bleeding), dysmenorrhea (painful menses), premenstrual syndrome, acne, hirsutism, bleeding due to leiomyomas, pelvic pain due to endometriosis, and menstrual cycle regulation. Some COCs with specific progestins are approved for treatment of acne (e.g., DRSP- and NGM-containing COCs) and PMDD (only DRSP-containing COCs), although approval of DRSP-containing COCs for treating these conditions (in addition to contraception) is fairly recent (2006-2007). ESHRE and ACOG Guidelines[32, 33] and other published reports mention the purported anti-androgenic benefits of DRSP and desogestrel for treating these conditions, which could possibly lead to channeling bias. The FDA-funded study did not capture information on many of these conditions during the risk assessment phase, other than acne, PCOS, migraines, dysmenorrhea, and premenstrual tension. The presence of these health conditions by themselves does not necessarily bias the results of the study, even if present disproportionally across treatments being compared, unless they also increase the woman's risk of having a TTE. Information on the TTE risk for women with these conditions, however, is scant.

The FDA-funded study (and most postmarketing studies) identified users of study CHCs from claims databases or electronic medical records. Therefore, it is very likely that these studies would capture the experience of all CHC users not just that of prescribers and women who volunteered to participate in a study. If women who use CHCs mostly for possible non-contraceptive benefits instead of prevention of pregnancy are at increased risk of VTE by nature of a medical condition or disease, and if specific CHC products are preferred in treating these conditions (channeling), then differences in risk estimates observed between

CHCs may be mistakenly attributed to a specific CHC. The differences in risk estimates, however, may be due, at least in part, to the health condition or disease.

A detailed discussion is presented in FDA's review of the FDA-funded study in Appendix A.

3.4 Unmeasured but Suspected Confounders

Information on age, duration of current product use, and selected covariates (dysmenorrhea, acne, migraines, and premenstrual tension) were available for evaluation in the FDA-funded study and provided in the Final Report. Information on other concomitant diagnoses such as anemia, menorrhagia, endometriosis, and hirsutism might have been available, but was not collected. Unfortunately, other likely important variables such as BMI, smoking, lifetime contraception use, and family and personal history of VTE were unavailable for this analysis. Those potential important confounders were also not available for most of the published DRSP postmarketing studies. Non-availability of the potential confounders remains a concern, although some investigators used proxies, such as codes for obesity or calendar year, or imputed missing values sometimes for up to 50% of the population. Such strategies are interesting but highly unreliable. Some preliminary examinations of drug utilization data available to FDA suggest that women prescribed DRSP may differ somewhat from users of other products with regard to the prevalence of certain diagnoses, including PCOS, acne, hirsutism, and premenstrual tension (see Appendix B for details). These reported frequencies were small and therefore only suggestive, but may be worth examining further in other populations where an increased risk of VTE has been detected.

There were two postmarketing studies requested by the FDA or European regulatory agencies and funded by the Sponsor that reported no increase in VTE risk for users of a DRSP-containing COC (Yasmin) compared to users of LNG-containing COCs or COCs containing other progestins. Interestingly, these studies were able to obtain information or address the important confounders not available in claims databases or electronic medical records either by direct interview with the women[10] or by matching on the probability of having similar baseline characteristics to the DRSP initiator using the information available at the time of initial use.[13] Although other methodological differences exist between these earlier studies and those conducted later, having the ability to capture or match on important VTE confounders may be a very important difference.

At the time the FDA-funded study was conceptualized, two phases were considered. The first phase (which has been reported[27]) would include a risk assessment component that would also obtain patient and prescribing characteristics as allowed with the use of claims data and hospitalized records. If an increased risk were observed, a second phase would be considered. The second phase (which is under consideration) would include more extensive medical record review and possible physician and patient interviews to obtain the information on the important but missing confounders.

4. Conclusions

All of the studies reviewed refer only to the DRSP-containing products with 30 μg EE, known as Yasmin or its generic equivalent, in the US. No published study to date reports on YAZ, which contains the same amount of DRSP (3 mg) as Yasmin but has only 20 μg of EE in each active tablet. The dosing regimen for YAZ is also different, consisting of 24 days of

active tablets instead of 21 days. The effect of these differences (dose of EE and dosing regimen) on the risk of VTE for users of YAZ has not been evaluated.

Review of the epidemiologic studies show certain trends that cannot be ignored.

1. Newly approved CHCs appear to have a higher risk of VTE than the older CHCs used for comparison.
2. Sponsor-funded studies, designed to closely match treatment groups, show no increase in risk for VTE or ATE in users of a DRSP-containing COC compared to users of COCs containing other progestins.
3. Studies (EURAS and Dinger 2010[29]) that are able to capture and adjust analyses with information on BMI, smoking, personal and family history of VTE, and lifetime use of any CHC show no increase in VTE, ATE, and mortality risks for users of DRSP compared to other COCs.
4. Risk estimates and risk ratios are consistent within investigator groups as long as exposure definitions remain consistent across treatment groups in the study. Differences in risk estimates and risk ratios across studies may depend largely on differences in exposure definitions.
5. Covariates identified as known risk factors for VTE do not appear to be confounders when comparing one contraceptive type to another.
6. Channeling (selective prescribing) by providers for non-contraceptive benefits or perceived differential safety of CHCs has largely been ignored in the published studies, but may be contributing to observed increased risks in some studies.

5. Future Activities

None of the studies to date provides a definitive answer as to the safety of DRSP-containing COCs with regard to the risks of VTE and ATE. The entire body of studies provides conflicting evidence that cannot easily be reconciled by consideration of any single difference among studies. Most of these studies have unique strengths and limitations, but the challenge lies in trying to reconcile multiple methodological differences between studies conducted in very different populations, often using different comparators and different exposure definitions. There is a history that newer hormonal contraceptive products have been observed to have associations with increased risk for VTE, and the Agency would like to better understand whether channeling of newer products to patients already at higher risk for these events may play a role. The FDA-funded study, which was reported in October 2011,[27] was designed to be the first phase in a multi-phase program designed to address many of the unresolved questions perceived by the Agency as possibly providing explanations for the differences in VTE and ATE risks reported for specific CHCs in different published studies.

Based on the current studies, it is unclear whether the increased risk seen for thrombotic and thromboembolic events in some of the epidemiologic studies is actually due to use of DRSP-containing COCs. However, because a number of the studies indicate an increased risk of VTE associated with the use of a DRSP-containing COC, FDA believes that these issues warrant Advisory Committee input. Therefore, we would like the Advisory Committee a) to discuss how best to interpret and communicate the findings from the

epidemiologic studies and b) to consider the overall risk/benefit profile of DRSP-containing COCs.

The Agency also advocates further study of the issue of thrombotic and thromboembolic risk associated with the use of CHCs in general as part of a larger effort to better understand this risk, particularly for all newer CHCs. Such studies should include the following features that have been identified in our reviews as being crucial to understanding these risks:

1. Population source:
    a. Better understanding of the products used, such as by whom and for what purpose. Available information should include formularies, age, indications, and comorbid conditions.
    b. All products need to be compared within one population source.
    c. The population should be US based and not voluntary or selective.
    d. The population size should be sufficient to study the risk of ATEs and death.
2. Design: Nested case-control study within a defined exposure cohort.
3. More comprehensive exposure definitions:
    a. Lifetime exposure to contraceptives as opposed to just what is recorded in the claims histories
    b. Effects of switching and gaps in exposure
4. More complete capture and better adjustment for variables that have not been controlled adequately or at all in prior studies. These include:
    a. Age
    b. Non-contraception indication for use of the CHC, which may increase the risk for VTE or ATE
    c. Comorbid conditions that may increase the risk for VTE or ATE (e.g., gynecological conditions)
    d. Confounders typically unmeasured in claims database studies:
        i. BMI
        ii. Smoking

6. REFERENCES

[1] Vessey M, Mant D, Smith A, Yeates D. 1986. Oral contraceptives and venous thromboembolism: Findings in a large prospective study. Br Med J; 292(6519): 526.

[2] Collaborative group for the study of stroke in young women. 1973. Oral contraception and increased risk of cerebral ischemia or thrombosis. N Engl J Med; 288(17): 871-8.

[3] Mann J, Vessey M, Thorogood M, Doll S. 1975. Myocardial infarction in young women with special reference to oral contraceptive practice. Br Med J; 2(5965): 241-5.

[4] Silverstein M, Heit J, Mohr D, Petterson T, O'Fallon W, Melton L. 1998. Trends in the incidence of deep vein thrombosis and pulmonary embolism: A 25-year population. Arch Intern Med; 158(6): 585-93.

[5] Heit J, Kobbervig C, James A, Petterson T, Bailey K, Melton L. 2005. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: A 30-year population-based study. Ann Intern Med; 143(10): 697.

[6] Boston Collaborative Drug Surveillance Programme. 1973. Oral contraceptives and venous thromboembolic disease, surgically confirmed gallbladder disease and breast tumors. Lancet; 1(7817): 1399-1404.

[7] Royal College of General Practitioners. 1978. Oral contraceptives, venous thrombosis, and varicose veins. J R Coll Gen Pract; 28(192): 393-9.

[8] Stadel BV. 1981. Oral contraceptives and cardiovascular disease (first of two parts). N Engl J Med; 305(11): 612-8.

[9] Jick H, Jick S, Gurewich V, Myers M, Vasilakis C. 1995. Risk of idiopathic cardiovascular death and nonfatal venous thromboembolism in women using oral contraceptives with differing progestagen components. Lancet; 346(8990): 1589-93.

[10] Dinger J, Heinemann L, Kühl-Habich D. 2007. The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance Study on oral contraceptives based on 142,475 women-years of observation. Contraception; 75(5): 344-54.

[11] Lidegaard Ø, Løkkegaard E, Svendsen AL, Agger C. 2009. Hormonal contraception and risk of venous thromboembolism: national follow-up study. Br Med J, 339: b2890 doi:10.1136/bmj.b2890.

[12] Goldstein L, Bushnell C, Adams R, Appel L, Braun L, Chaturvedi S. 2011. Guidelines for the primary prevention of stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke; 42(2): 517-84.

[13] Seeger J, Loughlin J, Eng P, Clifford C, Cutone J, Walker A. 2007. Risk of thromboembolism in women taking ethinylestradiol /drospirenone and other oral contraceptives. Obstet Gynecol;110(3): 587-93.

[14] van Hylckama Vlieg A, Helmerhorst F, Vandenbroucke J, Doggen C, Rosendaal F. 2009. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and

progestogen type: results of the MEGA case-control study. BMJ; 339: b2921 doi:10.1136/bmj.b2921.

[15] Parkin L, Sharples K, Hernandez R, Jick S. 2011. Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested case-control study based on UK General Practice Research Database. BMJ; 342: d2139 doi:10.1136/bmj.d2139.

[16] Jick S, Hernandez R. 2011. Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data. BMJ; 342: d2151 doi:10.1136/bmj.d2151.

[17] Pearce H, Layton D, Wilton L, Shakir S. 2005. Deep vein thrombosis and pulmonary embolism reported in the Prescription Event Monitoring Study of Yasmin. Br J Clin Pharmacol; 60(1): 98-102.

[18] Farinas E, Ouellet-Hellstrom R. 2003. Serious Reaction: Thromboembolic and Thrombotic Events, including Pulmonary Embolism, Deep Vein Thrombosis, Stroke, and Myocardial Infarction. Review Date: January 16, 2003. PID: D020374.

[19] Farinas E, Ouellet-Hellstrom R. 2004. Serious Reaction: Thromboembolic and Thrombotic Events, including Pulmonary Embolism, Deep Vein Thrombosis, Stroke, and Myocardial Infarction. Review Date: August 31, 2004. PID: D04041

[20] Dinger J, Heinemann L, Kühl-Habich D. 2007. The Safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance Study on oral contraceptives based on 142,475 women-years of observation. Contraception; 75(5): 344-354.

[21] Eng PM, Seeger J, Loughlin J, Clifford C, Mentor S, Walker A. 2008. Supplementary data collection with case-cohort analysis to address potential confounding in a cohort study of thromboembolism in oral contraceptive initiators matched on claims-base propensity scores. Pharmacoepidemiol Drug Saf; 17(3): 297-305.

[22] Long-term Active Surveillance Study for Oral Contraceptives (LASS) Final Study Report September 13, 2011.

[23] Ouellet-Hellstrom R. 2011. Review of the FDA-funded Study: Combined Hormonal Contraceptive (CHC) and the Risk of Cardiovascular Disease Endpoints, October 22, 2011 v2. Review Date: November 2, 2011. OSE RCM: 2008-1629.

[24] Lidegaard Ø, Løkkegaard E, Svendsen A, Agger C. 2009. Hormonal contraception and risk of venous thromboembolism: national follow-up study. BMJ; 339: b2890 doi:10.1136/bmj.b2890.

[25] Lidegaard Ø, Nielsen L, Skovlund C, Skjeldestad F, Løkkegaard E. 2011. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study. BMJ; 343: d6423 doi: 10.1136/bmj.d6423.

[26] Lidegaard Ø, Nielsen LH, Løkkegaard E, Skovlund C. 2011. Oral contraception and venous thromboembolism. Supplementary analyses of Danish Registry data. March 29,

2011. Submitted to the FDA on November 4, 2011 in a Periodic Safety Update Report by Bayer HealthCare Pharmaceuticals, Inc.

[27] FDA Office of Surveillance and Epidemiology. 2011. Combined hormonal contraceptives (CHCs) and the risk of cardiovascular disease endpoints. http://www.fda.gov/downloads/Drugs/DrugSafety/UCM277384.pdf

[28] Ouellet-Hellstrom R. Review of the 2011 BMJ Articles. Review Date: June 6, 2011. OSE RCM: 2011-1328.

[29] Dinger J, Assmann A, Mőhner S, Minh T. 2010. Risk of venous thromboembolism and the use of dienogest- and drospirenone-containing oral contraceptives: results from a German case-control study. J Fam Plann Reprod Health Care; 36(3): 123–9.

[30] Reid R, Leyland N, Wolfman W, Allaire C, Awadalla C, Awadalla A, et al. SOGC clinical practice guidelines: oral contraceptives and the risk of venous thromboembolism: An update No. 252, December 2010. Int J Gynecol Obstet; 112(3): 252–6.

[31] Bitzer J, Frey B, von Schönau M, Sabler N, Tschudin S. 2009. Twenty or thirty microgram ethinyl oestradiol in an oral contraceptive: Does it make a difference in the mind and the daily practise of gynaecologists and general practitioners? Eur J Contracept Reprod Health Care; 14(4): 258–67

[32] The ESHRE Capri Workshop Group. 2005. Noncontraceptive health benefits of combined oral contraception. Human Reproduction Update; 11(5): 513-25.

[33] American College of Obstetricians and Gynecologists;(ACOG). 2010. ACOG Practice Bulletin No 110. Noncontraceptive Uses of Hormonal Contraceptives. Obstet Gynecol; 115(1): 206-18.

Appendices

Appendix A: FDA Review of Final Report of FDA-Funded Study Entitled "Combined Hormonal Contraceptives (CHCs) and the Risk of Cardiovascular Disease Endpoints"

Appendix B: FDA Review of Drug Utilization Patterns for DRSP-containing Combination Oral Contraceptives and Other Combined Hormonal Contraceptive Products

Appendix C: US Approved Labeling for Yasmin (3 mg drospirenone/0.03 mg ethinyl estradiol)

Appendix D: US Approved Labeling for YAZ (3 mg drospirenone/0.02 mg ethinyl estradiol)

Appendix E: List of Selected References for Epidemiologic Studies for DRSP-containing Combination Oral Contraceptives

Appendix A

FDA Review of Final Report of FDA-Funded Study Entitled "Combined Hormonal Contraceptives (CHCs) and the Risk of Cardiovascular Disease Endpoints"

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology
Epidemiologist Study Comparison Review

Date:	November 3, 2011
Reviewer(s):	Rita Ouellet-Hellstrom, PhD, MPH Associate Director FDA Principal Investigator (PI) Division of Epidemiology II (DEPI II)
Office Director	Gerald Dal Pan, MD, MHS, Acting Director Office of Surveillance and Epidemiology (OSE)
Division Director	Judy Staffa, PhD, RPh, Director Division of Epidemiology II (DEPI II)
Drug Name(s):	3.0 mg of drospirenone with 30 µg of ethinyl estradiol (EE) (Yasmin); 6.0 mg norelgestromin with 750 µg EE (Ortho Evra); 11.7 mg etonogestrel/2700 µg EE (NuvaRing); ***Comparators*** 0.10 mg of levonorgestrel/20 µg EE (LNG1) 0.15 mg levonorgestrel and 30 µg EE (LNG2) 1.0 mg norethindrone acetate/20 µg EE (NETA) 0.18 – 0.25 mg of norgestimate/35 µg EE (NGM)
Subject:	Review of the FDA-funded Study: Combined Hormonal Contraceptive (CHC) and the Risk of Cardiovascular Disease Endpoints; October 22, 2011 v2.
OSE RCM #:	2008-1629
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EXECUTIVE SUMMARY

Several contraceptive products approved in 2001 quickly became very popular forms of contraception, particularly among young women, and were considered relatively safe because of their lower estrogen content compared to older hormonal products. Safety concerns for serious thrombotic and thromboembolic adverse events as well as death, however, became a public concern soon after their market introduction.

Although several epidemiologic studies were initiated by the manufacturers of these new contraceptive products at the request of U.S. and European regulatory authorities around the time of their approval, the studies were designed mainly to evaluate one specific product compared to one or a group of other contraceptive products. In addition, based on reports submitted to the Adverse Event Reporting System (AERS), the FDA had concerns about the ability of some of the epidemiologic studies to identify and characterize all thrombotic and thromboembolic events and deaths (including sudden deaths) that could be related to these products.

For these reasons, FDA sponsored an epidemiologic study involving data from insurance claims and medical record data. The objective of the FDA-funded study was to assess cardiovascular risks, including the risk of thrombotic and thromboembolic events and death. The newer products selected for study were those that had sufficient numbers of users to allow for an evaluation of these risks compared to those associated with use of older, more frequently prescribed contraceptives at the sites selected. If an increased risk was observed, the FDA-funded study would subsequently attempt to assess user characteristics and prescribing patterns that might help explain the increased risk. It was recognized at the time that a more in-depth assessment of potential reasons for increased risk would not be possible using only claims and electronic medical records and would require physician and patient contact, something that could be conducted later if needed.

The FDA-funded study was conducted at two HMO sites (Kaiser Permanente North and South California) and two state Medicaid programs (Tennessee and Washington) each associated with an academic institution. In addition to having access to data from a large group of young reproductive age women, reasons for selecting study sites included: 1) the ability of the investigators to validate study outcomes with medical records; 2) the ability of the sites to link to state vital status files to identify deaths quickly; and 3) the ability of the sites to facilitate physician and patient contact if and when needed. Diversity of populations was favored over similarity to maximize the capture of possible reasons for an increased risk if observed.

The FDA-funded study was designed as a retrospective cohort study of women age 10 to 55 years who were current users of the study contraceptives from January 1, 2001 to December 31, 2007. Two exposure cohorts, one of current users and the other of new users, were created for evaluation. The study contraceptives included Yasmin (3.0 mg of

drospirenone/30 μg of ethinyl estradiol)[a], referred to as DRSP in this review; Ortho Evra (6.0 mg norelgestromin and 0.750 μg EE), (referred to as NGMN); and the NuvaRing (0.18–0.25 mg etonorgestrel/ 2700 μg EE) referred to as ETON in this review. Although known to be underpowered, ETON was included nonetheless because of its potential to provide information on continuous hormonal exposure along with Ortho Evra.

For each study contraceptive in the primary analysis, the comparison group included a composite of frequently prescribed products that contained the progestin levonorgestrel, norethindrone, or norgestimate combined with 20 μg to 35 μg of ethinyl estradiol (COMP). As a secondary analysis following recent published studies, comparisons of the risk for serious thrombotic and thromboembolic events were also made for each study contraceptive with the levonorgestrel products containing 30 μg of estrogen (LNG2).

As expected, age-specific incidence rates per 10,000 person-years (PY) adjusted for site show a VTE and ATE risk increasing with age for DRSP, NGMN, and COMP. These rates were higher in New Users than All Users. Among All Users but not New Users, age and site-adjusted VTE incidence rates per 10,000 PY were higher for the exposure CHCs (DRSP - 10.2; NGMN – 9.8; ETON - 11.9) than for COMP (6.0) or LNG2 (6.6).

Similar to the EURAS study, age- and site-adjusted ATE incidence rates per 10,000 PY were higher for COMP (1.4) and LNG2 (1.6) than DRSP (1.1) and NGMN (1.1). Age-adjusted mortality rates were also slightly higher in the comparator groups also but only for All Users in the FDA-funded study.

In the Cox Proportional Hazard analyses which adjusted for age, site, and year of entry into the study, results show an increased VTE risk for DRSP (HR = 1.7), NGMN (HR = 1.6), and ETON (HR = 1.6) when compared to COMP in All Users and only for DRSP in New Users. Comparisons with LNG2 in these analyses show an increased risk only for DRSP for All Users and New Users. The increased VTE risks were reported for women younger than 35 years of age and the increased ATE risk was reported for women 35 years of age and older only for DRSP.

The results of the FDA-funded study are consistent with the published studies demonstrating an increased VTE risk among current users of DRSP and NGMN, particularly among women younger than 35 years of age. This study is also the first to report an increased ATE risk among older DRSP users. Linkage to state mortality files did not reveal any large discrepancy in missed ATE and VTE case identification. The increased VTE risk reported for ETON needs further evaluation because it is a new finding.

This study also demonstrated the importance of considering differences in population sources, population characteristics, and comparators when comparing one product type with another. Possible channeling by clinicians towards prescribing some CHCs for specific non-contraceptive benefits provided by these products (e.g., dysmenorrhea,

[a] *Although Yaz contains the same amount of drospirenone (3.0 mg) as Yasmin, it contains only 20 μg of ethinyl estradiol (EE) instead of 30 and is taken for an additional 3 days. Yaz was not included in the FDA-funded study nor was it analyzed in any of the studies discussed or referenced in this review.*

menorrhagia, acne, Polycystic Ovarian Syndrome) in addition to contraception needs to be considered.

The study was carefully done, is comprehensive, and all hospitalized outcomes have been validated with medical records. One site also validated outpatient deep vein thrombosis (DVTs). In addition, the study was able to link records to state mortality files, evaluated two different exposure cohorts (All Users and New Users), and the contribution of known confounders in two very different US populations (Medicaid and large HMO).

Like other claims-based studies, however, the study is limited in that it captures only information available in the claims databases or in electronic medical records for cases only. Limitations also include the absence of data on key covariates (obesity/ body mass index (BMI), smoking, personal and family history of VTE, lifetime use of hormonal contraceptives) and the inability to validate all outpatient DVTs by chart review (except at only one site). The small number of ATEs limited the power for analyses of these outcomes, though the rates were consistent with published data.

The FDA-funded study as well as most postmarketing studies, however, identified all users of study combined hormonal contraceptives (CHCs) from claims databases or electronic medical records. Therefore, the studies very likely would capture the experience of all CHC users, not just the experience of women who use CHCs mostly for contraception. And even though some studies excluded women with known risk factors for experiencing VTEs, none have assessed possible channeling by prescribers and potential risk associated with CHC use for non-contraceptive benefits. If women using CHCs mostly for the non-contraceptive benefits of CHCs are at increased risk of VTE by nature of their condition, and if specific CHC products are preferred in treating those conditions (channeling), then differences in risk estimates observed between the CHC products would be attributed to a specific product but would more likely be the result of the health condition.

None of the studies to date provides a definitive answer as to the safety of DRSP and NGMN with regard to thrombotic and thromboembolic events (TTE). The entire body of studies provides conflicting evidence that cannot be easily reconciled by any single difference among studies. Most of these studies have unique strengths and limitations, but the challenge lies in trying to reconcile multiple methodological differences between studies conducted in very different populations, often using different comparators and different exposure definitions. There is a history that newer contraceptive products are observed to have associations with increased risk for thrombotic and thromboembolic events, and the Agency would like to better understand whether channeling of newer products to patients already at higher risk for these events may play a role. The FDA-funded study was originally designed to be the first phase in a multi-phase study designed to address many of the unresolved questions perceived by the Agency to possibly provide alternative explanations for the risks seen, other than the individual drugs themselves.

Since FDA cannot at this time determine whether the increased risk seen for thrombotic and thromboembolic events in some of the epidemiologic studies is actually not due to use of the DRSP and NGMN products, we believe that, because of the consistency in recent reports for an increased risk, product labeling should reflect that very real possibility. However, the Agency advocates further study of this issue, as part of a larger

effort to better understand the risk for thrombotic and thromboembolic events associated with all newer contraceptive agents. Such studies should assure the comparability of population sources, study design, exposure definitions, and adequate capture and adjustment of age, non-contraceptive co-indications, other co-morbid diseases (e.g. ob/gynecological conditions), and known confounders such as BMI, smoking, and personal and family history of thrombotic and thromboembolic events.

The Final Report, presenting results from the risk assessment phase of this study achieved its objectives.

1 BACKGROUND

Several contraceptive products approved in the early 2000's quickly became very popular forms of contraception, particularly among young women, and were considered relatively safe because of their lower estrogen content compared to older hormonal products containing ≥ 50 μg of ethinyl estradiol (EE). Safety concerns for serious thrombotic and thromboembolic adverse events as well as death, however, became a public concern soon after their market introduction. Between 2002 and 2010, over 800 million prescriptions[b] for combined hormonal contraceptives (CHCs) have been dispensed, the majority of which were dispensed to women younger than 35 years of age. Of these, 55 million were prescriptions for the 3 mg drospirenone with 30 μg ethinyl estradiol (EE), 41 million were for norelgestromin with 0.75 μg EE prescriptions, and 28 million were for the approximately 11.7 mg etonorgestrel with 2700 μg EE.

These safety concerns stimulated adverse event reporting, which made appropriate review and interpretation of the reports received in FDA's Adverse Event Reporting System (AERS) challenging. Despite a low incidence of venous thromboembolic events in this population, an increase in risk for these adverse events among users could put many young women at risk of a major life-threatening event. FDA was concerned about its ability to interpret the postmarketing information available in the AERS database.

1.1 DROSPIRENONE

In May 2001, Yasmin (3.0 mg of drospirenone/30 μg EE), referred to as DRSP in this review, was the first drospirenone-containing contraceptive to be approved for contraception in May 2001 in the United States. Yaz was the second drospirenone containing contraceptive approved for contraception in March 2006. Although Yaz contains the same amount of drospirenone (3.0 mg) as Yasmin, it contains only 20 μg of ethinyl estradiol (EE) compared to Yasmin's 30 μg. In addition, one active Yaz pill is taken over 24 instead of 21 days. Yaz was also approved for premenstrual dysphoric disorder (PMDD) in October 2006, and acne in January 2007. None of the studies published to date (including the FDA-funded study) evaluated the VTE and ATE risk for Yaz that contains 20 μg EE.

Although labels for hormonal contraceptives (including Yasmin and Yaz) warn prescribers and users of the increased thrombotic risks associated with use of

[b] *Source: SDI Vector One®: National, Years 2002-2010 Data Extracted September 2011.*

contraceptive steroids, due to its spironolactone-like activity, drospirenone-containing contraceptive labels also contraindicate its use in women with

- Renal insufficiency
- Hepatic dysfunction
- Adrenal Insufficiency

The progestin drospirenone was thought to increase cardiac arrhythmia risks and sudden deaths among users because of its propensity to increase potassium levels. The label, therefore, has a bold warning that long-term users of drugs that could increase serum potassium such as NSAIDS, potassium-sparing diuretics, potassium supplementation, ACE inhibitors, angiotensin-II receptor, heparin and aldosterone antagonists "should have their serum potassium levels checked during the first treatment cycle" with a drospirenone product.

At approval in 2001, the Division of Reproductive and Urologic Drug Products (DRUP) requested a postmarketing plan and evaluation at the time of approval and modified later to include thrombotic and thromboembolic events and deaths. When concerns of thrombotic and thromboembolic risks surfaced, a US postmarketing study to assess the risks of venous thromboembolic events (VTE) as well as arterial thrombotic events (ATE) and death was initiated in addition to the European (German) Study.

Two prospective observational studies were funded by the sponsor and were ongoing at the time the FDA-funded study was initiated. The European Active Surveillance Study (EURAS)[1] included DRSP users and two groups of comparators: LNG and other contraceptives. Once enlisted, each woman was contacted every six months during the study period to obtain information on adverse events and changes in contraceptive use. The study implemented a very aggressive loss-to-follow-up protocol. The US-based study, conducted by i3 Ingenix[2,3], identified DRSP initiators quarterly for the first year beginning June 11, 2001 then semiannually through June 30, 2004 during which time the investigators matched each DRSP user to two other contraceptive initiators based on their respective propensity scores or probability of being prescribed DRSP. Neither of these two studies showed any increased risk of VTE, ATE, or death associated with use of DRSP compared to any comparator group evaluated. These studies capture the experience of contraceptive users who had comparable baseline characteristics and, in the EURAS study, used these products mainly for contraception.

While the FDA-sponsored study was underway, several retrospective observational studies[4,5,6,7] were published that did show an increased risk for VTE associated with use of DRSP. Neither these two sponsor-funded studies nor any of the studies published since nor the FDA-funded study has evaluated the VTE and ATE risks associated specifically with the product Yaz which contains a lower dose of EE although taken over 24 days instead of the 21 days for Yasmin.

1.2 NORELGESTROMIN

Ortho Evra (6.0 mg norelgestromin with 0.75 μg EE), (referred to as NGMN in this review), is a combination transdermal patch approved for the prevention of pregnancy on November 20, 2001. Like labels for most hormonal contraceptives, the NGMN label

warns prescribers and users of the possible increased thrombotic risks associated with being overweight and smoking. Because systemic estrogen exposure levels for the NGMN patch during use were reported to be 55% to 60% higher and peak concentrations lower than those produced by an oral contraceptive containing 0.18 to 0.25 mg norgestimate with 35 μg EE, FDA had concerns about the safety of the product.

The two postmarketing studies conducted by the sponsor were case-control studies.[8,9,10] The first study reported no increased VTE risk for NGMN (Odds Ratio (OR) 0.9; 95% confidence interval (CI) = 0.5-5.6)[9] for non-fatal idiopathic cases. The second study initially reported a 60% increased VTE risk for cases identified by codes only and a twofold increased VTE risk for chart verified cases (OR 2.2; 95% CI – 1.3-3.8).[8] These studies were initially considered complementary, but quickly became two separate studies when results differed. The studies were designed to measure the relative incident risk of ATE [acute myocardial infarction (AMI) and stroke] and VTE [pulmonary embolism (PE) and deep vein thrombosis (DVT)] in NGMN users compared to users of a norgestimate product containing 35 μg of ethinyl estradiol (EE), an estrogen dose believed to be more comparable to the newly revised levels of estrogen exposure in the patch. Both studies included two-year extensions funded by the sponsor as part of their phase IV postmarketing commitment. One added two years of additional data collection to the initial study,[11] while the other re-did the analyses at two additional time periods to identify new cases and controls then pooled the results of all three analyses.[12,13]

Because one of these two postmarketing studies showed a twofold increased VTE risk, the label was amended in November 2005 with a boxed warning that women 15 to 44 years of age who choose to use the NGNM patch may be at increased VTE risk.

1.3 ETONOGESTREL

NuvaRing, referred to as ETON in this review, is a non-biodegradable, flexible, transparent, and colorless combination contraceptive vaginal ring containing two active components, the progestin etonogestrel (ETON) and EE. When placed in the vagina, each ring releases on average 0.120 mg/day of etonogestrel and 0.015 mg/day of ethinyl estradiol over a three-week period of use. Once inserted, the ring remains in place continuously for three weeks. It is removed for a one-week break, during which a withdrawal bleed usually occurs. A new ring is inserted one week after the last ring was removed.

ETON is indicated for the prevention of pregnancy in women who elect to use this product as a method of contraception. The label is a standard hormonal contraceptive label and warns prescribers and users of the potential increase in serious cardiovascular side effects from using this combination hormonal contraceptive particularly for older women over 35 years of age and for heavy smokers but no specific postmarketing safety studies were completed at the time the FDA/OSE study was initiated

Prescriptions for the ETON product were increasing[c] especially after concern with the transdermal patch surfaced after 2004. Both products were designed to provide

[c] *Source: SDI Vector One®: National, Years 2002-2010 Data Extracted September 2011*

continuous delivery. Questions were being raised at the same time whether continuous hormonal delivery placed women at greater risk for thrombotic and thromboembolic events. This product was included in the FDA/OSE study to assist in evaluating continuous hormonal exposure although the team realized that the study would most likely be underpowered to independently assess VTE and ATE risk for this product alone.

1.4 COMBINED HORMONAL CONTRACEPTIVE (CHC) STUDY RATIONALE

It was unknown in 2007-2008 whether risk differences observed for each product were the results of reporting and measurement artifacts, population or exposure definition differences, or differences in the progestin drug delivery and metabolism.

The objective of the FDA/OSE study then was to evaluate use of DRSP and the transdermal patch (along with another new continuous use product) compared to other commonly prescribed older oral contraceptive product(s) in populations of prevalent and new users (incident cohort). In addition, another objective was to assess the risk, the public health impact, patterns of use, and eventually, the behavioral and environmental factors that could be related to use that could place a woman at greater risk for thrombotic and thromboembolic event and/or death.

Since there had been reports of sudden deaths associated with DRSP and NGMN, and given that not all deaths can be identified with use of claims-based or electronic medical records (used by many postmarketing studies whether prospective or retrospective), access to linked vital statistics death records, identified in the feasibility study at Vanderbilt, Washington State and Kaiser Permanente provided FDA/OSE with a valuable opportunity to assess this important public health concern.

2 REVIEW METHODS AND MATERIALS

This review evaluates the final study results dated October 22, 2011[14] by Stephen Sidney, MD, MPH, the Lead Site Principal Investigator. The Final Report, titled *Combination Hormonal Contraceptives (CHCs) and the Risk of Cardiovascular Disease Endpoints* consists of the main report with five appendices (A through E).

- Appendix A: Endpoints, Exclusion, Covariates
- Appendix B: Supplemental Analyses
- Appendix C: Study CHC NDC codes
- Appendix D: NDC Codes of Prescription Drugs Used as Covariates
- Appendix E: CHC Data Collection Documents

The Final Report is evaluated for its consistency in adequately addressing the study concept submitted for funding on August 7, 2007 and addressing the study objectives stated in the report with respect to the selected study design specified.

Review of the study is supplemented with data from the

a) SDI, Vector One®: National (VONA) database which measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions (Appendix B in this review). Information on age and comorbidity was obtained from this database.

b) IMS Health, IMS Health Lifelink™ database which represents over 95 managed care plans and covers approximately 60 million commercially insured, de-identified patients. Claims are captured from doctor's offices (including outpatient clinics), retail and mail order pharmacies, patient visits to specialists, and hospitalizations. They include information about diagnoses, emergency room visits, office visits, home care, diagnostic tests, procedures and injections. These data represent approximately 11 percent of the U.S. commercially insured population during that time period (see Appendix B for more details).

For this review, data were obtained for all patients who had a pharmacy claim for one of the contraceptives of interest between Jan 1 2001 and Dec 31 2007.

c) SDI Physician Drug and Diagnosis Audit, Years 2001-2007. [d] The SDI, Physician Drug & Diagnosis Audit (PDDA) with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

The FDA-funded study is summarized first in Section 3. OSE/DEPI II comments and discussion are then presented in Section 4 and with Conclusions and Recommendations in Section 5.

3 FINAL STUDY REPORT

The final study included most of the information requested of the investigators by FDA with some differences either based on the investigators' recommendations or the unavailability of the information in the databases identified.

3.1 OBJECTIVE

The final study objectives were to

- Determine prevalence and incidence rates for venous and arterial thrombotic and thromboembolic events (VTE and ATE) and all-cause and cause-specific mortality in women exposed to the three newer study hormonal contraceptives compared to older frequently prescribed low estrogen hormonal contraceptives (Phase I - funded, completed and reviewed in this document).

[d] *Source: Extracted October 2011. File: PDDA 2010-PDDA_2011-1044_CHC_Study_Concm_Product_10-7-11(1).xls.*

- Identify medical, pharmacological, and behavioral characteristics from claims and medical records to assess predictors of increased risk for VTE, ATE, and death (to be completed at a later date if possible).

3.2 STUDY DESIGN

The FDA-funded study is a retrospective cohort study of current CHC use, using data from four geographically diverse health plans, to evaluate the risk of thrombotic and thromboembolic events and all-cause and cardiovascular mortality for three newer preparations compared to four older CHCs with varying progestin and low estrogen levels.

3.2.1 Data Source

The study investigators utilized computerized data files from four geographically diverse health plans: Kaiser Permanente Northern California (KPNC) the Lead Site, Kaiser Permanente Southern California (KPSC), and two state Medicaid programs: Tennessee State Medicaid (Vanderbilt University) and Washington State Medicaid (University of Washington). These sites have access to files that contain enrollment data, demographic information, ambulatory prescriptions from pharmacy records or claims, hospitalizations and outpatient visit data with diagnoses from health plan records or claims and death records obtained from state mortality files. All files were linked at each site to create the study cohorts.

3.2.2 Study Population and Time Period

Across the four sites, 835,826 women were identified who were between the ages 10 and 55 years and had at least one prescription filled for a study CHC between January 1, 2001 and December 31, 2007 that was preceded by at least 6 months of continuous membership (5 months plus 1 day for the Washington Medicaid study population).

Women were followed until the end of continuous membership, the end of a prescription period (days-supply + 42 days), date of a study event, first date of a pregnancy, reaching age 56 years, or end of study follow-up (12/31/2007).

3.2.3 Study Contraceptives and Comparators

The exposure contraceptives included the following products

- **DRSP:** 3.0 mg of drospirenone and 30 μg of ethinyl estradiol
- **NGMN:** 6.0 mg norelgestromin (NGMN) and 750 μg ethinyl estradiol (EE)
- **ETON:** 11.7 mg etonogestrel and 2700 μg ethinyl estradiol

And the comparators **(COMP)** were

- **LNG1:** 0.10 mg of levonorgestrel and 20 μg of ethinyl estradiol
- **LNG2:** 0.15 mg levonorgestrel and 30 μg ethinyl estradiol
- **NETA:** 1 mg norethindrone acetate and 20 μg ethinyl estradiol
- **NGM:** 0.18 – 0.25 mg of norgestimate and 35 μg of ethinyl estradiol

3.2.4 Exclusion Criteria

Women were excluded from the cohort if a serious or life threatening illness was documented during the pre-exposure eligibility period. These included sickle cell disease, cystic fibrosis, cerebral palsy, cancer, HIV, organ transplant, liver failure, severe congestive heart failure (CHF), renal failure, respiratory failure, or hospitalization for acute myocardial infarction, stroke, or venous thromboembolic disease.

Criteria for exclusion required that codes for these illnesses were based on having one [or for congestive heart failure (CHF), two] inpatient ICD-9 or procedure codes with the codes of interest appearing anywhere in the primary and secondary discharge diagnoses or two outpatient ICD-9 or procedure codes separated by at least 30 days.

3.2.5 Exposure

For assessing VTE, ATE, and mortality risks, three study CHCs [the transdermal patch referred to in the report as NGMN, the vaginal ring referred to as ETON, and the drospirenone product referred to as DRSP] were compared with four products with low estrogen content CHCs (20 μg – 35 μg ethinyl estradiol) regularly prescribed at the study sites. The four study CHCs comparators are referred to as COMP in the Final Report. The LNG2 product in COMP is a levonorgestrel contraceptive (0.15 mg levonorgestrel and 30 μg ethinyl estradiol) that was also used separately as a comparator in a secondary analysis to compare the results with the recently (2009 and 2011) published studies for DRSP.

Two separate exposure cohorts were included in this study. The first and largest included prevalent users (All Users) with cohort entry initiated at the first recorded prescription during the study period regardless of prior use for both study CHCs or other CHCs. Women were eligible for more than 1 exposure episode in the All User cohort provided they satisfied eligibility criteria. The other cohort, basically a sub-cohort, was an evaluation of New Users (incident) of study contraceptives with no history of ANY hormonal contraception during the 182 days prior to the first recorded study prescription fill. In the New User cohort, women were censored when their exposure period ended.

An exposure period to any one of the study CHC was defined as the prescription period use (dates that are covered by a prescription or series of prescriptions for a single study CHC) plus 42 days (the period of indeterminate use) and is referred to as current use. The rationale to extend the exposure period for 42 days after the end of the actual prescription period was primarily to account for biological effects such as increased coagulability that might persist after CHC use was stopped.

Periods of non-study CHC exposure were not included in the analysis dataset, but were considered in constructing the study CHC exposure data so that non-study CHC use could impact on the actual dates of study CHC exposure by adjusting either the stop date or start date of a study CHC prescription period.

3.2.6 Outcome

The primary study endpoints were hospitalization for acute myocardial infarction (AMI), ischemic stroke (IS), and venous thromboembolic events (VTE), as well as cardiovascular and total mortality.

All potential hospitalized cases were identified by the sites using the following primary discharge codes: AMI (410.x), stroke (430, 431, 432.0, 432.9, 433.x, 434.x, 436), and VTE (pulmonary embolism code 415.1 and DVT codes 451.1, 451.1x, 451.2, 451.8, 451.81, 451.82, 451.84, 451.89, 453.0, 453.1, 453.2, 453.3, 453.4, 453.8, 453.9).

Outpatient DVTs were identified by having an outpatient diagnosis of DVT followed by a first prescription for an anticoagulant (low-molecular weight heparin or warfarin) during the 30-day period subsequent to the diagnosis.

Arterial thrombotic events (ATE) included AMI and IS.

VTE included hospitalized deep venous thrombosis (DVT), hospitalized pulmonary embolism (PE) and DVT diagnosed as an outpatient.

Cardiovascular mortality included deaths resulting from an identified VTE and/or ATE event in the databases as well as deaths identified only by linking to the mortality files.

All hospitalized cases with available medical records were abstracted at the study sites using standardized criteria. Admission and discharge summaries, laboratory tests, and imaging study results were de-identified and sent to the lead site for adjudication. Four physicians adjudicated the cases blinded to the CHC. A cardiologist reviewed all acute myocardial infarctions (AMIs) and a neurologist reviewed most of the stroke cases with the principal investigator (PI) doing the remaining adjudications. Questionable cases were discussed with the principal investigator and a 10% sample of adjudicated cases was independently reviewed by another adjudicator blinded to the study contraceptives.

Outpatient DVTs identified from claims databases cannot be easily validated since they would require access to outpatient records and permission from all treating physicians. For this study, however, medical records of outpatient VTEs from only the lead site were obtained and adjudicated by the PI. Results show an 89.3% positive predictive value (PPV) with use of the outpatient DVT study definition.

Mortality was assessed by linking membership with state mortality files for all women in the study and for the entire study period. Cardiovascular mortality was defined by having an ICD-10 code of I01 to I99 as the underlying cause of death. Mortality from the main study CVD endpoints was also defined by the following ICD-10 codes as the underlying cause of death: acute myocardial infarction (I21.x – I23.x), ischemic stroke (I63.0 – I63.5, I65.x, I66.x), and VTE (I80.x, I81.x, I82.x).

3.2.7 Covariates and confounders

Covariates that were potential confounders or effect modifiers were ascertained from the electronic databases at each site. For this study (and many of the published studies), the covariates assessed as potential confounders in the statistical models were those identified from studies where CHC users were compared to nonusers. When comparing one contraceptive to another, however, the same covariates are not necessarily

confounders and, when included in the statistical models, none seem to change the risk estimate by 10% or more. Potential confounders evaluated included diabetes, hypertension, hyperlipidemia, surgery, ischemic heart disease, acne, thyroid disease. They also included use of other medications such as ACE inhibitors, hormonal replacement therapy, warfarin, platelet inhibitors, NSAIDS. Information on potentially important confounders such as body mass index (BMI), smoking, personal or family history of VTE cannot be reliably captured from claims-based or electronic medical records for all individuals and were not assessed in this phase of the study. A complete list is provided in tables 7a and b of the Final Report and by age group in Appendix A of the Final Report.

Assessment of covariates of interest began during the 6-months prior to a study CHC exposure period and continued to be assessed throughout the exposure period.

Given that a time-varying analysis was planned, the covariates were defined in one of three ways: fixed (chronic conditions), ever-never (only during the current exposure period) and current (mostly concurrent medications and exposures that were considered only during current exposure period (the days supply period).

3.2.8 Statistical Analyses

Cox proportional hazards (PH) regression was used to estimate the relative risk of study endpoints associated with current use of exposure CHCs relative to the comparator CHCs. The Cox proportional hazards model accommodates unequal length of follow-up due to varying duration of CHC exposure, termination of health plan membership, and end of study (i.e. right censoring). Time since cohort entry (i.e. first day of first exposure period during study period) was the time scale used in the Cox regression model. CHC exposure was considered as a 4-level time-varying covariate, capturing current use of the NGMN transdermal patch, ETON vaginal ring, DRSP pill, and the 4 comparator CHCs combined as one category (COMP). In the <u>All Users</u> models, the periods without CHC exposure were considered unobserved or window-censored given that events were not ascertained during these periods.

Cox models were stratified for age using 5-year age intervals, providing tight control for age and freeing the investigators from having to specify the form of the relationship between age and outcomes in the regression models. Additional control for potential residual confounding within age strata was achieved via inclusion of age as a continuous covariate in the regression model.

Age, site, calendar year of entry into study were included in all the Cox PH models. Established CVD risk factors (e.g., hypertension, hyperlipidemia, and diabetes mellitus) were included as fixed covariates in these Cox PH models that included ATE or CVD mortality as outcomes.

Each of the other potential covariates was tested individually in these base models with a decision to include it in further model testing if the estimate of relative risk associated with any of the exposure CHCs (vs. comparators) was changed by 10% or more. Like other published studies, none of the covariates met this criterion for any of the models so that none were included in final modeling. Because hypertension is in the causal

pathway between CHC use and AMI/stroke, the analyses ran models with and without hypertension. Hypertension was retained in the models for ATE because it minimally affected the risk estimates associated with the study CHCs.

Cox proportional hazards modeling was conducted to estimate the relative risks for both All Users and New Users. Modeling was conducted with all four of the comparator CHCs combined (LNG1, LNG2, NETA, and NGM) and with the four comparators kept separate in the model. While the main analyses were planned using the combined comparators, the separation of the comparators in the analyses enabled the estimation of the risks associated with DRSP relative to LNG2, since these preparations both contained exactly 30 μg of EE while two of the other comparators contained less than 30 μg of EE (LNG1 and NETA) and one contained more (NGM with 35 μg EE).

Associations of new use and of all use of CHCs with study endpoints were examined within age strata (10-35 years and 36-55 years) and within two site strata (KP and Medicaid sites).

The New User analyses were confined to the subset of women entering the cohort with exposure to any study CHC but with no previous use of any CHCs (study or non-study) during the prior 6 month cohort entry eligibility interval. In the New User analysis, follow-up ended for each woman at the end of the study CHC exposure period. Duration of use was examined only in the New User cohort.

Age-adjusted rates were calculated using direct adjustment using the age distribution of the entire study population at cohort entry as the standard (5-year age groups). Age- and site-adjusted incidence rate ratios were estimated using Poisson regression modeling.

3.3 STUDY RESULTS

The final All User cohort included 835,826 women with 898,251 person-years of exposure. The New User cohort included 573,680 women with 367,138 person years of observation. The New User cohort included 109,070 women with 80,171 person-years of exposure to DRSP, 62,316 women with 30,152 person-years of exposure to NGMN, 19,143 women with 8,784person-years of exposure to ETON, and 383,151 women with 248,013 person-years of exposure to COMP.

After adjudication, the cohort included 60 AMIs, 78 ischemic strokes, and 625 VTEs. In addition, there were 41 CVD deaths, and 267 total deaths during study CHC exposure periods.

The age-specific incidence rates (Tables 10 a to d in the Final Report and Appendix C in this review) per 10,000 person-years (PY) show an increasing VTE and ATE risk with age for exposure CHCs and comparators alike but for the older age groups (35+ years), the rates were lower for the comparator groups than the exposure CHCs.

Age- and site-adjusted VTE rates per 10,000 PY were higher for the exposure CHCs (DRSP - 10.2; NGMN – 9.8; and ETON - 11.9) than for COMP (6.0) or LNG2 (6.6)). Consequently VTE age- and site-adjusted incidence rate ratios were higher for exposure CHCs regardless of which comparator was used.

On the other hand, age-and site-adjusted ATE rates per 10,000 PY were slightly higher for COMP (1.4) and LNG2 (1.6) than DRSP (1.1) or NGMN (1.1) for All Users but not for New Users.

Similarly, age-and site-adjusted mortality rates per 10,000 PY were also slightly higher for COMP (3.5) and LNG2 (4.5) than DRSP (2.4) or NGMN (3.7) for All Users. For New Users, age-and site-adjusted mortality rates per 10,000 PY were higher for COMP (3.5) and LNG2 (5.4) than DRSP (2.6) and ETON (3.7) but not NGMN (6.3).

In adjusted (age, site, and year of entry into the study) analyses using Cox Proportional Hazard models, DRSP, NGMN, and ETON were associated with a higher risk of VTE relative to low-estrogen comparators (Table 1) in All Users even when only hospitalized VTEs were considered.

Table 1 Relative Hazard* of venous thromboembolic events (VTE) for exposure combined hormonal contraceptives (CHC) among All Users (prevalent use) and New Users (no prior CHC use), All Sites Combined 2001-2007 (Summarized from table 12 a in the Final Report 111022v2).

All VTE (inpatient and outpatient)

	All Users		New Users	
Exposure CHCs	**Relative Hazard**	**95% CI**	**Relative Hazard**	**95% CI**
DRSP	**1.7**	**1.4 - 2.1**	**1.8**	**1.3 - 2.4**
NGMN	**1.6**	**1.2 - 2.1**	1.4	0.9 - 2.0
ETON	**1.6**	**1.0 - 2.4**	1.1	0.6 - 2.2

Hospitalized VTE only

	Relative Hazard	**95% CI**	**Relative Hazard**	**95% CI**
DRSP	**1.8**	**1.4 - 2.3**	**2.1**	**1.5 - 3.0**
NGMN	**1.7**	**1.2 - 2.4**	1.4	0.9 - 2.4
ETON	**1.6**	**1.0 - 2.8**	0.9	0.3 - 2.5

**From Table 12 a in the Final Report. All models were adjusted for age, site, and year of entry into the study and compared to COMP (4 comparators combined)*

Hosp = hospitalized; CI = confidence interval; DRSP = drospirenone with 30 ug ethinyl estradiol; NGMN = norelgestromin transdermal patch; ETON =etonogestrel vaginal ring

Unlike the age-and site-specific and age-adjusted VTE incidence rates which were higher for New Users than All Users, the adjusted risk estimates (hazard ratios) were slightly lower for New Users except for DRSP where the relative hazard estimate was slightly higher than for All Users.

There was no increased risk observed for ATE in this study for any user except for new DRSP users. A relative ATE hazard and 95% confidence interval of 2.0 (1.1 – 3.8) was noted for this group.

Among New Users, duration-of-current use analysis showed a higher VTE risk during the first 3 months for all exposure CHCs but risk estimates for longer durations in these analyses appear to be sensitive to the comparator used in the model and show inconsistent variations.

In analyses the Cox PH analyses stratified by the age groups 10-34 and 35-55 years, the risk of VTE for all 3 exposure CHCs was higher in the younger than in the older age group for All Users and only for DRSP in New User group. There was also an increased risk of ATE associated with DRSP in New Users age 35 years and older. Interaction terms, that is non-additive modifiers of the effect for age, were significant for DRSP for both VTE and ATE ($p<0.001$). VTE risk estimates were also more likely to be statistically significant at the KP sites than in the Medicaid populations. Consequently, all models were adjusted for age, site, and year of entry into the study cohort. The increased VTE risk for younger CHC users has been noted elsewhere. [6,15]

Secondary analyses, using LNG2 alone as the comparator, were conducted since both DRSP and LNG2 products contain 30 μg of ethinyl estradiol. The findings with LNG2 as the comparator generally paralleled the findings for the combined comparators though not as many comparisons reached statistical significance.

The investigators concluded that the NGMN transdermal patch and DRSP were associated with higher risk of VTE relative to standard CHC pills, particularly in women younger than 35 years of age. DRSP was associated with higher risk of ATE in New Users overall with only this finding restricted to women 35-55 years of age. The finding of an increased VTE risk with the ETON vaginal ring relative to standard CHCs is new and raises concern but, due to the small numbers, needs to be replicated in other studies.

4 COMMENTS/DISCUSSION

OSE/DEPI II comments here on the effects of known confounders adjusted in the analysis, the possible influence of potential confounders for which covariates were incompletely captured by the study, and identify important but unmeasured confounders. This section also compares the incidence rates reported by this study with those of other DRSP and NGMN published and unpublished studies.

4.1 FDA-FUNDED STUDY RESULTS HIGHLIGHTS

As expected, age-specific incidence rates per 10,000 person-years (PY) show an increasing VTE and ATE risk with age for study contraceptives and comparators alike. The rate of increase in age-specific incidence rates, however, was lower for the comparator group than for the newer exposure CHCs: DRSP, NGMN, and ETON. Age-adjusted VTE incidence rate ratios were higher for study contraceptives regardless of which comparator was used.

Generally, VTE and ATE age-specific and age-and site-adjusted incidence rates were higher in New Users than All Users. This contrasts with the Cox Proportional Hazard Ratios (adjusted for age, site, and calendar time) which were slightly lower for New Users than All Users except for DRSP where risk estimates did not change (Table 2) but the differences are very small. The differences are likely due to the fact that the Cox PH model adjusted more tightly for age whereas the age-specific rates were presented in approximately 10-year age groups, and the age-and site-adjusted rates were standardized to the age distribution of the entire study population. The Cox PH models also adjusted for calendar time as well as being a time-varying analysis.

Table 2 Relative Hazard* of venous thromboembolic events (VTE) and arterial thrombotic events (ATE) for study combined hormonal contraceptives (CHC) among All Users (prevalent use) and New Users (no prior CHC use), All Sites Combined 2001-2007 (Summarized from Table 12a in the Final Report 111022v2).

Venous Thromboembolic Events (VTE). Includes inpatient and outpatient events				
Exposure CHCs	**All Users**		**New Users**	
vs. COMP	**Relative Hazard**	**95% CI**	**Relative Hazard**	**95% CI**
DRSP	**1.7**	**1.4 - 2.1**	**1.8**	**1.3 - 2.4**
NGMN	**1.6**	**1.2 - 2.1**	1.4	0.9 - 2.0
ETON	**1.6**	**1.0 - 2.4**	1.1	0.6 - 2.2
vs. LNG2 (30 µg EE)	**Relative Hazard**	**95% CI**	**Relative Hazard**	**95% CI**
DRSP	**1.5**	**1.2 - 1.8**	**1.6**	**1.1 - 2.2**
NGMN	**1.3**	**1.0 - 1.8**	1.2	0.8 - 1.9
ETON	1.3	0.8 - 2.0	1.0	0.5 - 2.0
Arterial Thrombotic Events (ATE)				
vs. COMP	**Relative Hazard**	**95% CI**	**Relative Hazard**	**95% CI**
DRSP	1.0	0.6 - 1.7	**2.0**	**1.1 - 3.8**
NGMN	1.3	0.6 - 2.7	1.1	0.4 - 3.2
ETON	1.7	0.6 - 4.8	1.7	0.4 - 7.1
vs. LNG2 (30 µg EE)	**Relative Hazard**	**95% CI**	**Relative Hazard**	**95% CI**
DRSP	0.8	0.5 - 1.4	1.6	0.8 - 3.4
NGMN	1.1	0.5 - 24.8	0.9	0.3 - 2.9
ETON	1.4	0.5 - 4.1	1.3	0.3 - 6.1

**All models were adjusted for age, site, and year of entry into the study*

CI = confidence interval; DRSP = drospirenone with 30 ug ethinyl estradiol; NGMN = norelgestromin transdermal patch; ETON =etonogestrel vaginal ring
COMP = 4 comparators combined

Table 3 shows that the lower bound of the confidence intervals for the VTE relative hazard was higher than 1.0 for all 3 exposure CHCs younger than in the older age group for All Users and only for DRSP in New User group. Again this is contrast with an increased ATE risk associated with DRSP in older New Users (age 35 years and older). Comparisons with LNG2 generally paralleled the findings for the combined comparator group although not as many comparisons reached statistical significance.

Table 3 Relative Hazard* of venous thromboembolic events (VTE) and arterial thrombotic events (ATE) for study combined hormonal contraceptives (CHC) among All Users (prevalent use) and New Users (no prior CHC use) by age groups, All Sites Combined 2001-2007 (Summarized from Table 14a, b andc in the Final Report 111022v2).

Venous Thromboembolic Events (VTE). Includes inpatient and outpatient events				
Age 10 to 34 Years	**All Users**		**New Users**	
vs. COMP	**Relative Hazard**	**95% CI**	**Relative Hazard**	**95% CI**
DRSP	**1.9**	**1.4 - 2.5**	**2.1**	**1.4 – 3.2**
NGMN	**1.6**	**1.1 - 2.3**	1.5	0.9 - 2.4
ETON	**2.1**	**1.3 - 3.4**	1.7	0.8 – 3.8
vs. LNG2 (30 µg EE)	**Relative Hazard**	**95% CI**	**Relative Hazard**	**95% CI**
DRSP	**1.7**	**1.2 - 2.3**	**2.2**	**1.3 – 3.5**
NGMN	1.4	0.9 - 2.1	1.4	0.8 – 2.6
ETON	**1.9**	**1.1 – 3.1**	1.7	0.7 – 4.1
Age 35+ years				
vs. COMP	**Relative Hazard**	**95% CI**	**Relative Hazard**	**95% CI**
DRSP	1.4	1.0 – 1.8	1.2	0.8 - 1.8
NGMN	1.4	0.9 - 2.3	1.3	0.7 – 2.5
ETON	0.7	0.3 – 1.9	0.6	0.1 – 2.3
vs. LNG2 (30 µg EE)	**Relative Hazard**	**95% CI**	**Relative Hazard**	**95% CI**
DRSP	1.2	0.8 - 1.7	1.1	0.7 – 1.7
NGMN	1.2	0.7 – 2.0	1.0	0.5 - 2.1
ETON	0.6	0.2 – 1.6	0.5	0.1 – 2.0

**All models were adjusted for age (5-year age groups), site, and year of entry into the study*

CI = confidence interval; DRSP = drospirenone with 30 ug ethinyl estradiol; NGMN = norelgestromin transdermal patch; ETON =etonogestrel vaginal ring

This study, like other retrospective observational studies published since market approval, shows an increased VTE risk for DRSP among All Users and New Users compared to older products (COMP and LNG2) and an increased ATE risk among New Users when compared to COMP but not to LNG2 (Table 2).

For NGMN, the study shows an increased VTE risk among All Users and, although not statistically significant, the risk is higher for New Users when compared to COMP but not when compared to LNG2. No increased ATE risk for this product was observed when compared to any study comparator.

Risk estimates comparing exposure CHCs to LNG2 are generally lower than when comparing to the entire COMP group. This might be explained by the smaller number of users in the LNG2 group. The confidence intervals, however, are not wider. The main difference between the two groups is that 30% of the COMP contraceptives (LNG1 and

NETA) contain lower estrogen levels (20 μg) than the exposure CHCs and may represent a different population of CHC users. Consequently, COMP represents a more heterogeneous mix of CHC users.

The study was carefully done, is comprehensive, and all hospitalized outcomes have been validated. In addition, one site validated outpatient DVTs. The study was able to link all records to state mortality files, evaluated two different exposure cohorts (All Users and New Users), and the contribution of known confounders in the two very different US populations.

Like other claims-based studies, however, this study is limited in that it captures only information available in the claims databases or in electronic medical records for the outcome cases. Limitations also include the absence of data on key covariates (obesity/BMI, smoking, personal and family history of VTE, lifetime previous use of hormonal contraceptives) and the inability to validate outpatient DVTs by chart review (except at only one site). The small number of ATEs limited the power for analyses of these outcomes, though the rates of these outcomes were consistent with published data.

The Final Report does not provide specific information on the number of VTE and ATE deaths identified only through linkage to the death files and whether the inclusion of at least the CVD deaths would modify the risk estimates reported. This was an important question for which the information is available but which was not provided in the report. This information which will be requested in future analyses.

The study achieved the objectives of the risk assessment phase of the study. The next sections will comment on potential patient and provider characteristics that could be indentified or surmised from this Final Report and others that could be explored. OSE/DEPI II will also comment on potential confounders that could not be addressed by this study.

A key question for the FDA was why some large epidemiology studies show a negative VTE risk for DRSP and NGMN whereas others show an increase VTE risk? The following sections will attempt to answer this question.

4.1.1 Exposure Definitions

Although the results of this study are consistent with other published studies that show an increased VTE risk for DRSP and NGMN when compared to other CHCs, the comparators and the exposure definitions vary across studies.

Comparators

Several earlier studies compared DRSP to LNG only.[4,15,16,17] Others, including the FDA funded study, also compared DRSP to a combined CHC group[8] and still others to non-users as well[18]. Another study compared DRSP to a combined CHC group only.[2]

Unlike the FDA-funded study which compared NGMN both with LNG and with a combined CHC group, other studies compared NGMN with only one other contraceptive type. Two sponsor-funded nested case-control studies and their updates compared NGMN with a norgestimate (NGM) contraceptive containing 35 ug EE[8,11,9,12,13] whereas

another study compared NGMN with LNG only[4]. All these studies used varying definitions of exposure.

Exposure Definitions

Unlike the EURAS study[1] which interviewed women about their lifetime exposures to hormonal contraceptives, studies using insurance claims and electronic medical records cannot capture information on lifetime CHC exposures and are limited to capturing this information in a pre-specified look-back period. Consequently many older women are survivors of previous exposures. Therefore, a definition of a new user usually includes women who are naïve users, switchers with or without a gap, and re-starters, each defined differently in many studies.

Exposure definitions in the published studies referenced in this review usually included a first new prescription fill for the exposure CHC during the study period, with only some studies imposing a new user or initiator design that included only a **study**-contraceptive-free period (or gap) during the specified look-back period allowing use of non-study CHCs.[2, 17] Only three studies required the look-back period to exclude study and non-study CHCs, two of these studies evaluated DRSP only,[15,17] the third was the FDA-funded study which evaluated both DRSP and NGMN. The FDA-funded study evaluated two exposure definitions; one definition basically not imposing any prior use requirement; the other, using a much stricter new user definition and excluded women with any prior CHC use in the prior six months not just the study CHCs. These two extreme exposure definitions using the same design for two different populations (HMO and Medicaid) in one study allows for a better assessment of different exposure definitions across analyses that evaluate risk in different population sources. The comparator group included several contraceptive products that contain either 20 μg, 30 μg or 35 μg of estrogen rather than limiting to one dose as originally proposed. This allows for secondary assessment of patient and provider characteristics although numbers of exposed users are much reduced in the subsets.

All studies, whether designed as cohort or case-control, evaluated current use of the CHCs although many also considered past use or duration of current use separately. The EURAS[1] and Dinger et al[16] studies were the only ones that could consider lifetime use because that information can only be obtained by personal interview.

The published cohort studies[1, 2] recruited first-ever users or switchers to any new study CHC product with one[2] of these studies also imposing no previous dispensing of the study CHCs in the previous 6 months. Lidegaard's 2009 study[18] identified a cohort of contraceptive users with exposure defined as current, previous, or never (included former) used. VTE risk among users was compared to no use. Lidegaard's reanalysis[17] also included a sub-analysis of new users having no CHC use in the previous 12 weeks. Most of these cohort studies evaluated risks for DRSP only. The only case-control study[16] showed no increased risk with DRSP. This study, however, also interviewed cases and community controls to obtain CHC exposure information (current, past, or never use) at the index date. Therefore, differences in VTE risk cannot likely be attributed to differences in study design (cohort versus case-control) but more dependent on study investigators and their ability to capture unmeasured confounders. However

unmeasured confounders can usually only be obtained with direct patient interviews (consenting users), possibly leading to a design that may be subject to selection bias.

All studies that evaluated the NGMN product were case-control studies said to be nested and required both cases and controls to be current users (± 30 days around the index date) of the study contraceptives.[8, 9] The FDA-funded study was the only cohort study that evaluated VTE, ATE, and mortality risks for both DRSP and NGMN. .

Variations in exposure definitions alone, whether it be utilizing a new user or initiator definition (whether study CHC only or all CHCs) or whether an exposure gap is imposed, does not seem to explain the differences seen in VTE risk estimates for DRSP and NGMN provided that study restrictions are applied equally to both exposure groups being compared in the same population source. This is clearly demonstrated in the FDA funded study where the increased risk between DRSP or NGMN and comparators is evident in All Users as well as New Users. The few exceptions may be seen in Lidegaard's DRSP reanalysis.[17] Based on requests from the European regulators, Lidegaard reanalyzed the information from the Danish database and applied the requested restrictions. Although the relative risk estimates, compared to non-users, differed based on the restrictions applied (the relative risk estimates ranged from 2.0 to 6.1 for LNG and from 5.6 to 10.0 for DRSP in the first year of exposure), the ratio of the relative risks for DRSP compared to LNG remained around 1.6 with 2 exceptions. The risk ratio increased to 2.2 and to 2.3 with the inclusion of only confirmed outcome events or the imposition of a CHC-free gap suggesting possible differences between users of the two treatments.

When comparing risk estimates across studies, differences observed may be the result of differences in population characteristics, exposure definitions, study design and/or comparators used. When comparing risk estimates within a study such as the FDA-funded study or Lidegaard's re-analysis, however, differences in risk estimates depend mostly on the selection and exclusion criteria applied. But when applied consistently, to all treatment groups, the resulting risk estimates differ but the relative ratios between a study contraceptive and its comparator should not differ unless the inclusion/exclusion criteria represents differences in treatment for the groups compared (channeling bias). Therefore, caution should be exercised when comparing rates and relative risks across studies.

4.2 KNOWN CONFOUNDERS ADJUSTED IN THE STUDY

Population characteristics that were available for evaluation and included in the statistical model for the control of confounding in the FDA-funded study include age, site, and calendar year of entry. Interaction for age terms (or treatment differences by age) were significant for DRSP both for VTE and ATE ($p<0.001$). For example, the interaction terms can explain if the effect is smaller or larger for younger women. The test for interaction by site in New Users was significant for DRSP only at the $p<0.001$ level in the VTE analysis with COMP. Close examination of these variables and their impact on risk provides some insight into possible population source and user differences among treatment groups.

4.2.1 Age and Age-Specific Incidence Rates

When comparing contraceptive products, investigators for most published studies have either adjusted or matched users on year of birth (exact year or five-year age groups) to control for this important confounder. As a result, CHC use by age cannot be independently examined. Investigators in the FDA-funded study chose not to pre-specify the age relationship. Instead, the Cox models were stratified by 5-year age intervals with the exact age included as a continuous covariate in the regression model to provide additional control for potential residual confounding within the age strata. This provided tight control for age, freed the investigators from having to pre-specify the nature of the relationship between age and outcomes in the regression models, but also allowed for the independent evaluation of the age effect. Several differences across study CHC groups are worth noting.

First, the age-specific VTE and ATE incidence rates increased with age for all contraceptive products examined in this study (Appendix 1). This was true for both New Users and All Users. The magnitude of the difference in the increase of incidence rates between the New User and All Users also increased with age suggesting that older New Users may be at greater risk than younger New Users. For users in the age-group 10 to 24 years, the difference between the DRSP incidence rate per 10,000 for New Users and All Users is only 1.4 whereas for women 35 to 44 years it is 2.6 and for women 45 to 55 years it is 13.6. For LNG2, the comparable differences are 0.0, 5.6, and 9.6 respectively. The increase in rate differences is also seen for COMP: 0.3, 7.3, and 6.3 respectively.

Secondly, as can be seen in Table 4 below, the mean age for women filling prescriptions for DRSP, NGMN and ETON at all sites combined is lower than the mean age for either COMP or LNG2. Only 38% of the COMP users at the KP sites but over 60% of the Medicaid users were younger than age 25 years. These slight differences in the mean age of study cohorts reveal more significant age differences in the groups being compared. The Medicaid sites had proportionally more (73%) women age 10 to 24 years prescribed NGMN compared to the KP sites but the proportion prescribed DRSP and ETON who were young was also high (66%) compared to KP sites.

Table 4: Mean age at first prescription of study contraceptive products (CHC) and proportion of users younger than 25 years by site (Summary of Table 4a1-3 Final Report 111022v2)

	All sites		KP Sites		Medicaid Sites	
CHC	Mean age	Age: 10-24 (%)	Mean age	Age: 10-24 (%)	Mean age	Age: 10-24 (%)
DRSP	25.9	50.0	26.3	47.7	22.9	65.6
NGMN	23.6	52.5	26.6	44.6	22.0	72.8
ETON	25.8	50.3	27.7	39.0	23.3	65.6
LNG2	27.9	42.1	28.7	38.2	23.8	62.1
COMP	27.7	44.7	29.2	37.8	22.8	67.6

Table 5 shows that the age distribution of users at the KP site, however, is more aligned with the age distribution of a nationally projected US population of CHC users identified from the SDI database (Appendix B). As noted previously in the FDA-funded study, the Medicaid user population was much younger than the KP users but that is likely due to the fact that Medicaid covers medical needs of a young population in general.[19] When information from the two sites is combined, the combined population, although slightly younger than the population represented by the nationally projected data, is more representative of users from the general US population.

Also of interest is the greater differences observed in the age distribution of the single CHC product types (see Table 5 or Appendix C in this review for all products) compared to the combined comparator products (COMP). For example, there is a higher proportion of older LNG2 users than NGMN users regardless of database used but that difference is more evident when comparing Medicaid users to KP users or to a nationally projected population of users. Although the differences observed only address age differences, age differences may be a proxy to other population differences as well. By matching DRSP initiators to other CHC initiators on propensity probability scores using insurance information from the 6 months prior to CHC initiation, Seeger[2] may have adjusted for these differences.

Consequently, conclusions reached about the safety of CHC products derived by comparing results across studies should be believed only after it is determined that the populations being treated are similar.

Table 5: Distribution of CHC Use by Age Group, FDA-funded Study (2001-2007 All Users) Compared to US Projected Total Prescriptions (SDI 2002-2007, Tables 4 a1 to a3, Final Report 111022v2).

	Age Group	SDI*	FDA-funded Study	KP**	Medicaid
NGMN	0-25 years	47.6	62.5	44.6	72.8
	26-34 years	34.5	29.2	39.9	23.2
	35+ years	17.5	8.3	15.6	4.1
DRSP_30	0-25 years	44.3	50.0	47.7	65.6
	26-34 years	31.0	34.7	35.9	26.8
	35+ years	24.5	15.2	16.5	7.6
COMP	0-25 years	41.4	44.7	37.8	67.6
	26-34 years	31.2	31.9	31.4	24.2
	35+ years	27.2	23.4	28.1	8.1
LNG2	0-25 years	28.8	42.1	38.2	62.1
	26-34 years	31.6	34.6	35.7	28.8
	35+ years	39.4	23.3	26.1	9.0

**Source: SDI Vector One®: National, Years 2002-2010 Data Extracted September 2011 (only years 2002-2007 shown).*
***KP = Kaiser Permanente*

4.2.2 Incidence Rate Comparisons

One objective of the FDA-funded study was to assess the incidence of ATE, VTE, and death among contraceptive users. For All Users, the overall incidence rate per 10,000 woman years was 6.96 for VTE; 0.67 for AMI, 0.87 for ischemic stroke, 0.46 for CVD mortality and 2.97 for all cause mortality. In this study, the incidence rates were higher for New Users (Appendix B in Final Report) compared to All Users.

The overall VTE incidence rate reported by Lidegaard[18] (4.00 per 10,000 person-years-) is lower than that reported in Table 9 of the FDA-funded study report (6.96 per 10,000). This is generally true for incidence rates reported by other investigators as well although some report age-specific rates only. [20] Other investigators only report product-specific incidence rates.[1,8,9,28] differences in what rate is reported makes direct comparisons challenging. To further complicate comparisons, some investigators report only crude incidence rates[1, 18] whereas others[2,8] also report adjusted rates such as was done for the FDA-funded Study. Variables included in the models for adjustment, however, vary across studies although most include age. The incidence rates for the FDA-funded Study were adjusted for age, site and calendar time.

Venous Thromboembolic Events (VTE)

When reported, age-specific rates increase with age but the rate of increase in some of the published studies is less than that observed in the FDA-funded Study. Lidegaard's[18] overall VTE unadjusted age specific incidence rates increase from 3.0 per 10,000 for women age 20 to 24 years up to 6.6 per 10,000 person-years for women age 40 to 44 years. In the FDA-funded Study, the DRSP age-specific incidence rates for the All User

comparator group increase from 3.4 per 10,000 for the 10 to 24 year age group to 27.4 per 10,000 for women 45 to 55 years. For NGMN, the age-specific incidence rates per 10,000 increase from 5.6 for users 10 to 24 years up to 62.0 for women 45 to 55 years. The age-specific VTE incidence rates per 10,000 among the All User in the FDA-funded study's comparator group are lower and range from 2.8 in women 10 to 24 years up to 16.1 in women age 45 to 55 years. These incidence rates are more comparable to those reported by van Hylckama Vlieg (3.7 per 10,000 in women < 30 years up to 13.3 per 10,000 in women age 40 to 50 years)[20].

Product-specific VTE incidence rates from published studies are similar to those for the FDA-funded study for some products and much lower for others. For DRSP (Table 6), Lidegaard[18] reported a crude incidence rate of 9.1 per 10,000 for DRSP, 8.0 for LNG and 5.2 for other contraceptives compared to the FDA-funded Study. The FDA-funded study reported age and site adjusted VTE rates per 10,000 for All Users of 10.2 for DRSP, 6.6 for LNG2, and 6.0 for all comparators (Table 10 b of the Final Report) although Seeger reported adjusted rates per 10,000 of 13.3 for DRSP and 14.0 per 10,000 for other contraceptives (rates for New Users are higher in the FDA-funded study). Rates reported by Seeger[2] were adjusted for age, calendar time, health plan, history of oral contraceptive use, health service consumption, and chronic medical conditions identified at baseline. In addition, the investigators note that these rates could include women with continuing preexisting conditions. Crude incidence rates among new users were also reported by Parkin[15] for the GPRD study which represents use in the United Kingdom and are much lower than other reported rates: 2.3 per 10,000 for DRSP and 0.9 per 10,000 for LNG with an adjusted risk ratio of 2.7 (1.5-4.7).

Table 6 Incidence rates per 10,000 person-years - DRSP

	All Users			New Users	
Contraceptive	**Lidegaard*[18]**	**Seeger**[2]**	**FDA****	**Parkin[15]**	**FDA**
DRSP	9.1	13.3	10.3	2.3	13.6
LNG	8.0	--	6.5	0.9	9.1
Other	5.2	14.0	5.9		8.4

DRSP = drospirenone with 30 ug EE; LNG = levonorgestrel
**Crude incidence rates*
*** Adjusted rates*

For NGMN (Table 7), however, published VTE incidence rates were lower than those reported in the FDA-funded study likely due to the differences in study design (case-control deemed nested compared to a cohort). Cole[8] reported an age-adjusted VTE incidence rate per 10,000 of 4.1 for NGMN and 1.8 for NGM. The comparable rates per 10,000 in the FDA-funded study were 9.8 for NGMN and 6.0 per 10,000 for the combined comparators which include NGM. Using the PharMetrics database, Jick[9] reported rates per 10,000 of 5.3 for NGMN and 4.2 for NGM. In another study[28] comparing NGMN with LNG, the PharMetrics incidence rates per 10,000 were 5.6 for NGMN and 3.8 for LNG. These rates differed with her use of MarketScan database: 2.5 per 10,000 for NGMN and 2.0 per 10,000 for LNG. For both Cole and Jick studies, incidence rates were only reported with the initial study report and not updated in the follow-up analyses.

Table 7 Incidence rates per 10,000 person-years - NGMN

	All Users		Jick[28]		
Contraceptive	**Cole*[8]**	**Jick[9]**	**FDA**	**PharMetrics**	**MarketScan**
NGMN	4.1	5.3	9.8	5.6	2.5
NGM	1.8	4.2	--	--	--
Other	--	--	6.0	--	--
LNG	--	--	6.6	3.8	2.0

NGMN – norelgestromin patch; NGM – norgestimate with 35 ug EE; LNG – levonorgestrel
** Adjusted rates*

It is noteworthy that incidence rates for all comparators are always lower than those for the newer products. Nonetheless, although differences in incidence rates could be attributed to differences in products used or differences in study design (cohort for DRSP and case-control for NGMN) and case selection, differences reported by Jick's analyses using a similar study design with two different populations (Pharmetrics and Marketscan) underscore the importance of considering differences in population sources selected for a given study. The FDA-funded study also emphasizes the importance of population source since the analyses showed an interaction by site. The KP site captures information from an HMO population compared to the Medicaid population at the other sites.

Arterial Thrombotic Events (ATE)

There are fewer published reports of ATE incidence rates and these are limited to the sponsor funded studies for both DRSP and NGMN. In the EURAS study, Dinger[1] reports crude ATE incidence rates per 10,000 of 0.7 for DRSP, 2.9 for LNG, and 1.7 for other contraceptives. This compares to age- and site-adjusted incidence rates per 10,000 in the FDA-funded study's of 1.1 for DRSP, 1.6 for LNG2, and 1.4 for other comparators. With the exception of other contraceptives, the CHC age-adjusted ATE incidence rates are generally higher than those reported in the EURAS study. As noted for VTE, the incidence rates for the i3 Ingenix[8] and Jick[9] studies were presented only in the initial report and not in the follow-up reports and the number of initial ATE events were too few to allow meaningful comparisons in the initial report. Although each study was extended for two years to obtain information on additional ATE events, risks estimates were reported as odds ratios in the updated reports but incidence rates were not updated with the additional data. This may be explained by the fact that the basic design of the NGMN studies was more of a case-control design although it was reported as a nested and obtaining incidence rates was mostly an after thought that could not be easily updated with the follow-up data.

Mortality

The EURAS study was the only published study reporting on all-cause mortality incidence. Dinger[1] reported a crude mortality incidence rate per 10,000 of 1.4 for DRSP, 2.5 for LNG, and 1.7 for other contraceptives. The FDA-funded Study reported an all-cause mortality rate per 10,000 of 2.4 for DRSP, 4.5 for LNG2, and 3.5 for other comparators.

For NGMN, the FDA-funded study is the only one reporting an incidence mortality rate. The NGMN age-adjusted mortality rate per 10,000 was 3.7 compared to 4.5 for LNG2 and 3.5 for the combined comparators.

The FDA-funded Study is also the only study reporting on adjusted CVD mortality incidence rates. The CVD mortality rate per 10,000 was 0.13 for DRSP, 0.07 for NGMN, 0.48 for LNG2 and 0.60 for all comparators.

The all-cause and CVD mortality rates in these studies are higher for the LNG and other comparator products than for DRSP or NGMN. Whether this is due to an inherent increase risk for LNG when using the product or whether it reflects channeling bias by medical providers who prescribe a perceived safer product to high risk women remains unknown.

Of significant interest both in the EURAS study[1] as well as the FDA-funded Study, incidence rates for ATE and mortality rates (all-cause and CVD deaths) were higher in the LNG/LNG2 group than for DRSP or NGMN. *Whether the higher incidence rates represent a truly higher risk of cardiovascular events and death among LNG/LNG2 users or whether prescribers channel the perceived safer LNG/LNG2 products to higher risk women remains to be evaluated.*

When comparing incidence rates (or any rates) across studies, it is important to note population and database differences as well as the evaluation methods used by the investigators (e.g. crude or adjusted rates). But even when comparing studies conducted by the same investigators, population differences can affect rates obtained. Jick's[28] evaluation of the incidence rates for NGMN and LNG in the PharMetrics compared to the MarketScan, databases is a good example.

4.2.3 Site or Population Source

The FDA-funded Study Medicaid users were on average 4.5 years younger than the KP users. In addition to the age differences, however, the number of users for study CHCs differed by site (Table 8). Medicaid women were more likely to use NGMN prescriptions (24%) than DRSP women (9%) and less likely to use LNG2 (15%) than KP women (27%). The trends were similar for All Users and New Users although New Users were more likely to use DRSP and NGMN than COMP. The differences in use across CHC types at both sites suggest that use of only one CHC type comparator, when evaluating VTE risk in multiple population sources, may be misleading. Type of CHC use varies by populations studied, as demonstrated in this study, and may be affected by differential prescribing, insurance formularies, and site-specific preferences. Several studies have evaluated prescribing patterns among European prescribers who, before prescribing, use indirect markers they consider relevant for differential diagnosis such as family history of venous thromboembolic disease (VTE), headache, smoking, age beyond 35 years, stability of the menstrual cycle, breast tenderness, body mass index, irregular bleeding and acne before prescribing. [21,22] . It is unknown whether there are similar prescribing analyses in U.S. populations.

Table 8. Number of women filling study CHC prescriptions by Site, 2001-2007 (From Tables 4a2 and 3, Final Report 111022v2)

All Users	Kaiser Permanente		Medicaid		Sites Combined	
	Number	Percent	Number	Percent	Number	Percent
Total	**617,943**		**217,883**		**835,826**	
DRSP	123,536	20.0	18,630	8.6	142,166	17.0
NGMN	30,092	4.9	52,845	24.3	82,937	9.9
COMP*	450,214	72.9	136,064	62.4	586,278	70.1
LNG2*	165,838	26.8	33,001	15.1	198,839	23.8
New Users						
Total	**415,654**		**158,026**		**573,680**	
DRSP	95,052	22.9	14,018	8.9	109,070	19.0
NGMN	22,091	5.3	40,225	25.5	62,316	10.9
COMP*	287,320	69.1	95,831	60.6	383,151	66.8
LNG2*	116,787	28.1	20,524	13.0	137,311	23.9

**All LNG2 users are included in COMP therefore percent total add to more than 100.0*

4.2.4 Exclusions

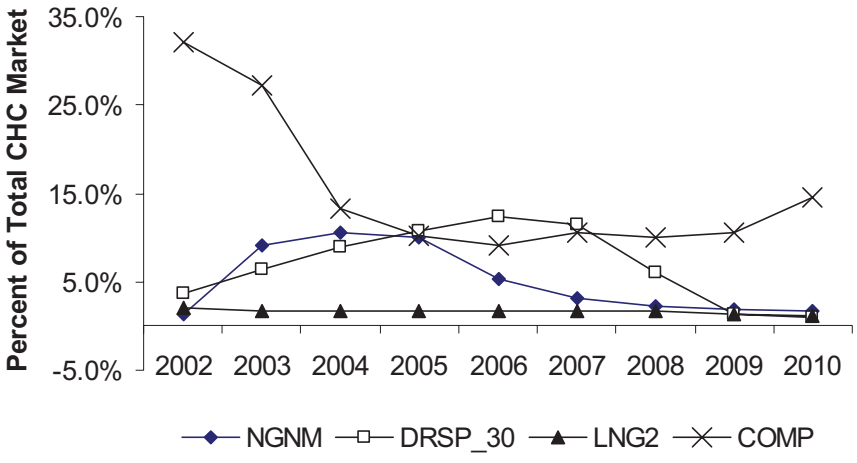
Published studies differed in which women were included in the study. The two DRSP sponsor-funded studies[1,2] did not exclude any women for any reason from the cohort. The only women excluded from the EURAS study were those that refused participation. The Seeger study matched each DRSP initiators to two other non-DRSP initiators using propensity probabilities. It should be noted that there were 428 (2%) of DRSP initiators that could not be matched and were therefore excluded from the cohort analysis. Other studies[18,20] including the FDA-funded study and studies reporting on NGMN[4,5,8], excluded prior to cohort assembly or case and control selection, users who were pregnant or had serious health conditions such as cancer, history of cardiovascular disease, and renal failure. Finally, other studies evaluated[8] or excluded [9,10,12,13,28] users who had any conditions associated with a high risk of VTE and considered only non-fatal, idiopathic VTE cases for analysis. Some of the exclusion or censoring criteria were also applied after cohort entry. These exclusions, if applied equally to each treatment group, do not necessarily bias the study results but may affect the interpretation when results are compared across studies if studies being compared apply different exclusion criteria. A good example is seen in the Lidegaard reanalysis.[17] With no exclusion, the risk estimates during the first year of use was 5.2 (95% CI - 2.2-12.6) for LNG and 8.5 (95% CI - 6.0-11.9) for DRSP. With exclusions implemented, the risk estimates increased to 6.1 (95% CI - 2.7-13.6) for LNG and 9.8 (95% CI - 7.1-13.5) for DRSP. Although the risk estimates increase when the exclusions are applied, the overall DRSP/LNG risk ratios for both are exactly 1.6. Therefore, if comparisons between studies rely solely on absolute risk estimates, than comparisons may be misleading. If comparisons are made using incidence or risk ratios, differences in estimates are less likely to be misleading if only exclusion criteria are considered.

4.2.5 Time Trends

Although the FDA-funded Study did not report on changes in use over time, the analyses did adjust for calendar year. The study report also presents information on length and duration of CHC current use.

Although the FDA-funded study report did not present use information on time trends, nationally projected information from SDI Vona (Figure 1) shows the total number of dispensed prescriptions nationwide for the study contraceptives by year beginning in 2002 through 2010. Dispensed prescriptions for DRSP were increasing during the study period (January 1, 2001 through December 31, 2007) whereas dispensed prescriptions for LNG2 remained relatively steady. The later decreases in dispensed prescriptions for DRSP that begins in 2007 may be related more to the introduction of other drospirenone contraceptives to the market than to adverse publicity. Papers questioning the safety of DRSP were first published in 2009. Dispensed prescriptions for NGMN were increasing until 2005 then decreased to the LNG2 levels by 2007, the decrease for this product was likely due to adverse publicity. Trends for the COMP prescriptions were higher than DRSP or NGMN mostly driven by prescriptions for NGM between 2002 and 2004 and for NETA beginning in 2009. Prescriptions for the study products combined, however, represent less than 25% of total CHC prescriptions. With the exception of COMP in the early years of the study, dispensed prescriptions for all study contraceptives did not exceed 20% of the total combined hormonal contraceptive market. Differences in use over time, at least in the US, mandates the importance that calendar time be considered in any analyses. Incidence rates and hazard ratio results in the FDA-funded study were all adjusted for age, site, and calendar time. Other studies considered the time effect mostly by matching on year of birth, index date, or time or enrollment in the clinical practice.

Figure 1: Total Prescriptions of FDA-funded Study Contraceptives by Year



Source: SDI Vector One®: National, Years 2002-2010 Data Extracted September 2011.

4.2.6 Duration of Use

Although DRSP and NGMN were both approved in 2001, persistency or average duration of use among women in this study is longer (268 days) for DRSP than for

NGMN (177 days) and comparable to COMP (236 days) and LNG2 (259 days). Persistency for the products included in COMP also varies and range from 184 days to 259 days. DRSP had the largest proportion (21.7%) of New Users continuing use for more than 365 days. Consequently, comparison of ATE, VTE, and mortality risks by duration of use between NGMN and COMP or LNG2 may be unreliable for any time period longer than 180 days (6 months). Questions on whether the low NGMN persistency in this study is the result of adverse publicity, problems (such as adverse events and acceptability) with the product, or whether it is an enrollment artifact remains unresolved (continuous enrollment in Medicaid may be of short duration due to the nature of the benefit design and eligibility criteria). Low persistency for NGMN product, however, has been reported elsewhere.[23,24]

Table 9: Mean Number of Days and Proportion of New Use by Study Combined Hormonal Contraceptives (CHC), All Sites 2001-2007 (Adapted from Table 5, Final Report 111022v3)

CHC	Mean (days)	% < 90 days	% >365 days
DRSP	268.3	18.6	21.7
NGMN	176.6	37.3	11.4
ETON	167.4	34.9	9.8
LNG2	*258.6*	*18.6*	*19.9*
COMP	*236.3*	*21.4*	*17.2*

4.2.7 Duration of Use: Comparison of VTE Risk

When comparing DRSP to COMP, the hazard ratios for VTE among New Users show an statistically significant increased risk for DRSP for use less than 3 months among (HR 1.9; 95% CI - 1.2-3.0) and a non-statistically significant but elevated risk for NGMN (HR - 1.6; 95% CI - 0.9-2.8) during the same period of use. Statistical significance is reversed, however, when using LNG2 as comparator (DRSP = HR 1.6; 95% CI - 0.9-2.7; NGMN = HR - 2.5; 95% CI - 1.4-4.5).

The risks are lower for use between 3 to 6 months for all study products but only for DRSP when compared to COMP. Risk estimates for duration of use for 12 months or longer are unreliable due to the decrease in number of exposure episodes lasting this long among New Users of DRSP, NGMN, COMP and LNG2. Although the risk estimates do not necessarily change direction, whether one interprets the results as a statistically significant different or not, the results are heavily dependent on the comparator used as well as changes in use over time for each product.

4.3 Other Potential Confounders and Prescribing Patterns

All approved CHCs are effective in preventing pregnancy. Therefore which CHC formulation is prescribed may depend on patient preferences, existing health conditions, prescriber knowledge and preferences, and economic factors that include reimbursable products and insurance formulary restrictions. The current study captures some but not all of these potential confounders, some of which may influence the results observed in

the FDA-funded and all other studies. Although not always measured, these potential confounders and their potential impact on observed risk estimates cannot be ignored.

4.3.1 Measured Covariates

Although the investigators for the FDA-funded study included some known cardiovascular risk factors in the ATE analytic models, other covariates, known to predict VTE risk in users compared to non-users, were tested individually for possible inclusion in the VTE analytical models. Because none of these covariates changed the risk estimate by 10% or more, none were included in the final analysis. The same observation was reported by investigators for the i3 Ingenix DRSP and NGMN studies. Nonetheless, the CHC Final Report provides a summary of these covariates in tables 7a (New Users) and 7b (All Users). The same information is also provided in Appendix B for New Users separately by age group 10-34 years, 35-55 years (Table 10). Although none of the covariates contributed to a 10% change in the analytical models for the entire study cohort, some covariates such as acne, premenstrual tension, and potassium sparing diuretics were present more frequently in DRSP users and particularly in New Users younger than 35 years of age, the group with the higher VTE risk in this study. No covariate was present as prominently for NGMN although there was a tendency to have more New Users with codes for heart disease, coagulopathy, migraine, and drug dependency among younger users (< 35 years of age) suggesting possible prescribing differences and channeling.

Table 10: Proportion of Study CHC Users with Select Covariates by Age Groups and Study Contraceptives, All Sites 2001-2007.

Covariates		All ages		Age 10-34	Age 35-55
		New Users	All Users	New Users	New Users
Acne	DRSP	4.2	4.3	4.6	1.9
	NGMN	0.7	0.9	0.7	0.4
	COMP	2.1	2.5	2.5	0.8
Premenstrual Tension	DRSP	0.2	0.2	0.1	0.7
	NGMN	0.0	0.1	0.0	0.0
	COMP	0.1	0.1	0.1	0.3
Diuretic K sparing	DRSP	0.9	1.2	0.7	2.0
	NGMN	0.4	0.6	0.3	1.7
	COMP	0.8	1.2	0.4	2.2
Polycystic ovarian syndrome (PCOS)	DRSP	0.0	0.0	0.0	0.0
	NGMN	0.0	0.0	0.0	0.1
	COMP	0.0	0.0	0.0	0.0

Although not captured in the FDA-funded study, other gynecological disorders besides menstrual disorders may also be responsible for an increase VTE risk. The NGMN extension study completed by i3 Ingenix report a lower VTE risk when adjusting for gynecological disorders (OR 1.5; 95% CI 0.7-3.6)[25] for the extension year 2005-2006 compared to the unadjusted VTE risk (OR 2.1; 95% CI 1.2-3.6) for the same extension

year 2001-2006 and a five-adjusted VTE risk (OR of 2.1; 95% CI 1.2-3.3) which accounts for matching and initiator status[26] Although it could be argued that comparing risk estimates from different years is misleading, the interim report[27] does provide the VTE risk estimates for only the 2005-2006 year (OR 2.1; 95% CI 1.2-3.6). This risk estimate is similar to that reported for the whole study.

The BCDSP investigators, in their 2010 manuscript,[28] provided univariate risk estimates for the covariates selected for analysis. When comparing currently exposed (NGMN and LNG) cases and controls, gynecological disorders (menstrual disorders, endometriosis, uterine fibroids) showed a twofold increased risk of VTE in the MarketScan database (OR 2.0; 95% CI 1.2-3.5) although this was not seen in the PharMetrics database (OR 1.2; 95% CI 0.5-3.2).

4.3.2 Prescribing Patterns

The Society of Obstetrics and Gynecology of Canada (SOGC) Clinical Practice Gynecology Committee (whose guidelines were approved by the Executive and Council of the SGOC)[29] suggest that because newer products tend to be prescribed to women who already have VTE and ATE risk factors, occurrence of outcomes may be selectively biased towards certain products, giving a misleading impression of risk. If this statement is true for many CHC prescribers, any resulting epidemiologic analyses should seriously consider and adjust for potential channeling bias. This statement is also consistent with the observation that the newer (at study initiation) products, at least in the more recent published studies and the FDA-funded study, are nearly always associated with an increased risk of thrombotic and thromboembolic events when compared to older products. The FDA-funded Study was initiated to begin a deeper examination of these concerns.

The literature assessing prescribing patterns, however, is overwhelmingly European and describes prescribing patterns of European clinicians who may have different prescribing patterns than US clinicians. Nonetheless, the findings by Bitzer and colleagues[21] are worth considering. The authors note that Swiss gynecologists and general practitioners use indirect markers for differential prescribing. The most relevant criteria were family history of VTE, headache, smoking, stability of the menstrual cycle, breast tenderness, body mass index, irregular bleeding, age beyond 35 years and acne. The 20 μg EE dosage was preferred for women older than 35 years, those smoking more than 15 cigarettes per day, those with a family history of VTE, and those complaining of breast tenderness or headache. The 30 μg EE dosage was preferred for patients with a history of irregular bleeding, a family history of osteoporosis, expected poor compliance and acne.

With the exception of the Dinger and the Vlieg studies where investigators were able to interview the women, all other studies (including the FDA-funded study) rely on information captured in claims or electronic databases. Therefore information on family history of VTE, headache, smoking, stability of the menstrual cycle, breast tenderness, body mass index, irregular bleeding is not readily available or available only for hospitalized cases. Information on irregular bleeding, poor compliance, acne and other diagnosed conditions may be available but are frequently not captured.

4.3.3 Unmeasured Covariates

As suggested in the previous section, serious consideration needs to be given to the possibility for channeling bias when comparing progestin types. Both the 2004 European Society of Human Reproduction and Embryology (ESHRE) Workgroup[30] and the 2010 American College of Obstetricians and Gynecologists Guidelines[31] address the non-contraceptive benefits of hormonal contraceptive use, summarize scientific studies that support these benefits, and provide prescribing recommendations. The potential benefits of interest that may influence the results of this and other epidemiologic studies include use of hormonal contraceptives to treat menorrhagia (heavy menstrual bleeding), dysmenorrhea (painful menses), premenstrual syndrome, acne or hirsutism, bleeding due to leiomyomas, pelvic pain due to endometriosis, and menstrual cycle regulation. Some CHCs are approved for treatment of acne (DRSP and NGM) and PMDD (DRSP) although approval of DRSP for treating these conditions (in addition to contraception) is very recent (2006-2007). ESHRE and ACOG Guidelines[30,31] and other published reports mention the anti-androgenic benefits of DRSP and desogestrel for treating these conditions which could possibly lead to channeling bias. The FDA-funded Study did not capture information on many of these conditions during the risk assessment phase other than acne, polycystic ovary syndrome, migraines, dysmenorrhea, and premenstrual tension. The presence of these health conditions by themselves does not necessarily bias the results of the study even if present disproportionally across treatments being compared unless they also increase the woman's risk of having a thrombotic or a thromboembolic event. Information on the VTE risk for these women, however, is scant.

The FDA-funded Study (and most postmarketing studies) however, identified users of study CHCs from claims databases or electronic medical records. Therefore, they very likely would capture the experience of <u>all</u> CHC users, not just that of women who use CHCs mostly for contraception. If women using CHCs mostly for the non-contraceptive benefits of CHCs are at increased risk of VTE by nature of their condition, and if specific CHC products are preferred in treating those conditions (channeling), then differences in risk estimates observed between the CHC products may be attributed to a specific product but would likely be the result of the health condition.

Acne, hirsutism, alopecia and PCOS: There is no reason to believe, based on the available literature, that the presence of acne by itself places a woman at greater risk for VTE. Acne, however, is thought to be present in about 10 to 34% of women with polycystic ovary syndrome (PCOS)[32] and is one of the symptoms, in addition to hirsutism and alopecia (conditions not captured in the FDA-funded Study) frequently associated with PCOS. PCOS women tend to be overweight and possibly at increased risk of experiencing a VTE (1.8; 95% CI 1.1-2.9) when compared to women without PCOS[33]. Based on the results of the Chuan study, it remains unclear whether this increase in risk was solely a treatment effect, due to the disease, or an effect of both disease and treatment. Spironolactone is one product used for treating acne in these women and hormonal contraceptive use is recommended while on spironolactone treatment[32]. Although there were very few women with a diagnosis of PCOS in the FDA-funded Study (Table 10), given that the drospirenone in DRSP is known to have anti-androgenic activity and that DRSP is also a hormonal contraceptive, it is highly likely that this product would be preferentially prescribed to women whose acne, as determined by their

health care providers, might be a marker for developing PCOS. Whether women with PCOS are at increased risk of VTE is not clear. The 2010 Guidelines[31] summarize two small randomized clinical trials (RCT) that demonstrated DRSP and the third generation desogestrel benefits in treating acne and hirsutism were as effective as other CHC products compared.

In the FDA-funded Study, acne was present twice as frequently among DRSP users than COMP users despite the fact that COMP also included an NGM product approved for the treatment of acne. What proportion of women with acne using DRSP in the FDA-funded study that also had hirsutism and/or alopecia is unknown at this time.

Menorrhagia and Bleeding

The ESHRE guidelines[30] note that approximately 10 % of fertile women suffer from menorrhagia and menstrual blood loss. Anemia could be present if the blood loss is severe. Treatment benefits with use of CHCs containing 30 to 35 ug EE have been reported to reduce bleeding by as much as 50%. Very few studies, however, have evaluated the risk of VTE among menorrhagic women. In a case-control study, Sundström[34] noted an association between an increased VTE risk and recent diagnosis of anemia or hemoglobin values less than 11.5 g/dl (odds ratio 2.2; 95% confidence interval 1.0-4.9). The results suggested that a diagnosis of anemia or having low hemoglobin levels during 14 days before or after a record of menorrhagia could be a predictor of disease severity as well as susceptibility to VTE. Other confounders, however, were also observed in this study since cases also had a high BMI and were likely to be smokers. The Guidelines[31,30] note that all CHCs (LNG, desogestrel) may provide short term benefits in reducing bleeding but that continuous or extended use CHCs may be most beneficial. The FDA-funded Study did not capture information on menorrhagia.

Migraines

According to the SOGC 2010 Guidelines[31], menstrual migraines (with no aura) occur in 8% to 14% of reproductive age women. These migraines are experienced exclusively at the time of menstruation with very few also occurring at ovulation. The Guidelines summarize studies that show the benefit of extended cycle or continuous hormonal contraceptives. The Guidelines and others[35], however, caution about use of combined hormonal contraceptives for migraines due to the possible increase risk for a experiencing a cerebrovascular stroke.

The FDA-funded Study shows a higher proportion of younger women with a code for migraine with NGMN (2.1%) and ETON (2.5%) than COMP (1.9%) or DRSP (1.9).

IMS Pharmetrics –Non-contraceptive Diagnoses

It is unclear what proportion of CHC users is prescribed CHCs for non-contraceptive benefits in addition to their contraceptive benefit. Information from the FDA-funded study captured only some of these associated diagnoses and it is also not representative of the US population. To obtain a better understanding on whether use of CHCs for related non-contraceptive indications could be an important confounder in a larger US

population (PharMetrics[e]), we examined recorded diagnoses within 30 days of a first CHC prescription close to the same time period (2002 and 2007) as the FDA-funded study. The same new user exposure definition was applied to the selected cohort and the same CHC products were selected using the FDA-funded study's NDC numbers.

In reviewing information from this US database, 252,943 unique patients were identified that filled a prescription from any CHC drug class. After selecting CHCs with the same NDC number in the FDA-funded study, and selecting only women who were incident users (no CHCs in the prior six months), 38,872 (15.4%) users were selected for evaluation. Diagnoses of interest, representing possible non-contraceptive indications for use, were examined. Only the first diagnosis of interest that occurred within 30 days of the first CHC prescription drug claim was identified. Among the incident cohort, NGM was used more frequently (32%) followed by DRSP (19%), NGMN (15%), and LNG1 (13%).

In this population, there were 4,946 diagnoses of interest temporally associated with first new use of the study CHC. Although all study CHCs had temporally associated diagnoses of interest, DRSP and NGM were dispensed more frequently to women with codes for all conditions except menorrhagia (heavy bleeding). Women with codes for PCOS, PMTS, and hirsutism were more frequently taking DRSP (Table 11).

Table 12 shows the distribution of codes for the selected conditions among women dispensed each CHC. Again, all CHCs were associated temporally with all selected conditions although DRSP was more frequently temporally associated with PCOS, PMTS, and hirsutism. The older CHCs, on the other hand, were temporally associated more with dysmenorrhea (pain) and menorrhagia (heavy bleeding) although DRSP was dispensed just as frequently with codes for dysmenorrhea. The study CHCs were more frequently associated temporally with PCOS, dysmenorrhea, hirsutism, and acne in users younger than 35 years of age than older users. Although these diagnoses have not been validated (e.g. medical charts obtained to determine that these women indeed meet a case definition for these disorders), these data are suggestive of differential prescribing of contraceptives to women with and without these conditions, particularly for younger women.

In the FDA-funded study, more women dispensed DRSP had codes for acne (4.3%) and PMTS (0.2) compared to COMP (2.5% acne and 0.1% PMTS) whereas more women dispensed NGMN had codes for PCOS (0.04%) than COMP (0.01%). Hirsutism was not captured. These proportions are lower than those observed in PharMetrics (Table 12).

[e] *IMS Health, IMS Health Lifelink™, 1/1/2002 to 12/31/2007.*

Table 11. Distribution of study CHCs (%) for Selected Health Conditions, 2002-2007

	PCOS	Pain*	PMTS**	Bleeding*	Hirsutism	Acne
	100.0	100.0	100.0	100.0	100.0	100.0
DRSP	47.6	18.6	33.2	16.7	47.4	24.4
NGM	22.9	29.0	17.3	14.5	26.6	49.3
NGMN	5.9	14.1	7.3	8.3	8.4	6.5
ETON	3.1	3.0	5.9	5.2	2.0	3.6
NETA	6.1	10.8	10.7	18.8	2.6	3.8
LGN2	3.8	8.3	8.0	7.3	3.3	4.0
LGN1	10.7	16.3	17.7	29.2	9.7	8.5

Source: IMS Health, IMS Health Lifelink™, 1/1/2002 to 12/31/2007
CHC – all-time use of study combined hormonal contraceptive;
Dx – diagnosis occurring within 30-days of first CHC prescription date (index date);
PCOS – polycyctic ovarian syndrome;
** pain - dysmenorrhia; bleeding - menorrhagia*
*** PMTS – premenstrual tension syndrome*

Table 12. Distribution (%) of Selected Health Conditions among study CHCs, 2002-2007

	PCOS	Pain*	PMTS**	Bleeding*	Hirsutism	Acne
DRSP	4.4	11.2	2.3	0.4	1.7	8.2
NGM	1.0	8.8	0.6	0.2	0.5	8.2
NGMN	0.6	8.9	0.5	0.2	0.3	2.2
ETON	0.8	4.6	1.1	0.3	0.2	3.2
NETA	1.1	12.3	1.4	0.8	0.2	2.5
LGN2	0.8	11.5	1.2	0.4	0.3	3.1
LGN1	1.1	11.0	1.4	0.8	0.4	3.3

Source: IMS Health, IMS Health Lifelink™, 1/1/2002 to 12/31/2007
CHC – all-time use of study combined hormonal contraceptive;
PCOS – polycyctic ovarian syndrome;
** pain - dysmenorrhia; bleeding - menorrhagia*
*** PMTS – premenstrual tension syndrome*

In conclusion, the IMS data show possible prescribing preferences or channeling for non-contraceptive benefits may exist in the U.S. Whether channeling effects are seen in other study populations remains to be evaluated.

4.4 UNMEASURED BUT SUSPECTED CONFOUNDERS

Information on age, duration of current product use, and selected covariates (dysmenorrheal, acne, migraines, and premenstrual tension) were available for evaluation in the FDA-funded study and provided in the Final Report. Information on other concomitant diagnoses such as anemia, menorrhagia, endometriosis, and hirsutism might be available but was not collected. Unfortunately, other likely important variables, noted in the previous sections, such as body mass index (BMI), smoking, lifetime contraception use, and family and personal history of VTE were unavailable for this analysis. Those

potential important confounders were also not available for most of the DRSP published postmarketing studies and all the published NGMN studies and remain a concern.

There were two postmarketing studies required by the FDA or European regulatory agencies that reported no increase VTE risk between DRSP and LNG or other progestins. The studies were able to obtain information or address the important confounders not available in claims databases or electronic medical records either by direct interview with the women[1] or by matching on the probability of having similar baseline characteristics to the DRSP initiator using the information available at the time of initial use.[2] Although other methodological differences exist between these early studies and those conducted later, having the ability to capture or match on important VTE confounders may be the most important difference.

At the time this FDA-funded Study was conceptualized, two phases were considered. The first would include a risk assessment component that would also obtain sufficient patient and prescribing characteristics allowed with the use of claims data and hospitalized records. If an increased risk was observed, however, a second phase would be considered. The second phase would include more extensive medical record review and possible physician and patient interviews to obtain the information on the important but missing confounders. Whether this second phase is completed depends on its feasibility at this time and the availability of funds.

5 CONCLUSIONS AND RECOMMENDATIONS

The results of the FDA-funded study are consistent with the published studies demonstrating an increase VTE risk among current users of DRSP and NGMN particularly among women younger than 35 years of age. This study is also the first to report an increase ATE risk among older DRSP users. Linkage to state mortality files did not reveal any large discrepancy in missed ATE and VTE case identification. The increase VTE risk for ETON needs further evaluation.

The FDA-study showed that incidence rates increase with age both in all users and new users. Age-specific incidence rates were higher for new users than for all users but not for the adjusted rates. This study also demonstrated the importance of considering differences in population sources, population characteristics, and comparators when comparing product types including the possible channeling by prescribers for non-contraception benefits provided by these products.

The study was carefully done, is comprehensive, and all hospitalized outcome have been validated with medical records. One site also validated outpatient DVTs. In addition, the study was able to link records to state mortality files, evaluated two different exposure cohorts (All Users and New Users), and the contribution of known confounders in the two very different US populations (Medicaid and a large HMO).

Like other claims-based studies, however, the study is limited in that it captures only information available in the claims databases or in electronic medical records for cases only. Limitations also include the absence of data on key covariates (obesity/BMI, smoking, personal and family history of VTE, lifetime use of hormonal contraceptives) and the inability to validate outpatient DVTs by chart review (except at only one site).

The small number of ATEs limited power for analyses of these outcomes, though the rates of these outcomes were consistent with published data.

The FDA-funded study as well as most postmarketing studies, however, identified all users of study CHCs from claims databases or electronic medical records. Therefore, the studies very likely would capture the experience of all CHC users, not just the experience of women who use CHCs mostly for contraception. And even though some studies excluded women with known risk factors for experiencing VTEs, none have assessed whether channeling by prescribers and potential risk associated with CHC use for non-contraceptive benefits. If women using CHCs mostly for the non-contraceptive benefits of CHCs are at increased risk of VTE by nature of their condition, and if specific CHC products are preferred over other CHCs in treating those conditions (channeling), then differences in risk estimates observed between the CHC products may be attributed to a specific product but would more likely be the result of the health condition.

None of the studies to date provides a definitive answer as to the safety of DRSP and NGMN with regard to thrombotic and thromboembolic events (TTE). The entire body of studies provides conflicting evidence that cannot be easily reconciled by any single difference among studies. Most of these studies have unique strengths and limitations, but the challenge lies in trying to reconcile multiple methodological differences among studies conducted in very different populations, often using different comparators and different exposure definitions. There is a history that newer contraceptive products being observed often have associations with increased risk for thrombotic and thromboembolic events and the Agency would like to better understand whether channeling of newer products to patients already at higher risk for these events may play a role. The FDA-funded study was originally designed to be the first phase in a multi-phase study designed to address many of the unresolved questions perceived by the Agency to possibly provide alternative explanations for the risks seen, other than the individual drugs themselves.

Since FDA cannot at this time determine whether or not the increased risk seen for thrombotic and thromboembolic events in some of the epidemiologic studies is actually due to use of the DRSP and NGMN products, we believe that, because of the consistency in recent reports for an increased risk, product labeling should reflect that very real possibility. However, the Agency advocates further study of this issue, as part of a larger effort to better understand the risk for thrombotic and thromboembolic events associated with all newer contraceptive agents. Such studies should assure the comparability of population sources, study design, exposure definitions, and adequate capture and adjustment of age, non-contraceptive co-indications, other co-morbid diseases (e.g. ob/gynecological conditions), and known confounders such as BMI, smoking, and personal and family history of thrombotic and thromboembolic events.

For contractual purposes, the Final Report, presenting results from the risk assessment phase of this study achieved its objectives.

6 REFERENCES

[1] Dinger JC, Heinemann LAJ, Kühl-Habich D. 2007. *The Safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance study on oral contraceptives based on 142,475 women-years of observation.* Contraception, 75:344-354.

[2] Seeger JD, Loughlin J, Eng PM, Clifford CR, Cutone J, and Walder AM. 2007. *Risk of thromboembolism in women taking ethinylestradiol/drospirenone and other oral contraceptives.* Obstetrics and Gynecology; 110(3):587-593.

[3] Eng PM, Seeger JD, Loughlin J, Clifford CR, Mentor S, and Walker AM. 2008. *Supplementary data collection with case-cohort analysis to address potential confounding in a cohort study of thromboembolism in oral contraceptive initiators matched on claims-base propensity scores.* Pharmacoepidemiology and Drug Safety, 17:297-305.

[4] Jick SS, Hernandez RK. 2011. *Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data*. BMJ 2011;340:d2151 doi:10.1136/bmj.d2151.

[5] Parkin L, Sharples K, Hernandez RK, Jick SS. 2011. *Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested case-control study based on UK General Practice Research Database*. BMJ 2011;340:d2139 doi:10.1136/bmj.d2139

[6] Lidegaard Ø, Løkkegaard E, Svendsen AL, and Agger C. 2009. *Hormonal contraception and risk of venous thromboembolism: national follow-up study*. BMJ 2009;339:b2890 doi:10.1136/bmj.b2890

[7] van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, Doggen CJM, Rosendaal FR. 2009. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. BMJ 2009;339:b2921 doi:10.1136/bmj.b2921

[8] Cole JA, Norman H, Doherty M, and Walker AM. 2008 *Venous Thromboembolism, Myocardial Infarction, and Stroke among Transdermal Contraceptive System Users*. Obstetrics & Gynecology 2007; 109(2): 339-346. Erratum 2008: 111(6):1449.

[9] Jick SS, Kaye JA, Russmann S, and Jick H. 2006. *Risk of nonfatal venous thromboembolism in women using a contraceptive transdermal patch and oral contraceptives containing norgestimate and 35 μg of ethinyl estradiol*. Contraception; 73:223-228.

[10] Jick SS and Jick H. 2007. *The Contraceptive Patch in Relation to Ischemic Stroke and Acute Myocardial Infarction.* Brief Reports. Pharmacotherapy; 27:218-220.

[11] Dore DD, Norman H, Loughlin J, Seeger JD. 2010. *Extended case-control study results on thromboembolic outcomes among transdermal contraceptive users.* Contraception; 81:408-413.

[12] Jick S, Kaye JA, Li L and Jick H. 2007. *Further results on the risk of nonfatal venous thromboembolism in users of the contraceptive transdermal patch compared to users of oral contraceptives containing norgestimate and 35 μg of ethinyl estradiol.* Contraception 2007; 76:4-7.

[13] Jick SS, Hagberg KW, Kaye JA. 2010. *Ortho Evra and Venous Thromboembolism: An Update*. Letter to the Editor. Contraception; 81:452-453.

[14] FDA Office of Surveillance and Epidemiology. 2011. *Combined hormonal contraceptives (CHCs) and the risk of cardiovascular disease endpoints*. October 22, 2011 http://www.fda.gov/downloads/Drugs/DrugSafety/UCM277384.pdf

[15] Parkin L, Sharples K, Hernandez RK, Jick SS. 2011. *Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested case-control study based on UK General Practice Research Database*. BMJ 2011;340:d2139 doi:10.1136/bmj.d2139

[16] Dinger J, Assmann A, Mőhner S, and Minh TD. 2010. *Risk of venous thromboembolism and the use of dienogest- and drospirenone-containing oral contraceptives: results from a German case-control study*. *J Fam Plann Reprod Health Care*; 36(3): 123–129.

[17] Ouellet-Hellstrom R. 2011. *Review of Lidegaard's Reanalysis*. September 3, 2011. RCM 2011-1764.

[18] Lidegaard Ø, Løkkegaard E, Svendsen AL, and Agger C. 2009. *Hormonal contraception and risk of venous thromboembolism: national follow-up study*. BMJ 2009;339:b2890 doi:10.1136/bmj.b2890

[19] U,S,DHHS Health Care Financing Administration. 2000. *A Profile of Medicaid*, Chart Book. September 2000.

[20] van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, Doggen CJM, Rosendaal FR. 2009. *The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study.* BMJ 2009;339:b2921 doi:10.1136/bmj.b2921

[21] Bitzer J, Frey B, von Schönau M, Sabler N, and Tschudin S. 2009. *Twenty or thirty microgram ethinyloestradiol in an oral contraceptive: Does itmakea difference in the mind and the daily practise of gynaecologists and general practitioners?* The European Journal of Contraception and Reproductive Health Care; 14(4):258–267

[22] Sannisto T and Kosunen E. 2010. *Provision of contraception: a survey among primary care physicians in Finland*. Acta Obstetricia et Gynecologica; 89: 636–645.

[23] Nelson AL, W C, and Schnare SM. 20087. *Real-World Patterns of Prescription Refills for Branded Hormonal Contraceptives. A Reflection of Contraceptive Discontinuation*; Obstetrics & Gynecology, 112(4): 782-787.

[24] Murphy PA and Bixner D. 2008. *Hormonal contraceptive discontinuation patterns according to formulation: investigation of associations in an administrative claims database*. Contraception; 77: 257-263.

[25] i3 Ingenix. 2008. *The Risk of Venous Thromboembolism, Myocardial Infarction, and Ischemic Stroke Among Women Using the Transdermal Contraceptive System Compared to Women Using Norgestimate-Containing Oral Contraceptives With 35 μg Ethinyl Estradiol Nested Case-Control Extension 2005-2006*. Interim Report. June 18 2008

[26] i3 Ingenix. 2009. *The Risk of Venous Thromboembolism, Myocardial Infarction, and Ischemic Stroke Among Women Using the Transdermal Contraceptive System Compared to Women Using Norgestimate-Containing Oral Contraceptives With 35 μg Ethinyl Estradiol Nested Case-Control Study*. Final Report. June 29, 2009.

[27] i3 Ingenix. 2008. *The Risk of Venous Thromboembolism, Myocardial Infarction, and Ischemic Stroke Among Women Using the Transdermal Contraceptive System Compared to Women Using Norgestimate-Containing Oral Contraceptives With 35 μg Ethinyl Estradiol Nested Case-Control Study Extension 2005-2006 Interim Report June 18, 2008.* Prepared for Johnson & Johnson PRD Confidential

[28] Jick SS, Hagberg KW, Hernandez R, and Kaye JA. 2010. *Postmarketing study of OrthoEvra® and levonorgestrel oral contraceptives containing hormonal contraceptives with 30 mcg of ethinyl estradiol in relation to nonfatal venous thromboembolism.* Contraception 81:16-21.

[29] SOGC Clinical Practice Guidelines. 2011. *Oral contraceptives and the risk of venous thromboembolism: An update No. 252, December 2010.* International Journal of Gynecology and Obstetrics 112 (2011) 252–256.

[30] The ESHRE Capri Wrokshop Group. 2005. *Noncontraceptive health benefits of combined oral contraception.* Human Reproduction Update; 11(5): 513-525.

[31] The American College of Obstetricians and Gynecologists. 2010. *Noncontraceptive Uses of Hormonal Contraceptives Clinical Management Guidelines for Obstetrician-Gynecologists, Number 110, Janu ary 2010.* OBSTETRICS & GYNECOLOGY, 115(1): 206-218.

[32] Chuan SS and Chang RJ. 2010. *Polycystic Ovary Syndrome and Acne*. Skin Therapy Lett; 15(10):1-4.

[33] Seaman HE, de Vries CS, and Farmer RDT. 2004. *Venous thromboembolism associated with cyproterone acetate in combination with ethinyloestradiol*

(Dianette1): observational studies using the UK General Practice Research Database. PDS 13:427-436.

[34] Sundström A, Seaman H, Kieler H, Alfredsson L. 2009. *The risk of venous thromboembolism associated with the use of tranexamic acid and other drugs used to treat menorrhagia: a case-control study using the General Practice Research Database*. BJOG.;116(1):91-7. Epub 2008 Nov 11

[35] Moschiano F, D'Amico D, Ciusani E, Erba N, Rigamonti A, Schieroni F, Bussone G. 2004. *Coagulation abnormalities in migraine and ischaemic cerebrovascular disease: a link between migraine and ischaemic stroke?* Neurol Sci (2004) 25:S126–S128 DOI 10.1007/s10072-004-0269-5.

7 APPENDIX A

Table 1A: Age-Specific VTE Incidence Rates per 10,000 person-years (PY) for New and All Users by Selected Study Hormonal Contraceptive, 2001-2007 (From Table 10b, Final Report 111022v2)

	New Users			All Users		
DRSP	**PY**	**Events**	**Rate/10k**	**PY**	**Events**	**Rate/10k**
10 to 24	39,452	19	4.8	79,590	27	3.4
25 to 34	27,362	26	9.5	72,346	54	7.5
35 to 44	10,672	18	16.9	29,968	43	14.3
45 to 55	2,684	11	41.0	7,306	20	27.4
NGMN						
10 to 24	17,680	11	6.2	37,602	21	5.6
25 to 34	9,424	12	12.7	22,781	26	11.4
35 to 44	2,651	8	30.2	6,515	14	21.5
45 to 55	397	2	50.4	967	6	62.0
LNG2						
10 to 24	39,977	10	2.5	80,454	20	2.5
25 to 34	33,843	15	4.4	89,057	33	3.7
35 to 44	17,544	33	18.8	54,546	72	13.2
45 to 55	5,896	16	27.1	20,550	36	17.5
COMP						
10 to 24	103,683	32	3.1	218,616	62	2.8
25 to 34	77,191	39	5.1	207,964	80	3.9
35 to 44	42,631	79	18.5	121,685	136	11.2
45 to 55	24,526	55	22.4	69,000	111	16.1

Age-adjusted VTE rates per 10,000 person-years (PY) and Incidence Rate Ratios (IRR)

ALL USERS

EXPOSURE	**Age-adjusted rate**	**Incidence Rate Ratio**	**95% CI**	**Incidence Rate Ratio**	**95% CI**
DRSP	10.2	1.7	1.4 – 2.1	1.5	1.2 – 1.9
NGMN	9.8	1.5	1.2 – 2.0	1.3	0.9 – 1.7
LNG2	6.6			Reference	--
COMP	6.0	Reference	--		

NEW USERS

EXPOSURE	**Age-adjusted rate**	**Incidence Rate Ratio**	**95% CI**	**Incidence Rate Ratio**	**95% CI**
DRSP	13.7	1.6	1.2 – 2.1	1.5	1.1 – 2.1
NGMN	12.3	1.3	0.9 – 1.9	1.1	0.7-1.7
LNG2	9.2			Reference	--
COMP	8.2	Reference	--		

Table 2A: Age-Specific ATE Incidence Rates per 10,000 person-years (PY) for New and All Users by Study Hormonal Contraceptive, 2001-2007 (From Table 10a Final Report 111022v2)

	New Users			All Users		
DRSP	**PY**	**Events**	**Rate/10k**	**PY**	**Events**	**Rate/10k**
10 to 24	39,452	-	-	79,590	-	-
25 to 34	27,362	3	1.1	72,346	3	0.4
35 to 44	10,672	5	4.7	29,968	8	2.7
45 to 55	2,684	6	22.4	7,306	6	8.2
NGMN						
10 to 24	17,680	1	0.6	37,602	2	0.5
25 to 34	9,424	2	2.1	22,781	6	2.6
35 to 44	2,651	1	3.8	6,515	1	1.5
45 to 55	397	-	-	967	-	-
LNG2						
10 to 24	39,977	2	0.5	80,454	7	0.9
25 to 34	33,843	4	1.2	89,057	6	0.7
35 to 44	17,544	3	1.7	54,546	12	2.2
45 to 55	5,896	8	13.6	20,550	19	9.3
COMP						
10 to 24	103,683	5	0.5	218,616	12	0.6
25 to 34	77,191	9	1.2	207,964	19	0.9
35 to 44	42,631	13	3.1	121,685	29	2.4
45 to 55	24,526	18	7.3	69,000	48	7.0

Age-adjusted ATE rates per 10,000 person-years (PY) and Incidence Rate Ratios (IRR)

ALL USERS

EXPOSURE	**Age-adjusted rate**	**Incidence Rate Ratio**	**95% CI**	**Incidence Rate Ratio**	**95% CI**
DRSP	1.1	0.8	0.9 – 3.1	1.4	0.7 – 2.8
NGMN	1.1	1.1	0.3 – 2.5	0.7	0.2 – 2.2
LNG2	1.6			Reference	--
COMP	1.4	Reference	--		

NEW USERS

EXPOSURE	**Age-adjusted rate**	**Incidence Rate Ratio**	**95% CI**	**Incidence Rate Ratio**	**95% CI**
DRSP	2.6	1.7	0.9 – 3.1	1.4	0.7 – 2.8
NGMN	1.8	0.9	0.3 – 2.5	0.7	0.2 – 2.2
LNG2	2.3			Reference	
COMP	1.8	Reference			

8 APPENDIX B

SDI, Vector One®: National (VONA)

The SDI, Vector One®: National (VONA) database measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.4 billion prescription claims per year, representing over 120 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing over 200 million unique patients.

Prescriptions are captured from a sample from the universe of approximately 59,000 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from approximately one-third of stores and a significant sample of prescriptions from many of the remaining stores.

IMS Health, IMS Health Lifelink™ database

The IMS Health, IMS Health Lifelink™ database was used to evaluate the utilization of oral contraceptives, Ortho Evra, and NuvaRing from 1/1/2002 – 12/31/2007. The IMS Health Plan Claims Database represents over 95 managed care plans and covers approximately 60 million commercially insured, de-identified patients. Claims are captured from doctor's offices (including outpatient clinics), retail and mail order pharmacies, patient visits to specialists, and hospitalizations. They include information about diagnoses, emergency room visits, office visits, home care, diagnostic tests, procedures and injections. These data represent approximately 11 percent of the U.S. commercially insured population during that time period. Claims for these products are primarily submitted for insurance payment by dispensing pharmacies.

However, since pharmacists typically do not have access to the patient's medical record, pharmacy claims are submitted without supporting ICD-9 diagnostic codes. To assess the indication for use of the contraceptive products, medical claims filed closest (within 30 days before and after the patient's first contraceptive prescription to the claim date for the contraceptive prescription) were examined. Medical claims are required to be submitted with at least one, and up to four supporting diagnosis ICD-9 codes. When several ICD-9 codes of interest were supplied, he code appearing first was used. Patients were eligible for inclusion if there was a prescription claim for a contraceptive between January 1, 2002 and December 31, 2011 and no previous claim for an oral contraceptive in the preceding 180 days prior to their first claim with insurance eligibility during that 6 month look-back period. Since this analysis was concerned with a patient's first medical claim during the study period, continuous eligibility throughout the study period was not required. The diagnoses selected are listed below

Code Description
706.1 ACNE NEC
704.1 HIRSUTISM
256.4 POLYCYSTIC OVARIES
625.4 PREMENSTRUAL TENSION
625.3 DYSMENORRHEA
627.0 PREMENOPAUSE MENORRHAGIA
346.4 MENSTRUAL MIGRAINE
346.42 MENSTRUAL MIGRAINE W/O INTRA
346.43 MENSTRUAL MIGRAINE INTRACT
346.41 MENSTL MGRN W NTRC WO ST
346.40 MENSTRUAL MIGRAINE W/O INTRA

SDI, Physician Drug & Diagnosis Audit (PDDA) with Pain Panel

The SDI, Physician Drug & Diagnosis Audit (PDDA) with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

9 APPENDIX C

Table 13B: Distribution of CHC Use by Age Group, FDA-funded Study (2001-2007 All Users) Compared to US Projected Total Prescriptions (SDI 2002-2007).

	Age Group	SDI*	FDA-funded Study	KP**	Medicaid
NGMN	0-25 years	47.6	62.5	47.7	72.8
	26-34 years	34.5	29.2	39.9	23.2
	35+ years	17.5	8.3	15.6	4.1
DRSP_30	0-25 years	44.3	50.0	47.7	65.6
	26-34 years	31.0	34.7	35.9	26.8
	35+ years	24.5	15.2	16.5	7.6
ETON	0-25 years	40.6	50.3	39.0	65.6
	26-34 years	37.4	37.2	43.1	29.3
	35+ years	21.9	12.5	17.8	5.2
COMP	0-25 years	41.4	44.7	37.8	67.6
	26-34 years	31.2	31.9	31.4	24.2
	35+ years	27.2	23.4	28.1	8.1
LNG2	0-25 years	28.8	42.1	38.2	62.1
	26-34 years	31.6	34.6	35.7	28.8
	35+ years	39.4	23.3	26.1	9.0
LNG1	0-25 years	35.4	60.4	34.3	65.9
	26-34 years	27.3	25.7	38.1	23.1
	35+ years	37.1	13.8	27.6	10.9
NGM	0-25 years	48.4	56.5	49.7	73.3
	26-34 years	34.0	33.8	38.6	22.0
	35+ years	17.5	9.6	11.6	4.7
NETA	0-25 years	21.6	26.0	23.9	56.3
	26-34 years	22.6	26.7	26.8	26.5
	35+ years	55.8	47.2	49.3	17.2

**Source: SDI Vector One®: National, Years 2002-2010 Data Extracted September 2011 (only years 2002-2007 shown) and Tables 4a1-3, Final Report 111022v2).*

*** KP = Kaiser Permanente*

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/s/

RITA P OUELLET-HELLSTROM
11/04/2011

GERALD J DALPAN
11/04/2011

Appendix B

FDA Review of Drug Utilization Patterns for DRSP-containing Combination Oral Contraceptives and Other Combined Hormonal Contraceptive Products

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Drug Use Review

Date:	November 9, 2011
Reviewer(s):	Patty Greene, Pharm.D., Drug Use Data Analyst Division of Epidemiology II (DEPI II)
Team Leader (Acting):	Grace Chai, Pharm.D. Division of Epidemiology II (DEPI II)
Director:	Judy A. Staffa, Ph.D., R.Ph. Division of Epidemiology II (DEPI II)
Drug Name(s):	Yasmin®, Yaz® (drospirenone and ethinyl estradiol)
Application Type/Number:	NDA 21-098; NDA 21-676; NDA 21-893; NDA 22-045
Applicant/sponsor:	Bayer HealthCare Pharmaceuticals, Inc.
OSE RCM #:	RCM 2011-1044

This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

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EXECUTIVE SUMMARY

This review examines drug utilization patterns in women (0-25, 26-34, 35+ years) for Yasmin® and Yaz® and other drosperinone-containing contraceptives products, along with other combined hormonal contraceptive (CHC) products (USC class 33230, 33390) in the U.S. outpatient retail pharmacy setting for years 2002 through 2010.

- In year 2010, approximately 83.7 million prescriptions were dispensed in the contraceptive market. Although prescriptions dispensed in the contraceptive market increased by 6% from year 2002 to 2004, there was a notable decrease (-11%) from year 2004 to 2006. Prescriptions steadily decreased from year 2006 to year 2010 for a net decrease of 10% since year 2002
- The projected number of prescriptions dispensed for drosperinone-containing contraceptive products decreased from a peak in use of nearly 18.4 million prescriptions in year 2008 (21% of the CHC market) to 12.9 million prescriptions in year 2010 (16% of the CHC market). The projected number of patients who received dispensed prescriptions of drosperinone-containing contraceptive products also decreased from about 3.7 million patients in year 2008 (20% of CHC patients) to 2.5 million patients in year 2010 (14% of CHC patients). A similar decrease was noted when the prescription data was adjusted for population growth.
- For drospirenone 3mg/ethinyl estradiol 20 µg products (Yaz®), prescriptions dispensed to the younger female population accounted for a larger proportion of use than seen for drospirenone 3mg/ethinyl estradiol 30 µg products (Yasmin®) and other CHCs when compared as a group.
- The proportion of women aged 0-25 years with a BMI of 30+ was 10% of drug occurrences for Yaz® and 8% of drug occurrences for Yasmin® as reported by U.S. office-based physicians for year 2001 to 2007, cumulative. For women aged 26-34 years, the proportion of women with a BMI of 30+ was 15% for Yaz® and 13% for Yasmin®. For women aged 35+ years, the proportion of women with a BMI of 30+ was 10% for Yaz® and 14% for Yasmin®. The BMI data for Yaz® and Yasmin® were comparable to the other study CHCs, however, the BMI was unknown in a large proportion of drug occurrences, so these results should be interpreted with caution.
- Yaz® and Yasmin® patients had the highest proportion of patients with <u>one or more</u> diagnoses for Acne (ICD-9 706.1), Hirsutism (ICD-9 704.1), and/or Premenstrual Tension or PMDD (ICD-9 625.4) among the examined CHC product groups. However, of patients aged 0-25 years, only 2.3% of patients with a prescription claim for Yaz® and 2.0% of patients for Yasmin® had one or more of the examined diagnoses. Of patients aged 26-34 years, only 1.4% of patients with a prescription claim for Yaz® and 1.2% of patients for Yasmin® had one or more diagnoses. In patients 35 years and older, 1.4% of patients for Yaz® and 1.0% of patients for Yasmin® had one or more diagnoses. The frequency of these diagnoses was low, however, and should be interpreted with caution.

1 BACKGROUND

On December 8, 2011, the Advisory Committee for Reproductive Health Drugs and the Drug Safety and Risk Management Advisory Committee will meet to discuss the risks and benefits of combined hormonal contraceptives (CHC) products containing drospirenone and ethinyl estradiol. In the literature, there are several published studies which examined the association between oral contraceptives and the risk of venous thromboembolism (VTE). A recent nested-case control study from Jick et al. reported a 2-fold increase in the risk of non-fatal venous VTE among users of contraceptives with drosperinone-containing contraceptive products compared to levonorgestrel[1], but there are other published studies that do not report an increased risk.[2] The Division of Epidemiology II (DEPI II) will present findings from an FDA-funded study which found an increased risk of (VTE) associated with Yasmin® compared to CHC products containing ethinyl estradiol and levonorgestel. The purpose of the FDA-funded study was to assess cardiovascular risks, including the risk of thrombotic and thromboembolic events and death across multiple CHC product groups containing the progestins levonorgestrel, norethindrone, or norgestimate combined with 0.02 mg to 0.035 mg of ethinyl estradiol.

FDA has concerns about whether there may be sources of unmeasured confounding in studies of drosperinone-containing products and risk for thrombotic and thromboembolic events. Some of these unmeasured confounders may relate to co-morbid conditions of the women prescribed these products, that may or may not be related to the physician's decision to prescribe a drosperinone-containing contraceptive product. The decision was made to explore some of the drug utilization data available to the Agency to both better understand the overall utilization of contraceptive products, as well as to explore for sources of potential confounding.

In support of the Advisory Committee meeting, this review will provide national patterns of drug utilization data for Yasmin® and Yaz® and other drosperinone-containing contraceptive products by patient age (0-25, 26-34, 35+ years), as well as for other CHC products included in the FDA study (referred to as Study CHC products) for years 2002 to 2010. We examined medical diagnoses and body mass index (BMI) codes associated with the mention of each of these products during visits to office-based physicians. In addition, we used a large claims database to compare women treated with Yasmin®, Yaz®, and Study CHCs to examine the frequency of women with one or more diagnosis codes for Acne (ICD-9 706.1) and Hirsutism (ICD-9 704.1), and/or Premenstrual Tension or PMDD (ICD-9 625.4) in their recent claims history. It is possible that these conditions may be markers for more serious underlying gynecological conditions that may increase a woman's risk for VTE.

2 METHODS AND MATERIALS

2.1 DETERMINING SETTINGS OF CARE

The IMS Health, IMS National Sales Perspectives™ was used to determine the various retail and non-retail channels of distribution for drosperinone-containing contraceptive products. In year

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[1] Jick, S Hernandez, R. (2011). Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: a case-control study using United States claims data. *British Medical Journal*. 342 (1), d2151.

[2] Seeger JD, Loughlin J, Eng PM, Clifford CR, Cutone J, and Walker AM. 2007. Risk of thromboembolism in women taking ethinylestradiol/drospirenone and other oral contraceptives. Obstetrics and Gynecology; 110(3):587-593.

2010, sales data for drosperinone-containing contraceptive products indicated that 80% of blister packs (Eaches) were distributed to outpatient retail pharmacies; 10% were to non-retail settings; and 10% were to mail order pharmacies.[3] As a result, outpatient retail pharmacy utilization patterns were examined. Non-retail and mail order settings were not included in this analysis.

2.2 DATA SOURCES USED

Proprietary drug use databases licensed by the Agency were used to conduct this analysis (See Appendix 2 for full database descriptions).

IMS Health, IMS National Sales Perspectives™ was used to obtain the sales data for drospirenone-containing products by the number of eaches (boxes, packages, etc.) sold from manufacturers to retail (including mail order) and non-retail channels of distribution for years 2006 through 2010.

SDI, Vector One®: National (VONA) was used to obtain estimates of the nationally projected number of outpatient dispensed prescriptions for drospirenone-containing products, and the combined hormonal contraceptive (CHC) market, stratified by age (0-25, 26-34, 35+ years), in the outpatient retail pharmacy setting for years 2002 through 2010; we also examined the nationally projected number of outpatient dispensed prescriptions for study CHC products including drospirenone 3mg/ethinyl estradiol 20 µg products (Yaz® group) and drospirenone 3mg/ethinyl estradiol 30 µg products (Yasmin® group) for years 2002-2007 (See Appendix 3 for Study CHCs Product Groups).

U.S. Census data were obtained to account for population growth over time for years 2002 through 2010.[4,5] The frequency of drosperinone-containing contraceptive products prescriptions dispensed per 100,000 US women was calculated by dividing the number of prescriptions dispensed by U.S. Census population estimates for women, multiplied by 100,000. Utilization data was adjusted for females of child-bearing potential by combining U.S. census age groups (ages 5-13 years, 14-17 years, and 18-64 years) to account for population growth in the population of interest.

SDI, Vector One®: Total Patient Tracker (TPT) was used to obtain estimates of the nationally projected number of patients receiving a dispensed prescription for drospirenone-containing products, and the combined hormonal contraceptive (CHC) market, stratified by age (0-25, 26-34, 35+ years), in the outpatient retail pharmacy setting for years 2002 through 2010.

Selected diagnoses, including body mass index (BMI), associated with the use of Yasmin®, Yaz®, and comparator CHCs, stratified by age (0-25, 26-34, 35+ years), were obtained from the SDI, Physician Drug and Diagnosis Audit™ (PDDA) for years 2001 through 2007. Although Yaz® was not a part of the FDA-funded study, data for this product was also analyzed. (See Appendix 4 for ICD-9 Diagnosis Codes)

Wolters Kluwer Health's Source® Lx database was used to compare treatment with Yasmin®, Yaz®, and study CHC products in women with one or more diagnosis codes for Acne (ICD-9

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[3] IMS Health, IMS National Sales Perspectives™. Year 2010. Data extracted October 2011. File: NSPC 2011-1044 Yaz Yasmin sales by channel Y2010 10-11.xls

[4] Annual Estimates of the Resident Population by Sex and Selected Age Groups for the United States: April 1, 2002 to July 1, 2009. U.S. Census Bureau, Population Division, U.S. Dept of Commerce. September 2011.

[5] Projections of the Population by Selected Age Groups and Sex for the United States: 2010 to 2050 U.S. Census Bureau, Population Division, U.S. Dept of Commerce. September 2011.

706.1) and Hirsutism (ICD-9 704.1), and/or Premenstrual Tension or PMDD (ICD-9 625.4). We obtained the projected number of unique patients with a prescription claim for Yasmin®, Yaz®, and study CHC products, stratified by age (0-25, 26-34, 35+ years), in the outpatient retail pharmacy setting for years 2007 through 2010, cumulative, using selected national drug codes (NDC). Patients with a prescription claim for Yasmin®, Yaz®, and study CHC products had their claims histories searched for selected ICD-9 diagnosis codes within 60 days of the prescription claim (see Appendix 3 for full list of NDCs and Appendix 4 for ICD-9 diagnosis codes).

2.3 PRODUCTS INCLUDED[6,7]

Indication and Usage

Yasmin® is a combined hormonal contraceptive indicated for the prevention of pregnancy in women who elect to use an oral contraceptive.

Yaz® is a combined hormonal contraceptive approved for the following indications:

1. Prevention of pregnancy
2. Premenstrual Dysphoric Disorder (PMDD)
3. Acne

Dosage and Administration

Yasmin® consists of 21 tablets of a monophasic combined hormonal preparation plus 7 inert tablets. The dosage of Yasmin® is one yellow tablet daily for 21 consecutive days followed by 7 white inert tablets per menstrual cycle.
Yasmin® contains 3 mg drospirenone (DRSP) and 0.03 mg ethinyl estradiol (EE) and is available in the following package size:
• Blister packs (NDC 50419-402-03)

Yaz® consists of 24 tablets of a monophasic combined hormonal preparation plus 4 inert tablets. The dosage of Yaz® is one light pink tablet daily for 24 consecutive days followed by 4 white inert tablets per menstrual cycle.
Yaz® contains 3 mg drospirenone (DRSP) and 0.02 mg ethinyl estradiol (EE) and is available in the following package size:
• Blister packs (NDC 50419-405-03)

Study Combined Hormonal Contraceptive (CHCs)

Study combined hormonal contraceptives include drospirenone/ethinyl estradiol, etonogestrel/ethinyl estradiol and norelgestromin/ethinyl estradiol. Comparators include levonorgestrel/ethinyl estradiol, norethindrone/ethinyl estradiol and norgestimate/ethinyl estradiol products. For the purpose of the prescription, patient, and indication analyses, we examined drospirenone/ethinyl estradiol and comparator products only.

Study CHC: 3.0 mg Drospirenone and 30 ug of Ethinyl Estradiol (DRSP): **Yasmin®**

Study CHC: 11.7 mg Etonogestrel and 2700 µg Ethinyl Estradiol (ETON): **Nuvaring®**

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[6] Yasmin Patient Label (http://www.yasmin-us.com/index.html)

[7] Yaz Patient Label (http://www.yaz-us.com/)

Study CHC: 6.0 mg Norelgestromin and 750 µg Ethinyl Estradiol (NGNM): **Ortho Evra Patch®**

Comparator CHC: 0.10 mg of Levonorgesetrel and 20 µg of Ethinyl Estradiol **(LNG 1)**

Comparator CHC: 0.15 mg of Levonorgesetrel and 30 µg of Ethinyl Estradiol **(LNG 2)**

Comparator CHC: 1 mg Norethindrone Acetate and 20 µg of Ethinyl Estradiol **(NETA)**

Comparator CHC: 0.18-0.25 mg of Norgestimate and 35 µg of Ethinyl Estradiol **(NGM)**

Data for Yaz® (3.0 mg Drospirenone and 20 µg Ethinyl Estradiol) from approval in March 2006 to December 2007 were also analyzed with the Study CHC products.

(see Appendix 3 for Study CHCs Product Group and NDC Code)

3 RESULTS

3.1 DROSPERINONE-CONTAINING CONTRACEPTIVE PRODUCTS SALES DATA, Y2006-2010

Figure 1 shows the sales data for drospirenone-containing products by the number of eaches (packages, boxes, etc.) sold from manufacturers to various retail and non-retail channels of distribution for years 2006 through 2010. In year 2010, there were 10.7 million packages of drospirenone 3mg/ethinyl estradiol 20 µg products (Yaz® group) distributed, a decrease from a peak in sales in year 2009 (14.1 million packages). Sales of drospirenone 3mg/ethinyl estradiol 30 µg products (Yasmin® group) decreased by 47% in sales from 15.2 million packages sold in year 2006 to 8 million packages in year 2010.

3.2 PROJECTED NUMBER OF DISPENSED PRESCRIPTIONS FOR THE CONTRACEPTIVE MARKET, Y2002-2010

Table 1 displays the projected number of dispensed prescriptions for the hormonal contraceptive market by Uniform System of Classification code (USC code) in U.S. outpatient retail pharmacies. From year 2002 to 2004, there was a 6% increase in the projected number of dispensed prescriptions (from 92.8 million to 98.5 million prescriptions) primarily due to market growth in other contraceptives (USC 33390). The other contraceptive drug class includes combined hormonal contraceptives available in **non-oral** dosage form [(e.g. patch (Ortho Evra®) or vaginal ring (Nuvaring®)]. Between years 2004 to 2006, the total projected number of dispensed prescriptions for all contraceptives decreased by 11% (from 98.5 million to 87.3 million prescriptions). In year 2010, approximately 83.7 million prescriptions were dispensed in the hormonal contraceptive market, a net decrease of 10% since year 2002. Throughout the review period, the combined hormonal contraceptives class (USC 33230) and the other contraceptives class (USC 33390) accounted for 96%-97% of the annual prescription share combined. All other contraceptives accounted for 3%-4% of the annual prescription share combined.

3.3 PROJECTED NUMBER OF DISPENSED PRESCRIPTIONS FOR DROSPIRENONE-CONTAINING PRODUCTS, Y2002-2010

Table 2 shows the projected number of dispensed prescriptions for drospirenone-containing products by patient age in U.S. outpatient retail pharmacies. In year 2002, drosperinone-containing contraceptive products accounted for 4% of the combined hormonal contraceptive (CHC) market (USC 33230 and USC 33390). The projected number of dispensed prescriptions for drosperinone-containing contraceptive products increased 5-fold between years 2002 to 2008

(from 3.3 million to 18.4 million prescriptions). However from year 2008 to 2010, market share decreased from 21% of the CHC market in year 2008 to 16% in year 2010. By year 2010, drosperinone-containing contraceptive products accounted for 12.9 million prescriptions; a net 4-fold increase of drosperinone-containing contraceptive products prescriptions since year 2002.

For drospirenone 3mg/ethinyl estradiol 20 µg products (Yaz® group), women aged 0-25 years accounted for a larger proportion of prescriptions than for drospirenone 3mg/ethinyl estradiol 30 µg products (Yasmin® group). For the (Yasmin® group), women aged 0-25 years accounted for 36%-48% of the prescription share annually, followed by women aged 26-34 years at 29%-35% of the annual prescription share. Women 35 years or older accounted for 23%-29% of the annual Yasmin® group prescription share. For the (Yaz® group), prescriptions dispensed to women aged 0-25 years accounted for 49%-56% of the prescription share followed by women age 26-34 years at 24%-26% of the prescription share. Women 35 years or older accounted for 20%-25% of the prescription share.

Figure 2 shows the projected number of prescriptions for all drospirenone-containing products dispensed to U.S. women (prescriptions/100,000 women) from outpatient retail pharmacies for years 2002 through 2010. Utilization data was adjusted for U.S. females of child-bearing potential by U.S. census age groups (ages 5-13 years, 14-17 years, and 18-64 years) to account for U.S. population growth in the population of interest. In year 2010, there were 4659 Yasmin® group prescriptions per 100,000 U.S. women, a 46% decrease from a peak of 8664 Yasmin® group prescriptions per 100,000 U.S. women dispensed in year 2006. In year 2010, there were 5686 Yaz® group prescriptions per 100,000 U.S. women, a 31% decrease from a peak of 8221 Yaz® group prescriptions per 100,000 U.S. women dispensed in year 2008.

3.4 Projected Number of Patients for Drospirenone-Containing Products, Y2002-2010

Table 3 shows the projected number of patients for drospirenone-containing products by patient age in U.S. outpatient retail pharmacies. In year 2002, drosperinone-containing contraceptive products accounted for 4% of patients in the combined hormonal contraceptive (CHC) market (USC 33230 and USC 33390). The projected number of patients who received a dispensed prescription of drosperinone-containing contraceptive products increased from 863,000 patients in year 2002 to 3.65 million patients in year 2008. By year 2010, drosperinone-containing contraceptive products accounted for 14% of the CHC market (2.55 million patients). There was a net 3-fold increase in the number of patients who received a dispensed prescription for drosperinone-containing contraceptive products from year 2002 to 2010.

Similar to prescription data, for drospirenone 3mg/ethinyl estradiol 20 µg products (Yaz® group), women aged 0-25 years accounted for a larger proportion of patients than for drospirenone 3mg/ethinyl estradiol 30 µg products (Yasmin® group). For the Yasmin® group, women aged 0-25 years accounted for a slightly larger proportion of the patient share at 40%-50% followed by women aged 26-34 years at 31%-35% of the patient share. Women 35 years or older accounted for 21%-27% of the patient share. For the Yaz® group, women aged 0-25 years accounted for 50%-57% of the patient share followed by women aged 26-34 years at 26%-27% of the prescription share. Women 35 years or older accounted for 19%-24% of the Yaz® patient share.

3.5 Projected Number of Dispensed Prescriptions for Yasmin® and Study Combined Hormonal Contraceptives (CHCs), Y2002-2007

Table 4 provides the projected number of dispensed prescriptions for the selected combined hormonal contraceptives (CHCs) products included in the FDA-funded study, by product group

and patient age in U.S. outpatient retail pharmacies, years 2002 to 2007 (See Appendix 3 for full list of products). The projected number of dispensed prescriptions for all study and comparator CHC products ranged from 40.2 million to 49.2 million prescriptions, annually. Yasmin® (DRSP) accounted for the majority of the prescription share in the study CHCs group (39% to 70% of Study CHCs) and norgestimate (NGM) accounted for the majority of the prescription share in the comparator CHCs (44.5% to 60% of Comparator CHCs) for the study period.

For NGM, the age distribution was similar to Yasmin® with women aged 0-25 years accounting for a slightly larger proportion of the prescription share at 46%-50%, followed by women aged 26-34 years at 34%-35% of the prescription share. In other comparator CHCs, women 35 years or older accounted for a larger proportion of the prescription share for norethindrone acetate (NETA) at 42%-64% and levonorgestrel (LNG 2) products at 38%-42% of prescriptions. For levonorgestrel (LNG 1), women aged 0-25 years and 35 years or older accounted for a slightly larger proportion of the prescription share followed by women aged 26-34 years.

3.6 Selected Diagnoses Associated with the Use of Yaz®, Yasmin®, and Study Combined Hormonal Contraceptives (CHCs), Y2001-2007

We also examined selected diagnoses associated with the use of Yaz® ,Yasmin®, and FDA-funded study CHCs by patient age for year 2001 to 2007, cumulative (**Table 5**). Although Yaz® was not included in the FDA-funded study, data for Yaz® up to year 2007 were presented in this analysis. According to office-based physician practices in the U.S., the most common diagnosis codes associated with the use of study CHC products for all age groups were "Contraceptive Surveillance" (ICD-9 V25.4) or "Contraceptive Mgmt-Counsel" (ICD-9 V25.0) at a combined 84%-97% of drug mentions followed by "Dysmenorrhea" (ICD-9 625.3) at 2%-8% of drug mentions. For Yasmin®, Yaz®, and norgestimate (NGM), "Acne" (ICD-706.1) accounted for 2%-5% of drug mentions in women aged 0-25 years and 1%-2% of drug mentions in women aged 26-34 years. It is worth noting that polycystic ovary syndrome (PCOS) only appears in visits for Yasmin and Yaz, and not for the other contraceptive products. The frequencies, however, are quite low.

3.7 Yaz®, Yasmin®, and Study Combined Hormonal Contraceptives (CHCs) by BMI, Y2001-2007

Table 6 and Figure 3 show the proportion of drug occurrences for Yaz®, Yasmin®, and study CHC products by body mass index (BMI) in women aged (0-25 years) as reported by U.S. office-based physician practices for years 2001 to 2007, cumulative. For the study period, the proportion of women (0-25 years) with a BMI of 30 or greater was 10% or 200,000 drug occurrences (95% CI, 136,000-264,000) for Yaz® and 8% or 586,000 drug occurrences (95% CI, 477,000-696,000) for Yasmin®. Among the study CHC products, women with a BMI of 0-18 (underweight) ranged from 2%-5% of drug occurrences; BMI of 19-24 (normal weight) ranged from 42%-58%; BMI of 25-29 (overweight) ranged from 13%-22%; BMI of 30-39 (obese) ranged from 4%-10%; and a BMI of 40+ (morbidly obese) at 1%-3% of drug occurrences for study CHC products. BMI was unknown for approximately 14-35% of drug occurrences in women aged 0-25 years.

Table 6 and Figure 4 show the proportion of drug occurrences for Yaz®, Yasmin®, and study CHC products by body mass index (BMI) in women aged (26-34 years) as reported by U.S. office-based physician practices for years 2001 to 2007, cumulative. The proportion of women aged 26-34 years with a BMI of 30 or greater was 15% or 200,000 drug occurrences (95% CI, 136,000-264,000) for Yaz® and 13% or 735,000 drug occurrences (95% CI, 612,000-857,000)

for Yasmin®. Among the study CHC products, women with a BMI of 0-18 (underweight) ranged from 1%-2% of drug occurrences; BMI of 19-24 (normal weight) ranged from 33%-55%; BMI of 25-29 (overweight) ranged from 20%-23%; BMI of 30-39 (obese) ranged from 9%-12%; and a BMI of 40+ (morbidly obese) at 1%-3% for study CHC products. BMI was unknown for approximately 11-33% of drug occurrences in women aged 26-34 years.

Table 6 and Figure 5 show the proportion of drug occurrences for Yaz®, Yasmin®, and study CHC products by body mass index (BMI) in women aged (35+ years) as reported by U.S. office-based physician practices for years 2001 to 2007, cumulative. The proportion of women aged 35+ years with a BMI of 30 or greater was 10% or 73,000 drug occurrences (95% CI, 34,000-111,000 for Yaz® and 14% or 355,000 drug occurrences (95% CI, 270,000-440,000) for Yasmin® in women (35+ years). Among the study CHC products, women with a BMI of 0-18 (underweight) ranged from 1%-3.5% of drug occurrences; BMI of 19-24 (normal weight) ranged from 31%-45%; BMI of 25-29 (overweight) ranged from 17%-32%; BMI of 30-39 (obese) ranged from 6%-18%; and a BMI of 40+ (morbidly obese) at 2%-4% for study CHC products. BMI was unknown for approximately 13-29.5% of drug occurrences in women aged 35+ years.

3.8 YASMIN®/YAZ® AND STUDY COMBINED HORMONAL CONTRACEPTIVES (CHCS) FOR ONE OR MORE SELECTED DIAGNOSES, Y2007-2010

We also examined the projected number of patients (0-25, 26-34, 35+ years) with a prescription claim for a study CHC product either preceded or followed by a medical claim with one or more diagnosis codes for Acne (ICD-9 706.1), Hirsutism (ICD-9 704.1), and/or Premenstrual Tension or PMDD (ICD-9 625.4) for years 2007 to 2010. The percentages of patients with claims for any of these diagnoses were low across users of all contraceptive products. Of the study CHC products, Yaz® and Yasmin® patients had the highest proportion of patients with one or more diagnoses for Acne (ICD-9 706.1), Hirsutism (ICD-9 704.1), and/or Premenstrual Tension or PMDD (ICD-9 625.4) among the examined CHC product groups. Of patients aged 0-25 years, 2.3% of patients with a prescription claim for Yaz® and 2.0% of patients for Yasmin® had one or more of the examined diagnoses.(**Figure 6)** Of patients aged 26-34 years, 1.4% of patients with a prescription claim for Yaz® and 1.2% of patients for Yasmin® had one or more diagnoses.(**Figure 7)** In patients 35 years and older, 1.4% of patients for Yaz® and 1.0% of patients for Yasmin® had one or more diagnoses.(**Figure 8)**

4 DISCUSSION

By year 2010, drospirenone-containing contraceptive products accounted for 12.9 million prescriptions; a 4-fold increase in dispensed prescriptions since year 2002. However from year 2008 to 2010, market share decreased from 21% of the CHC market (18.4 million prescriptions) in year 2008 to 16% of the CHC market (12.9 million prescriptions) in year 2010. There was also a notable decrease in the use of the total contraceptive market from year 2004 to 2006, however the reasons are unknown at the time of this review, further investigations are pending. Our findings also show that users of Yasmin® and Yaz® were similar to users of norgestimate (NGM) products in relation to patient age, and to other comparator CHCs in terms of BMI distribution in women (0-25 years) for the study period. However, BMI was unknown for a large proportion of drug use mentions, so these findings should be interpreted with caution. Yasmin® and Yaz® products had the highest proportions of patients with one or more diagnoses for Acne (ICD-9 706.1), Hirsutism (ICD-9 704.1), and/or Premenstrual Tension or PMDD (ICD-9 625.4) for all age groups with a slightly larger proportion in younger women aged 0-25 years (2.3% of

Yaz® patients) and Yasmin® (2.0% of Yasmin® patients). The frequency of these diagnoses, however, was quite low.

The findings from this review should be interpreted in the context of the limitations of the data sources used to generate them. The sales analysis for drosperinone-containing contraceptive products was provided as the number of packages sold from the IMS Health, IMS National Sales Perspectives™. The sales estimates provided are national estimates, but no statistical tests were performed to determine statistically significant changes over time or between products. Therefore, all changes over time should be considered approximate, and may be due to random error. Furthermore, these data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution.

The data analyses for study CHCs by diagnosis and body mass index (BMI) were examined using office-based physician survey data. Analyses of data obtained from physician survey data should be interpreted with caution as sample sizes below 100,000 drug use mentions are very small with correspondingly large confidence intervals. It is important to note that several study CHC products captured in the prescription and patient data analyses were not captured in the PDDA database. SDI uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit. SDI uses the term "drug occurrences" to refer to the number of times a product has been reported on a patient information form during an office-based patient visit for that period. It is important to note that a "drug occurrence" does not necessarily result in a prescription being generated. A “drug occurrence” can result from a prescription written, a sample given, a recommendation for OTC products, recommendation with sample, a product dispensed or administered in the office, a hospital order, a nursing home order or a combination of these.

Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study. Furthermore, patient age subtotals may not sum exactly due to patients aging during the study period (“the cohort effect”), and may be counted more than once in the individual age categories. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts. It should also be noted that all prescription and patient-based analyses were based on dispensings from outpatient retail pharmacies, and do not apply to use of these products in other settings of care, such as clinics or mail order.

5 CONCLUSIONS

Findings for this analysis show that drospirenone-containing contraceptive products accounted for approximately 16% of the CHC market (12.9 million prescriptions) in year 2010. For users of the study combined hormonal contraceptive products (CHCs), Yasmin® (DRSP) and norgestimate (NGM), women aged 0-25 years accounted for a slightly larger proportion of the prescription share followed by women aged 26-34 years and women aged 35 years or older. The comparator CHCs, levonorgestrel (LNG 2) and norethindrone acetate (NETA) products accounted for a slightly larger proportion of the prescription share in women 35 years or older. For study CHC products, the proportion of women aged 0-25 years with a BMI of 30 or greater was 10% for Yaz® and 8% for Yasmin®. The proportion of women aged 26-34 years with a BMI of 30 or greater was 15% for Yaz® and 13% for Yasmin® and 10% for Yaz® and 14% for Yasmin® in women aged 35+ years. The BMI data for Yaz® and Yasmin® were comparable to

the other study CHCs, however the BMI was unknown in a large proportion of drug occurrences, so these results should be interpreted with caution. A diagnosis mention of polycystic ovary syndrome (PCOS) only appeared in visits for Yasmin and Yaz, and not for the other contraceptive products. The frequency of these diagnoses, however, was quite low. Yaz® and Yasmin® had the highest proportion of patients with one or more diagnoses for Acne (ICD-9 706.1), Hirsutism (ICD-9 704.1), and/or Premenstrual Tension or PMDD (ICD-9 625.4) for all age groups with a slightly larger proportion in younger women aged 0-25 years (2.3% of Yaz® patients) and Yasmin® (2.0% of Yasmin® patients). However, these frequencies were very low and should be interpreted with caution.

6 APPENDIX 1: FIGURES AND TABLES

Figure 1: Number of eaches (packages, boxes, etc.) sold of drospirenone-containing products from manufacturers to retail and non-retail channels of distribution, years 2006-2010

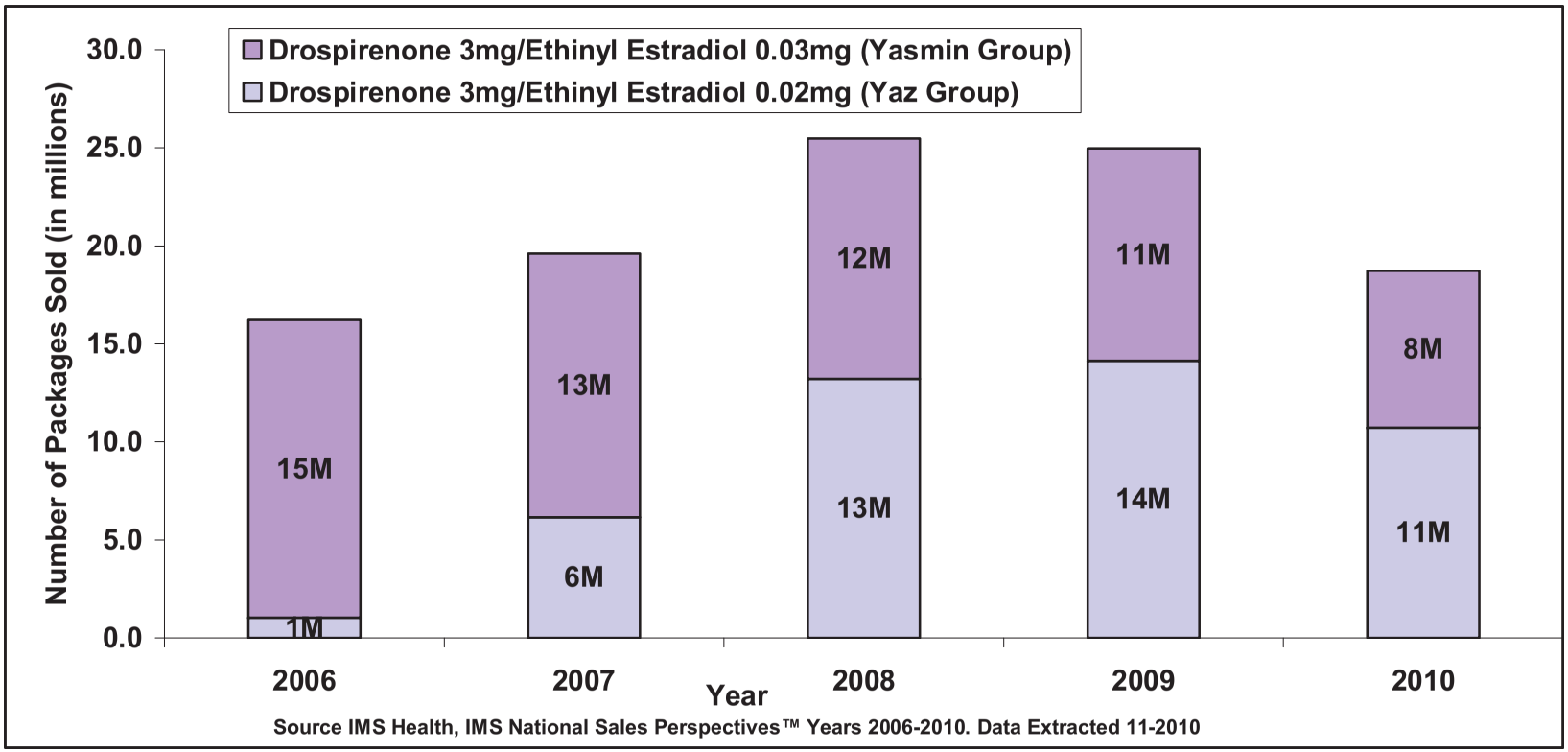


Table 1. Projected number of dispensed prescriptions for the Contraceptive Market by Uniform System of Classification (USC) Code in U.S. outpatient retail pharmacies, Y2002-2010

	2002		2003		2004		2005		2006		2007		2008		2009		2010	
	TRxs	Share	TRxs	Share	TRxs	Share	TRxs	Share	TRxs	Share	TRxs	Share	TRxs	Share	TRxs	Share	TRxs	Share
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Contraceptive Market	**92,791,653**	***100.0%***	**96,500,185**	***100.0%***	**98,513,793**	***100.0%***	**97,547,278**	***100.0%***	**87,342,536**	***100.0%***	**87,189,932**	***100.0%***	**89,198,244**	***100.0%***	**86,808,962**	***100.0%***	**83,699,314**	***100.0%***
33230 ESTROGEN-PROGEST.CMB,ORAL	88,307,131	*95.2%*	83,879,792	*86.9%*	83,238,580	*84.5%*	81,966,246	*84.0%*	75,628,399	*86.6%*	76,705,704	*88.0%*	79,324,352	*88.9%*	77,346,691	*89.1%*	74,335,607	*88.8%*
33390 CONTRACEPTIVES, OTHER*	1,585,995	*1.7%*	9,492,567	*9.8%*	11,792,324	*12.0%*	11,973,282	*12.3%*	8,287,607	*9.5%*	7,306,862	*8.4%*	6,634,733	*7.4%*	6,203,319	*7.1%*	6,069,124	*7.3%*
33210 W/O ESTROGENS, ORAL	2,768,283	*3.0%*	3,014,207	*3.1%*	3,381,397	*3.4%*	3,520,782	*3.6%*	3,354,818	*3.8%*	3,119,047	*3.6%*	3,193,006	*3.6%*	3,209,612	*3.7%*	3,263,123	*3.9%*
33330 DIAPHRAGMS & KITS	99,064	*0.1%*	80,718	*0.1%*	74,150	*0.1%*	62,564	*0.1%*	51,570	*0.1%*	43,005	*0.0%*	32,358	*0.0%*	38,067	*0.0%*	28,610	*0.0%*
33310 FOAMS	24,542	*0.0%*	26,702	*0.0%*	22,084	*0.0%*	18,557	*0.0%*	16,190	*0.0%*	10,853	*0.0%*	9,199	*0.0%*	6,545	*0.0%*	1,142	*0.0%*
33110 INTRA-UTERINE DEVICES	462	*0.0%*	636	*0.0%*	728	*0.0%*	1,781	*0.0%*	585	*0.0%*	1,348	*0.0%*	2,151	*0.0%*	2,499	*0.0%*	776	*0.0%*
33320 CREAMS & JELLIES	6,042	*0.0%*	5,329	*0.0%*	4,495	*0.0%*	4,031	*0.0%*	3,336	*0.0%*	2,995	*0.0%*	2,362	*0.0%*	1,959	*0.0%*	654	*0.0%*
33120 SUBDERMAL IMPLANTS	61	*0.0%*	21	--	--	--	--	--	4	--	95	*0.0%*	80	*0.0%*	267	*0.0%*	276	*0.0%*
33350 SUPPOSITORIES	73	*0.0%*	213	*0.0%*	35	--	35	--	28	--	22	--	2	--	2	--	1	--

Source: SDI Vector One®: National, Years 2002-2010 Data Extracted October 2011. File: VONA_2011-1044_OC_Market_by_Class__10-22-11(1).xls

*USC Class 33390 includes contraceptives available in non-oral dosage forms (e.g. patches (Ortho Evra®) or vaginal ring (Nuvaring®))

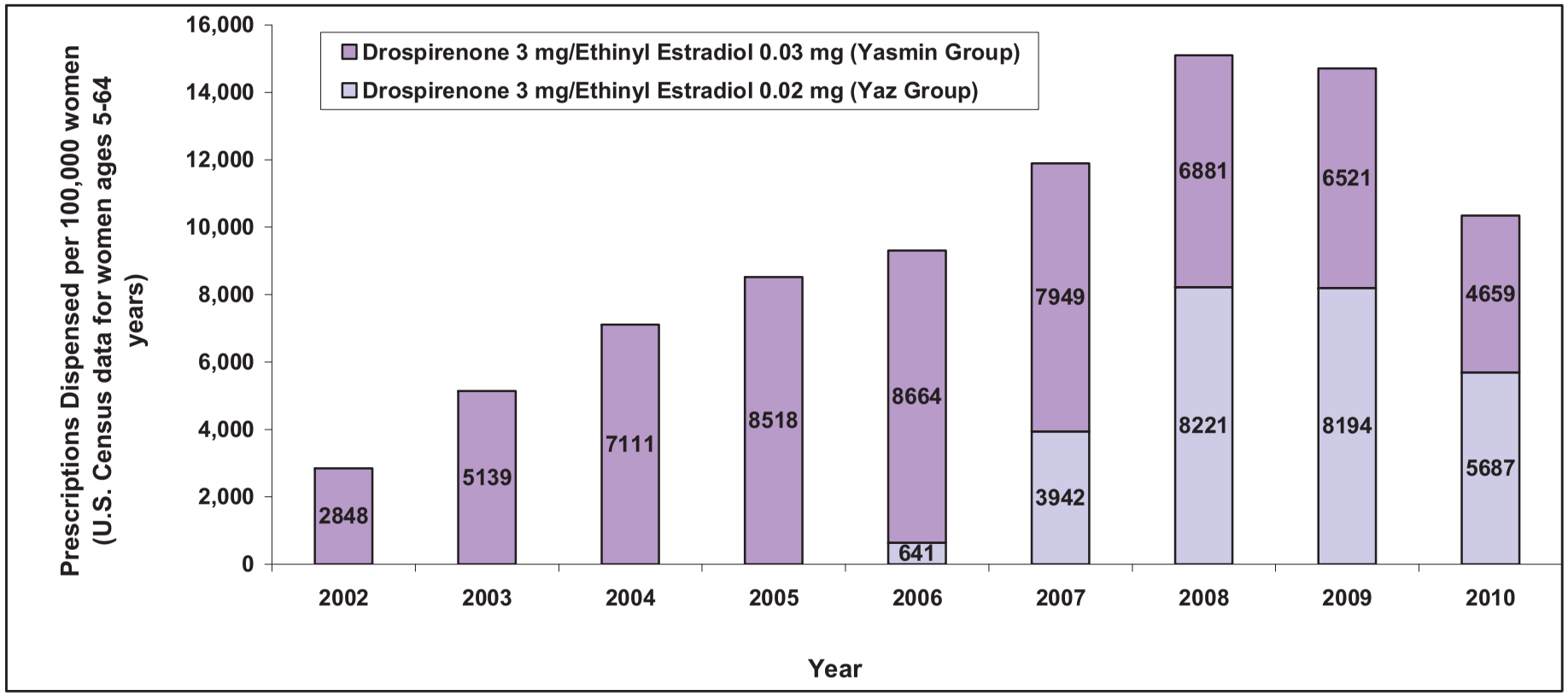
Table 2. Projected number of dispensed prescriptions for Drospirenone Products by Patient Age (0-25, 26-34, 35+ years) in Combined Hormonal Contraceptive (CHC) Market (USC 33230, 33390), Y2002-2010

	2002		2003		2004		2005		2006		2007		2008		2009		2010	
	TRxs	Share	TRxs	Share	TRxs	Share	TRxs	Share	TRxs	Share	TRxs	Share	TRxs	Share	TRxs	Share	TRxs	Share
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
CHC Market (USC 33230, 33390)	**89,895,285**	***100.0%***	**93,372,986**	***100.0%***	**95,030,774**	***100.0%***	**93,939,559**	***100.0%***	**83,916,005**	***100.0%***	**84,012,566**	***100.0%***	**85,853,585**	***100.0%***	**83,550,009**	***100.0%***	**80,404,731**	***100.0%***
ALL OTHER CHC	**86,584,712**	***96.3%***	**87,351,094**	***93.6%***	**86,622,722**	***91.2%***	**83,787,323**	***89.2%***	**72,758,842**	***86.7%***	**69,638,382**	***82.9%***	**67,484,925**	***78.6%***	**65,537,448**	***78.4%***	**67,551,204**	***84.0%***
0-25 years	28,121,773	*32.5%*	29,689,521	*34.0%*	29,819,039	*34.4%*	29,161,250	*34.8%*	27,248,546	*37.5%*	26,261,175	*37.7%*	25,680,972	*38.1%*	25,711,034	*39.2%*	27,809,092	*41.2%*
26-34 years	29,288,130	*33.8%*	28,879,913	*33.1%*	28,063,082	*32.4%*	26,433,838	*31.5%*	21,896,482	*30.1%*	20,861,904	*30.0%*	20,231,082	*30.0%*	19,434,377	*29.7%*	20,019,198	*29.6%*
35+ years	29,047,360	*33.5%*	28,640,256	*32.8%*	28,477,522	*32.9%*	27,918,440	*33.3%*	23,612,519	*32.5%*	22,514,776	*32.3%*	21,572,704	*32.0%*	20,391,831	*31.1%*	19,722,746	*29.2%*
Unknown Age	127,449	*0.1%*	141,404	*0.2%*	263,079	*0.3%*	273,795	*0.3%*	1,296	*0.0%*	526	*0.0%*	167	*0.0%*	206	*0.0%*	167	*0.0%*
Drospirenone Products	**3,310,507**	***3.7%***	**6,021,876**	***6.4%***	**8,408,057**	***8.8%***	**10,152,226**	***10.8%***	**11,157,163**	***13.3%***	**14,374,185**	***17.1%***	**18,392,449**	***21.4%***	**18,012,561**	***21.6%***	**12,853,527**	***16.0%***
Drospirenone 3 mg/Ethinyl Estradiol 0.02 mg (Yaz Group)	**0**	***0.0%***	**0**	***0.0%***	**0**	***0.0%***	**0**	***0.0%***	**768,255**	***6.9%***	**4,765,538**	***33.2%***	**9,999,242**	***54.4%***	**10,030,499**	***55.7%***	**7,064,780**	***55.0%***
0-25 years	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	376,920	*49.1%*	2,432,531	*51.0%*	5,457,650	*54.6%*	5,608,191	*55.9%*	3,805,212	*53.9%*
26-34 years	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	201,516	*26.2%*	1,255,369	*26.3%*	2,530,579	*25.3%*	2,432,471	*24.3%*	1,776,216	*25.1%*
35+ years	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	189,804	*24.7%*	1,077,612	*22.6%*	2,010,988	*20.1%*	1,989,826	*19.8%*	1,483,321	*21.0%*
Unknown Age	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	15	*0.0%*	26	*0.0%*	25	*0.0%*	11	*0.0%*	31	*0.0%*
Drospirenone 3 mg/Ethinyl Estradiol 0.03 mg (Yasmin Group)	**3,310,573**	***100.0%***	**6,021,892**	***100.0%***	**8,408,052**	***100.0%***	**10,152,236**	***100.0%***	**10,388,909**	***93.1%***	**9,608,647**	***66.8%***	**8,369,418**	***45.6%***	**7,982,062**	***44.3%***	**5,788,746**	***45.0%***
0-25 years	1,201,614	*36.3%*	2,392,633	*39.7%*	3,578,514	*42.6%*	4,495,409	*44.3%*	4,991,054	*48.0%*	4,576,617	*47.6%*	3,895,038	*46.5%*	3,722,323	*46.6%*	2,595,862	*44.8%*
26-34 years	1,144,026	*34.6%*	2,011,012	*33.4%*	2,690,542	*32.0%*	3,135,612	*30.9%*	3,029,583	*29.2%*	2,829,538	*29.4%*	2,523,513	*30.2%*	2,429,623	*30.4%*	1,825,759	*31.5%*
35+ years	960,355	*29.0%*	1,609,441	*26.7%*	2,118,985	*25.2%*	2,496,962	*24.6%*	2,368,127	*22.8%*	2,202,423	*22.9%*	1,950,846	*23.3%*	1,830,102	*22.9%*	1,367,119	*23.6%*
Unknown Age	4,578	*0.1%*	8,806	*0.1%*	20,011	*0.2%*	24,253	*0.2%*	145	*0.0%*	70	*0.0%*	21	*0.0%*	15	*0.0%*	6	*0.0%*

Source: SDI Vector One®: National, Years 2002-2010 Data Extracted October 2011. File: VONA_2011-1044_Drospirenone_by_Product_Age_11-1-11(1).xls; VONA 2011-1044 Dros products 2002-2010 TRx

†USC 33230 Oral CHCs; USC 33390 Non-oral CHCs (e.g. patch (Ortho Evra®) or vaginal ring (Nuvaring®)

Figure 2: Projected number of dispensed prescriptions for drosperinone-containing contraceptive products per 100,000 women (U.S. Census women ages 5-64 years) in U.S. outpatient retail pharmacies, Y2002-2010



*Annual Estimates of the Resident Population by Sex and Selected Age Groups for the United States: April 1, 2002 to July 1, 2009. U.S. Census Bureau, Population Division, U.S. Dept of Commerce. September 2011.

*Projections of the Population by Selected Age Groups and Sex for the United States: 2010 to 2050 U.S. Census Bureau, Population Division, U.S. Dept of Commerce. September 2011

Table 3. Projected number of patients for Drospirenone by Patient Age (0-25, 26-34, 35+ years) in Combined Hormonal Contraceptive (CHC) Market (USC 33230, 33390), Y2002-2010

	2002		2003		2004		2005		2006		2007		2008		2009		2010	
	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*
CHC Market (USC 33230, 33390)	17,401,974	*100.0%*	16,682,308	*100.0%*	17,104,745	*100.0%*	16,424,936	*100.0%*	14,919,816	*100.0%*	15,330,180	*100.0%*	15,222,087	*100.0%*	15,084,305	*100.0%*	15,349,371	*100.0%*
ALL OTHER CHC	16,774,602	*96.4%*	15,662,195	*93.9%*	15,647,499	*91.5%*	14,741,451	*89.8%*	13,002,952	*87.2%*	12,814,719	*83.6%*	12,208,796	*80.2%*	12,206,908	*80.9%*	13,186,396	*85.9%*
0-25 years	6,414,336	*38.2%*	6,302,332	*40.2%*	6,484,740	*41.4%*	6,192,061	*42.0%*	5,510,002	*42.4%*	5,439,977	*42.5%*	5,220,739	*42.8%*	5,322,350	*43.6%*	5,950,481	*45.1%*
26-34 years	5,769,149	*34.4%*	5,272,691	*33.7%*	5,217,280	*33.3%*	4,811,401	*32.6%*	4,163,006	*32.0%*	4,048,582	*31.6%*	3,873,118	*31.7%*	3,831,639	*31.4%*	4,115,943	*31.2%*
35+ years	5,051,246	*30.1%*	4,549,028	*29.0%*	4,438,497	*28.4%*	4,220,919	*28.6%*	3,736,850	*28.7%*	3,684,949	*28.8%*	3,455,074	*28.3%*	3,365,144	*27.6%*	3,440,492	*26.1%*
Unknown Age	7,006	*0.0%*	7,191	*0.1%*	960	*0.0%*	508	*0.0%*	303	*0.0%*	224	*0.0%*	106	*0.0%*	173	*0.0%*	129	*0.0%*
Drospirenone Products	862,744	*3.6%*	1,358,448	*6.1%*	1,819,513	*8.5%*	2,069,877	*10.2%*	2,342,862	*12.8%*	3,070,142	*16.4%*	3,651,370	*19.8%*	3,459,245	*19.1%*	2,552,573	*14.1%*
Drospirenone 3 mg/Ethinyl Estradiol 0.02 mg (Yaz Group)									322,047	*11.4%*	1,325,387	*39.3%*	2,230,479	*57.2%*	2,102,518	*57.3%*	1,506,713	*56.7%*
0-25 years									161,028	*50.0%*	700,736	*52.9%*	1,250,728	*56.1%*	1,201,027	*57.1%*	842,955	*56.0%*
26-34 years									87,132	*27.1%*	367,096	*27.7%*	600,957	*26.9%*	550,002	*26.2%*	404,949	*26.9%*
35+ years									76,400	*23.7%*	277,480	*20.9%*	420,759	*18.9%*	392,149	*18.7%*	288,286	*19.1%*
Unknown Age									7	*0.0%*	17	*0.0%*	21	*0.0%*	11	*0.0%*	10	*0.0%*
Drospirenone 3 mg/Ethinyl Estradiol 0.03 mg (Yasmin Group)	862,744	*100.0%*	1,358,448	*100.0%*	1,819,513	*100.0%*	2,069,877	*100.0%*	2,076,240	*88.6%*	1,863,582	*60.7%*	1,563,584	*42.8%*	1,475,550	*42.7%*	1,104,073	*43.3%*
0-25 years	344,550	*39.9%*	599,530	*44.1%*	861,699	*47.4%*	1,018,908	*49.2%*	1,045,862	*50.4%*	931,932	*50.0%*	772,839	*49.4%*	730,724	*49.5%*	531,141	*48.1%*
26-34 years	300,502	*34.8%*	459,347	*33.8%*	596,226	*32.8%*	655,277	*31.7%*	646,316	*31.1%*	581,954	*31.2%*	498,139	*31.9%*	473,620	*32.1%*	365,342	*33.1%*
35+ years	233,338	*27.1%*	330,017	*24.3%*	407,326	*22.4%*	451,425	*21.8%*	439,918	*21.2%*	398,872	*21.4%*	333,488	*21.3%*	310,353	*21.0%*	237,395	*21.5%*
Unknown Age	250	*0.0%*	417	*0.0%*	95	*0.0%*	59	*0.0%*	57	*0.0%*	56	*0.0%*	19	*0.0%*	12	*0.0%*	6	*0.0%*

*Subtotals may not sum exactly, due to rounding. Due to aging of patients during the study period ("the cohort effect"), patients may be counted more than once in the individual age categories. For this reason, summing across age bands is not advisable and will result in overestimates of patient counts. Source: SDI Total Patient Tracker. Years 2002-2010 Data Extracted October 2011 File: TPT 2011-1044 CHC Class by year 2002-2010 11-1-11.xls;TPT 2011-1044 CHC Class by year 2002-2010 no DRSP 11-1-11;TPT 2011-1044 Yasmin group by age 11-1-11.xls;TPT 2011-1044 Yaz group by age 11-1-11.xls

Table 4. Projected number of dispensed prescriptions for Study CHCs and Comparator Groups by Age, years 2002-2007

	2002		2003		2004		2005		2006		2007	
	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*
	N	%	N	%	N	%	N	%	N	%	N	%
Grand Total	**40,237,210**	***100.0%***	**47,121,338**	***100.0%***	**49,011,177**	***100.0%***	**49,191,419**	***100.0%***	**43,574,466**	***100.0%***	**42,788,698**	***100.0%***
Study CHCs	**4,723,969**	***11.7%***	**15,513,721**	***32.9%***	**20,200,316**	***41.2%***	**22,125,482**	***45.0%***	**18,676,490**	***42.9%***	**16,915,486**	***39.5%***
Yasmin 28	**3,310,573**	***70.1%***	**6,021,892**	***38.8%***	**8,408,052**	***41.6%***	**10,152,236**	***45.9%***	**10,388,909**	***55.6%***	**9,608,647**	***56.8%***
0-25 years	1,201,614	*36.3%*	2,392,633	*39.7%*	3,578,514	*42.6%*	4,495,409	*44.3%*	4,991,054	*48.0%*	4,576,617	*47.6%*
26-34 years	1,144,026	*34.6%*	2,011,012	*33.4%*	2,690,542	*32.0%*	3,135,612	*30.9%*	3,029,583	*29.2%*	2,829,538	*29.4%*
35+ years	960,355	*29.0%*	1,609,441	*26.7%*	2,118,985	*25.2%*	2,496,962	*24.6%*	2,368,127	*22.8%*	2,202,423	*22.9%*
Unknown Age	4,578	*0.1%*	8,806	*0.1%*	20,011	*0.2%*	24,253	*0.2%*	145	*0.0%*	70	*0.0%*
Norelgestromin (NGNM)	**1,273,010**	***26.9%***	**8,506,936**	***54.8%***	**9,955,957**	***49.3%***	**9,354,609**	***42.3%***	**4,481,192**	***24.0%***	**2,679,795**	***15.8%***
0-25 years	638,294	*50.1%*	4,137,175	*48.6%*	4,684,190	*47.0%*	4,360,220	*46.6%*	2,202,276	*49.1%*	1,235,504	*46.1%*
26-34 years	448,285	*35.2%*	3,026,884	*35.6%*	3,488,083	*35.0%*	3,189,801	*34.1%*	1,446,748	*32.3%*	893,421	*33.3%*
35+ years	182,993	*14.4%*	1,323,648	*15.6%*	1,726,721	*17.3%*	1,744,179	*18.6%*	832,104	*18.6%*	550,835	*20.6%*
Unknown Age	3,438	*0.3%*	19,229	*0.2%*	56,963	*0.6%*	60,409	*0.6%*	63	*0.0%*	35	*0.0%*
Etonogestrel (ETON)	**140,386**	***3.0%***	**984,893**	***6.3%***	**1,836,307**	***9.1%***	**2,618,637**	***11.8%***	**3,806,389**	***20.4%***	**4,627,044**	***27.4%***
0-25 years	51,594	*36.8%*	361,827	*36.7%*	668,149	*36.4%*	962,811	*36.8%*	1,627,623	*42.8%*	2,019,168	*43.6%*
26-34 years	56,208	*40.0%*	390,704	*39.7%*	714,925	*38.9%*	1,002,465	*38.3%*	1,387,804	*36.5%*	1,686,540	*36.4%*
35+ years	32,317	*23.0%*	230,788	*23.4%*	446,020	*24.3%*	641,269	*24.5%*	790,913	*20.8%*	921,298	*19.9%*
Unknown Age	267	*0.2%*	1,574	*0.2%*	7,213	*0.4%*	12,092	*0.5%*	49	*0.0%*	38	*0.0%*
Comparator CHCs	**35,513,241**	***88.3%***	**31,607,617**	***67.1%***	**28,810,861**	***58.8%***	**27,065,937**	***55.0%***	**24,897,977**	***57.1%***	**25,873,212**	***60.5%***
Norgestimate (NGM)	**21,330,636**	***60.1%***	**18,707,260**	***59.2%***	**15,551,890**	***54.0%***	**14,011,538**	***51.8%***	**12,255,994**	***49.2%***	**11,520,980**	***44.5%***
0-25 years	10,662,661	*50.0%*	9,271,377	*49.6%*	7,468,076	*48.0%*	6,439,629	*46.0%*	5,872,727	*47.9%*	5,368,966	*46.6%*
26-34 years	7,179,409	*33.7%*	6,281,596	*33.6%*	5,334,733	*34.3%*	4,927,957	*35.2%*	4,154,770	*33.9%*	3,963,849	*34.4%*
35+ years	3,453,252	*16.2%*	3,124,903	*16.7%*	2,702,269	*17.4%*	2,600,654	*18.6%*	2,228,223	*18.2%*	2,188,014	*19.0%*
Unknown Age	35,314	*0.2%*	29,384	*0.2%*	46,812	*0.3%*	43,298	*0.3%*	273	*0.0%*	151	*0.0%*
Norethindrone (NETA)	**4,028,417**	***11.3%***	**3,521,175**	***11.1%***	**3,551,615**	***12.3%***	**3,701,560**	***13.7%***	**4,101,372**	***16.5%***	**6,242,520**	***24.1%***
0-25 years	607,883	*15.1%*	540,496	*15.3%*	584,274	*16.5%*	637,618	*17.2%*	995,901	*24.3%*	2,084,504	*33.4%*
26-34 years	821,887	*20.4%*	720,810	*20.5%*	792,766	*22.3%*	854,491	*23.1%*	976,586	*23.8%*	1,541,226	*24.7%*
35+ years	2,596,266	*64.4%*	2,256,623	*64.1%*	2,169,160	*61.1%*	2,203,853	*59.5%*	2,128,818	*51.9%*	2,616,741	*41.9%*
Unknown Age	2,381	*0.1%*	3,246	*0.1%*	5,415	*0.2%*	5,598	*0.2%*	67	*0.0%*	49	*0.0%*
Levonorgestrel (LNG 1)	**7,159,073**	***20.2%***	**6,707,423**	***21.2%***	**6,456,520**	***22.4%***	**5,954,249**	***22.0%***	**5,326,680**	***21.4%***	**4,983,652**	***19.3%***
0-25 years	2,434,577	*34.0%*	2,284,265	*34.1%*	2,203,865	*34.1%*	2,032,186	*34.1%*	2,030,429	*38.1%*	1,964,105	*39.4%*
26-34 years	2,015,063	*28.1%*	1,845,169	*27.5%*	1,764,984	*27.3%*	1,630,665	*27.4%*	1,402,958	*26.3%*	1,336,061	*26.8%*
35+ years	2,698,320	*37.7%*	2,566,972	*38.3%*	2,471,015	*38.3%*	2,273,588	*38.2%*	1,893,179	*35.5%*	1,683,451	*33.8%*
Unknown Age	11,113	*0.2%*	11,017	*0.2%*	16,656	*0.3%*	17,810	*0.3%*	114	*0.0%*	36	*0.0%*
Levonorgestrel (LNG 2)	**2,995,115**	***8.4%***	**2,671,759**	***8.5%***	**3,250,836**	***11.3%***	**3,398,590**	***12.6%***	**3,213,931**	***12.9%***	**3,126,060**	***12.1%***
0-25 years	747,112	*24.9%*	668,837	*25.0%*	897,804	*27.6%*	1,002,266	*29.5%*	1,050,324	*32.7%*	1,013,960	*32.4%*
26-34 years	1,036,442	*34.6%*	885,304	*33.1%*	1,037,496	*31.9%*	1,045,382	*30.8%*	952,444	*29.6%*	935,484	*29.9%*
35+ years	1,207,155	*40.3%*	1,113,947	*41.7%*	1,306,126	*40.2%*	1,339,522	*39.4%*	1,211,143	*37.7%*	1,176,584	*37.6%*
Unknown Age	4,406	*0.1%*	3,671	*0.1%*	9,410	*0.3%*	11,420	*0.3%*	20	*0.0%*	31	*0.0%*

Source: SDI Vector One®: National, Years 2002-2007 Data Extracted October 2011. File: VONA_2011-1044_CHC_study_products_by_Age_10-27-11.xls

Table 5. Selected Diagnoses associated with the use* of Yasmin®/Yaz® and Study CHC Products† by patient age (0-25, 26-34, 35+) as reported by office-based physician practices, Y2001-2007

	1/2001-12/2007				
	Uses (000)	Share%		Uses (000)	Share%
Grand Total	**60,901**	***100.0%***		**60,901**	***100.0%***
Yasmin 28	**13,448**	***22.1%***	**Norgestimate (NGM)**	**17,451**	***28.7%***
0-25 years	6,269	*46.6%*	**0-25 years**	9,390	*53.8%*
V250 CONTRACEP MGMT-COUNSEL	3,253	*51.9%*	**V254 CONTRACEPT SURVEILLANCE**	4,961	*52.8%*
V254 CONTRACEPT SURVEILLANCE	2,390	*38.1%*	**V250 CONTRACEP MGMT-COUNSEL**	3,393	*36.1%*
6253 DYSMENORRHEA	341	*5.4%*	**6253 DYSMENORRHEA**	498	*5.3%*
2564 POLYCYSTIC OVARIES	114	*1.8%*	**7061 ACNE NEC**	448	*4.8%*
7061 ACNE NEC	100	*1.6%*	**All Others**	90	*1.0%*
All Others	70	*1.1%*	**26-34 years**	5,954	*34.1%*
26-34 years	5,056	*37.6%*	**V254 CONTRACEPT SURVEILLANCE**	3,797	*63.8%*
V254 CONTRACEPT SURVEILLANCE	2,434	*48.1%*	**V250 CONTRACEP MGMT-COUNSEL**	1,888	*31.7%*
V250 CONTRACEP MGMT-COUNSEL	2,205	*43.6%*	**7061 ACNE NEC**	141	*2.4%*
6253 DYSMENORRHEA	135	*2.7%*	**6253 DYSMENORRHEA**	92	*1.6%*
6254 PREMENSTRUAL TENSION	99	*2.0%*	**All Others**	36	*0.6%*
2564 POLYCYSTIC OVARIES	90	*1.8%*	**35+ years**	1,876	*10.8%*
7061 ACNE NEC	61	*1.2%*	**V254 CONTRACEPT SURVEILLANCE**	1,329	*70.9%*
All Others	32	*0.6%*	**V250 CONTRACEP MGMT-COUNSEL**	413	*22.0%*
35+ years	1,871	*13.9%*	**6253 DYSMENORRHEA**	83	*4.4%*
V254 CONTRACEPT SURVEILLANCE	1,017	*54.4%*	**All Others**	51	*2.7%*
V250 CONTRACEP MGMT-COUNSEL	634	*33.9%*	**UNSPEC**	232	*1.3%*
6253 DYSMENORRHEA	124	*6.6%*	**Levonorgestrel (LNG 1)**	**6,303**	***10.4%***
6254 PREMENSTRUAL TENSION	31	*1.7%*	**0-25 years**	2,753	*43.7%*
2564 POLYCYSTIC OVARIES	25	*1.4%*	**V254 CONTRACEPT SURVEILLANCE**	1,389	*50.5%*
3464 MENSTRUAL MIGRAINE	20	*1.1%*	**V250 CONTRACEP MGMT-COUNSEL**	1,197	*43.5%*
All Others	18	*1.0%*	**6253 DYSMENORRHEA**	138	*5.0%*
UNSPEC	253	*1.9%*	**All Others**	29	*1.1%*
Yaz	**3,443**	***5.7%***	**26-34 years**	2,077	*33.0%*
0-25 years	1,797	*52.2%*	**V254 CONTRACEPT SURVEILLANCE**	1,395	*67.2%*
V250 CONTRACEP MGMT-COUNSEL	1,044	*58.1%*	**V250 CONTRACEP MGMT-COUNSEL**	626	*30.2%*
V254 CONTRACEPT SURVEILLANCE	542	*30.2%*	**6253 DYSMENORRHEA**	28	*1.3%*
6253 DYSMENORRHEA	125	*6.9%*	**All Others**	28	*1.3%*
7061 ACNE NEC	36	*2.0%*	**35+ years**	1,419	*22.5%*
6254 PREMENSTRUAL TENSION	35	*1.9%*	**V254 CONTRACEPT SURVEILLANCE**	949	*66.9%*
All Others	16	*0.9%*	**V250 CONTRACEP MGMT-COUNSEL**	339	*23.9%*
26-34 years	1,073	*31.2%*	**6253 DYSMENORRHEA**	78	*5.5%*
V250 CONTRACEP MGMT-COUNSEL	608	*56.6%*	**6254 PREMENSTRUAL TENSION**	29	*2.0%*
V254 CONTRACEPT SURVEILLANCE	415	*38.7%*	**All Others**	24	*1.7%*
6253 DYSMENORRHEA	35	*3.3%*	**UNSPEC**	54	*0.9%*
All Others	15	*1.4%*	**Norethindrone (NETA)**	**4,864**	***8.0%***
35+ years	547	*15.9%*	**0-25 years**	1,665	*34.2%*
V250 CONTRACEP MGMT-COUNSEL	267	*48.8%*	**V250 CONTRACEP MGMT-COUNSEL**	897	*53.9%*
V254 CONTRACEPT SURVEILLANCE	195	*35.6%*	**V254 CONTRACEPT SURVEILLANCE**	693	*41.6%*
6253 DYSMENORRHEA	30	*5.5%*	**6253 DYSMENORRHEA**	58	*3.5%*
6254 PREMENSTRUAL TENSION	24	*4.4%*	**All Others**	18	*1.1%*
2564 POLYCYSTIC OVARIES	11	*1.9%*	**26-34 years**	1,472	*30.3%*
7061 ACNE NEC	10	*1.8%*	**V254 CONTRACEPT SURVEILLANCE**	741	*50.3%*
V252 STERILIZATION	6	*1.0%*	**V250 CONTRACEP MGMT-COUNSEL**	648	*44.0%*
All Others	5	*0.9%*	**6253 DYSMENORRHEA**	66	*4.5%*
UNSPEC	26	*0.7%*	**All Others**	17	*1.2%*
Norelgestromin (NGNM)	**7,520**	***12.4%***	**35+ years**	1,630	*33.5%*
0-25 years	3,918	*52.1%*	**V254 CONTRACEPT SURVEILLANCE**	1,050	*64.4%*
V250 CONTRACEP MGMT-COUNSEL	2,742	*70.0%*	**V250 CONTRACEP MGMT-COUNSEL**	492	*30.2%*
V254 CONTRACEPT SURVEILLANCE	1,023	*26.1%*	**6253 DYSMENORRHEA**	43	*2.6%*
6253 DYSMENORRHEA	142	*3.6%*	**All Others**	45	*2.7%*
All Others	11	*0.3%*	**UNSPEC**	97	*2.0%*
26-34 years	2,656	*35.3%*	**Levonorgestrel (LNG 2)**	**4,429**	***7.3%***
V250 CONTRACEP MGMT-COUNSEL	1,768	*66.6%*	**0-25 years**	1,389	*31.4%*
V254 CONTRACEPT SURVEILLANCE	816	*30.7%*	**V250 CONTRACEP MGMT-COUNSEL**	696	*50.1%*
6253 DYSMENORRHEA	68	*2.5%*	**V254 CONTRACEPT SURVEILLANCE**	562	*40.5%*
All Others	4	*0.2%*	**6253 DYSMENORRHEA**	110	*8.0%*
35+ years	874	*11.6%*	**All Others**	20	*1.5%*
V250 CONTRACEP MGMT-COUNSEL	535	*61.1%*	**26-34 years**	1,695	*38.3%*
V254 CONTRACEPT SURVEILLANCE	284	*32.5%*	**V250 CONTRACEP MGMT-COUNSEL**	821	*48.4%*
6270 PREMENOPAUSE MENORRHAGIA	35	*4.0%*	**V254 CONTRACEPT SURVEILLANCE**	797	*47.0%*
6253 DYSMENORRHEA	17	*2.0%*	**6253 DYSMENORRHEA**	54	*3.2%*
All Others	4	*0.5%*	**All Others**	23	*1.4%*
UNSPEC	72	*1.0%*	**35+ years**	1,264	*28.5%*
Etonogestrel (ETON)	**3,444**	***5.7%***	**V254 CONTRACEPT SURVEILLANCE**	738	*58.4%*
0-25 years	1,288	*37.4%*	**V250 CONTRACEP MGMT-COUNSEL**	395	*31.3%*
V250 CONTRACEP MGMT-COUNSEL	942	*73.1%*	**6253 DYSMENORRHEA**	95	*7.6%*
V254 CONTRACEPT SURVEILLANCE	301	*23.4%*	**3464 MENSTRUAL MIGRAINE**	22	*1.7%*
6253 DYSMENORRHEA	35	*2.7%*	**6254 PREMENSTRUAL TENSION**	14	*1.1%*
All Others	11	*0.8%*	**UNSPEC**	81	*1.8%*
26-34 years	1,572	*45.7%*			
V250 CONTRACEP MGMT-COUNSEL	1,060	*67.4%*			
V254 CONTRACEPT SURVEILLANCE	406	*25.8%*			
6253 DYSMENORRHEA	64	*4.1%*			
6254 PREMENSTRUAL TENSION	24	*1.6%*			
All Others	19	*1.2%*			
35+ years	535	*15.5%*			
V250 CONTRACEP MGMT-COUNSEL	364	*68.1%*			
V254 CONTRACEPT SURVEILLANCE	162	*30.3%*			
6253 DYSMENORRHEA	9	*1.6%*			
UNSPEC	49	*1.4%*			

Source: SDI Physician Drug and Diagnosis Audit, Years 2001-2007 Extracted October 2011. File: PDDA_2011-1044 _ CHC_ Study_ Products _by_AgeDx4_10-27-11.xls *Use - Projected uses for a product linked to a diagnosis. The projected number of times a product has been reported for treatment of a particular disease. See Appendix 4 for full list of ICD-9 Diagnosis Groups.

†Only study products with data available in PDDA were included

Table 6. Percentage of drug occurrences* for Yasmin/Yaz and Study CHC Products by BMI and patient age (0-25, 26-34, 35+) as reported by office-based physician practices, Y2001-2007

	01/2001-12/2007							
	Yasmin 28	Yaz	Levonorgestrel (LNG 1)	Levonorgestrel (LNG 2)	Norethindrone (NETA)	Norgestimate (NGM)	Ortho Evra	Etonogestrel (ETON)
	Vertical Share%							
0-25 years	**45.3%**	**49.6%**	**40.4%**	**31.3%**	**29.1%**	**53.1%**	**50.9%**	**36.8%**
BMI 0-18	3.7%	2.0%	4.5%	2.2%	2.2%	4.1%	3.2%	4.5%
BMI 19-24	54.3%	57.3%	58.1%	41.5%	57.9%	51.4%	52.3%	45.5%
BMI 25-29	13.8%	13.2%	16.7%	12.6%	15.4%	18.4%	21.9%	17.5%
BMI 30-39	6.4%	6.9%	4.4%	8.2%	8.1%	7.7%	7.6%	9.6%
BMI 40+	1.8%	2.8%	1.9%	0.8%	1.0%	0.9%	0.1%	2.5%
Unknown BMI	19.9%	17.9%	14.4%	34.7%	15.4%	17.5%	14.9%	20.5%
26-34 years	**36.5%**	**32.5%**	**30.9%**	**36.2%**	**25.4%**	**34.1%**	**35.1%**	**43.8%**
BMI 0-18	1.1%	1.9%	2.3%	0.8%	0.9%	2.1%	2.3%	1.6%
BMI 19-24	44.5%	44.8%	44.7%	32.6%	43.3%	48.8%	47.0%	54.6%
BMI 25-29	22.1%	21.2%	22.6%	20.3%	22.7%	20.9%	23.1%	22.5%
BMI 30-39	10.1%	12.1%	11.5%	10.2%	11.9%	10.7%	10.3%	9.3%
BMI 40+	2.6%	2.7%	2.0%	3.2%	1.8%	1.3%	1.3%	1.3%
Unknown BMI	19.6%	17.3%	16.9%	32.9%	19.5%	16.3%	16.0%	10.6%
35+ years	**16.3%**	**17.3%**	**27.8%**	**30.9%**	**43.6%**	**11.5%**	**13.1%**	**17.9%**
BMI 0-18	2.2%	0.0%	0.7%	0.5%	0.7%	3.5%	2.2%	1.2%
BMI 19-24	37.5%	39.5%	39.8%	36.0%	42.4%	45.2%	30.8%	42.3%
BMI 25-29	25.1%	31.8%	27.5%	21.6%	25.5%	17.3%	30.2%	25.7%
BMI 30-39	11.8%	5.9%	16.9%	10.2%	11.1%	11.4%	18.2%	11.5%
BMI 40+	2.0%	4.2%	2.0%	2.2%	2.8%	2.5%	1.7%	2.1%
Unknown BMI	21.4%	18.7%	13.1%	29.5%	17.5%	20.1%	17.0%	17.2%

Source: SDI Physician Drug and Diagnosis Audit, Years 2001-2007 Extracted October 2011. File: PDDA_2011-1044_CHC_Study_Products_by_BMI_10-27-11(1).xls A *Drug occurrence can result from a prescription written, a sample given, a recommendation for OTC products, recommendation with sample, a product dispensed or administered in the office, a hospital order, a nursing home order or a combination of these.

†**Only study products with data available in PDDA were included**

Figure 3: Proportion of Drug Occurrences of Yasmin®/Yaz® and Combined Hormonal Contraceptive (CHCs) Comparators by BMI for patients aged 0-25 years as reported by office-based physician practices, Y2001-2007

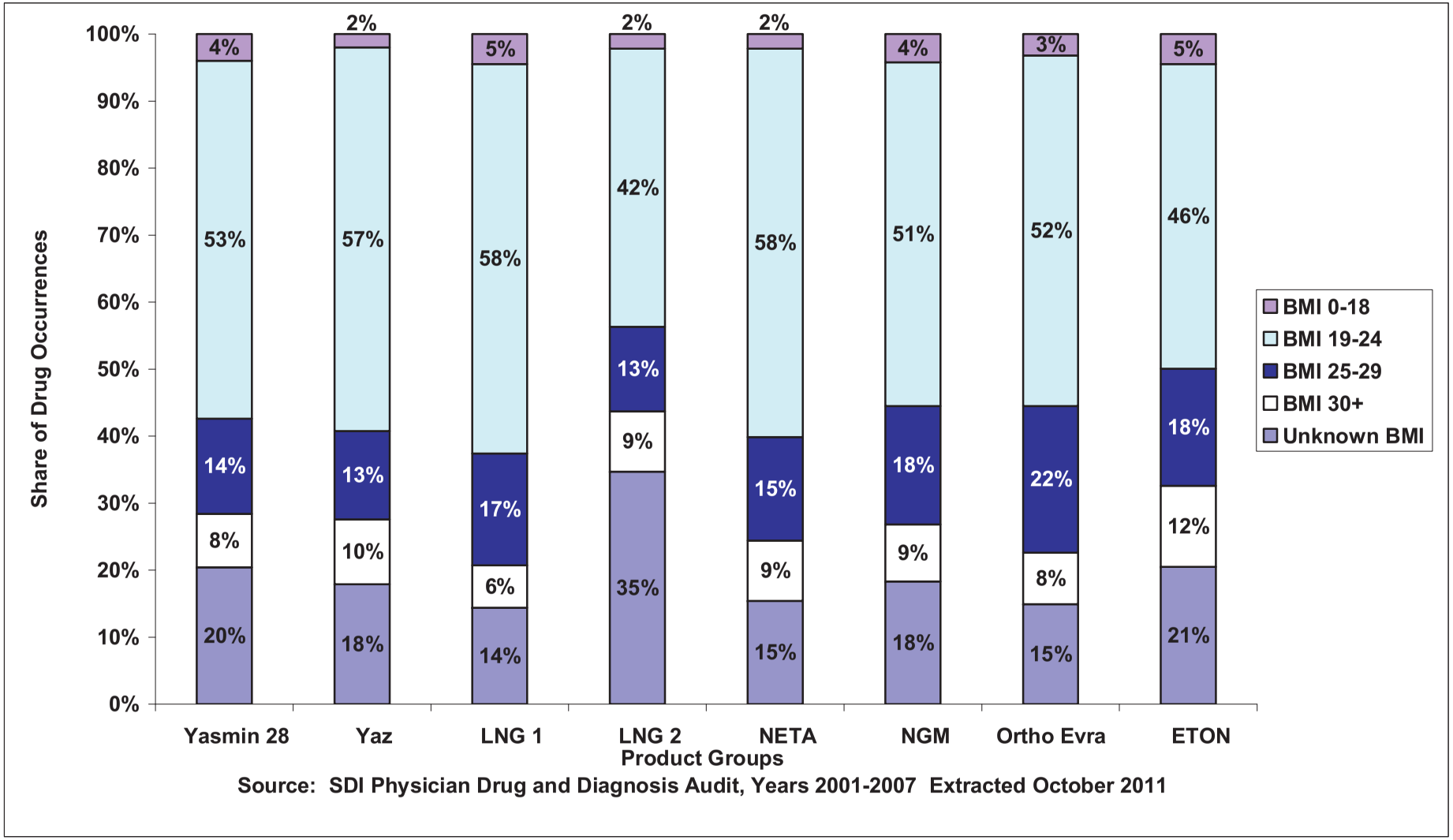


Figure 4: Proportion of Drug Occurrences of Yasmin®/Yaz® and Combined Hormonal Contraceptive (CHCs) Comparators by BMI for patients aged 26-34 years as reported by office-based physician practices, Y2001-2007

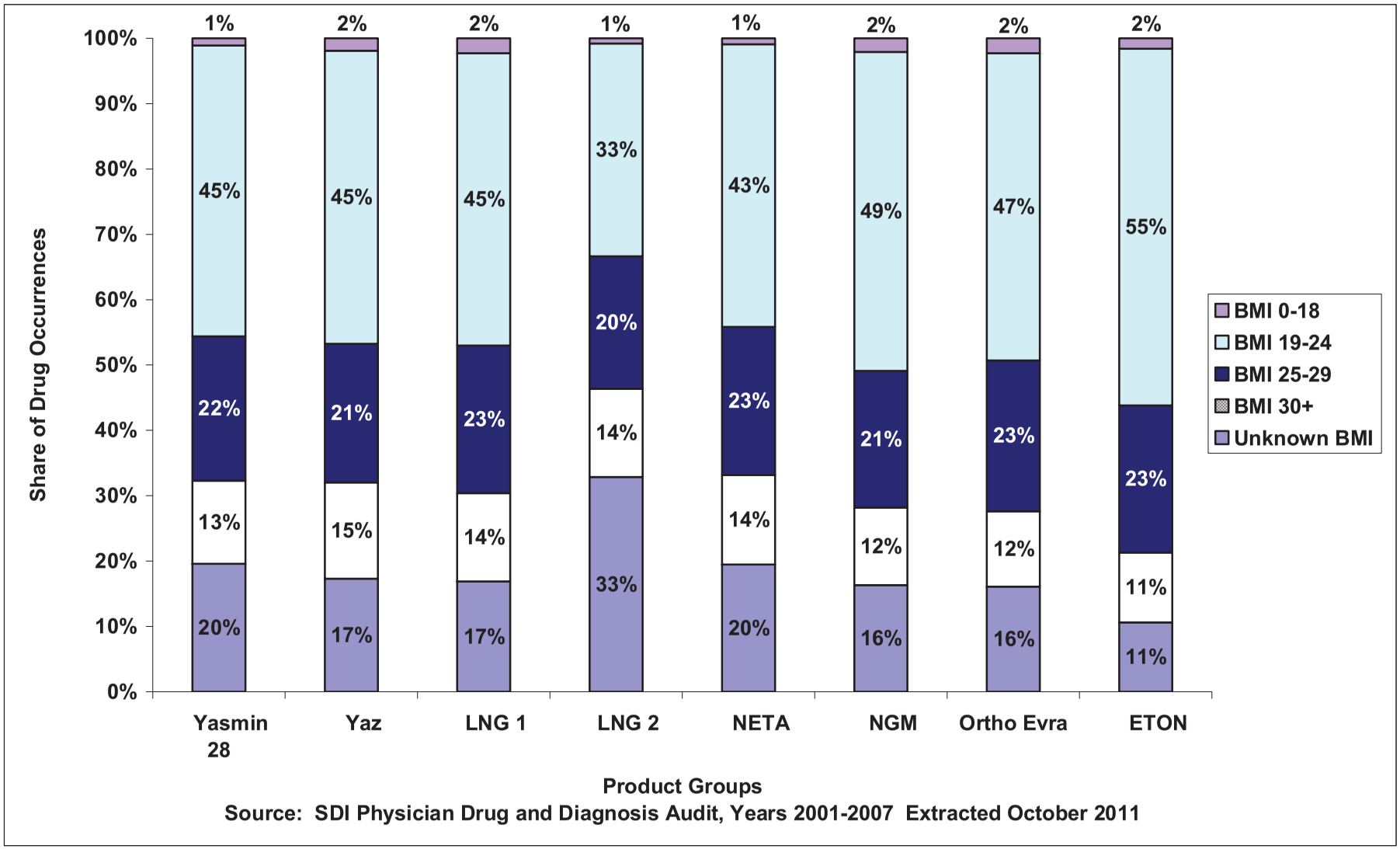
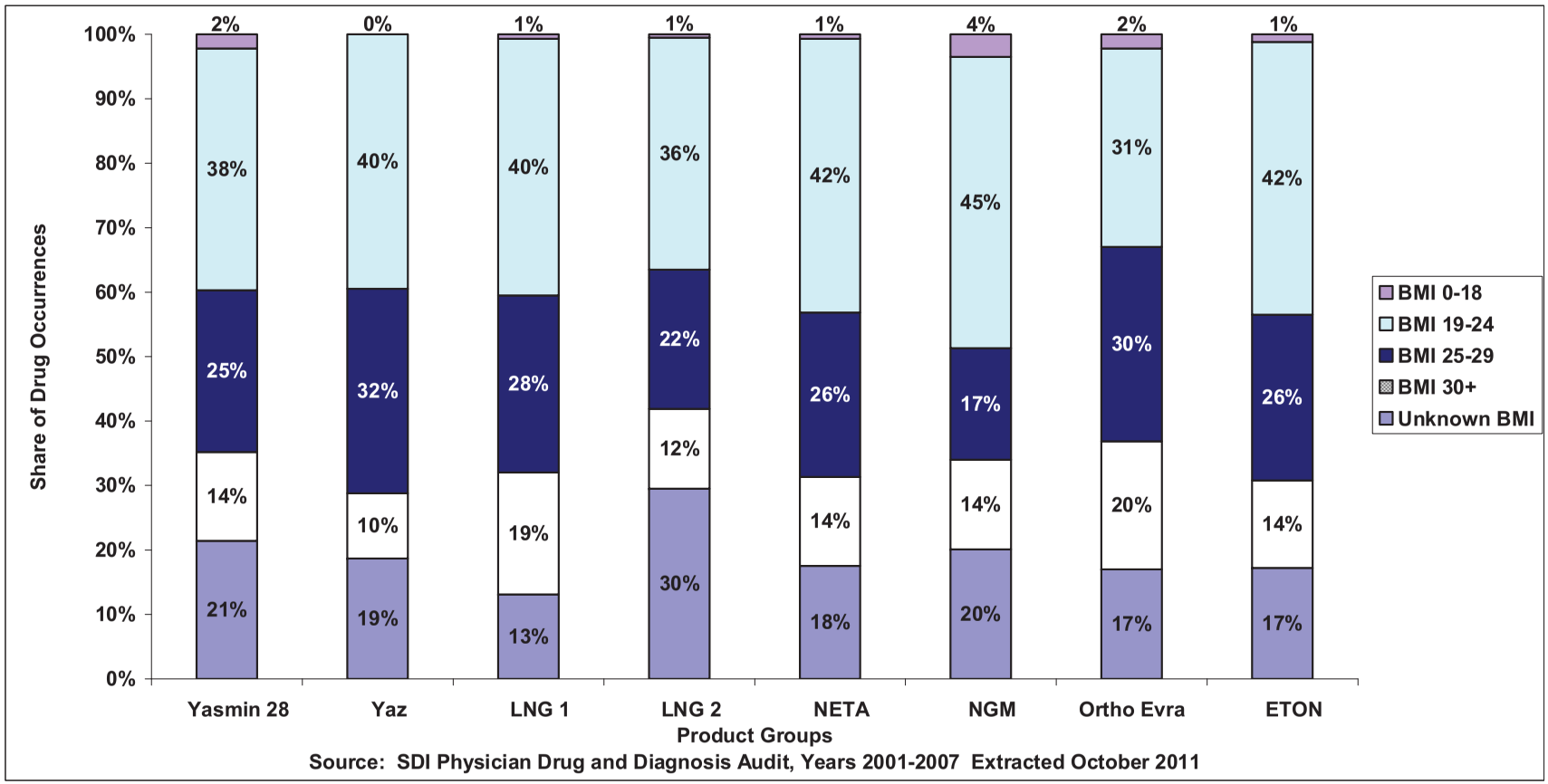


Figure 5: Proportion of Drug Occurrences of Yasmin®/Yaz® and Combined Hormonal Contraceptive (CHCs) Comparators by BMI for patients aged 35+ years as reported by office-based physician practices, Y2001-2007



Source: SDI Physician Drug and Diagnosis Audit, Years 2001-2007 Extracted October 2011

Figure 6: Yasmin®/Yaz® and Combined Hormonal Contraceptive (CHCs) Comparators for One or More Selected Diagnoses (Age 0-25 years), Y2007-2010

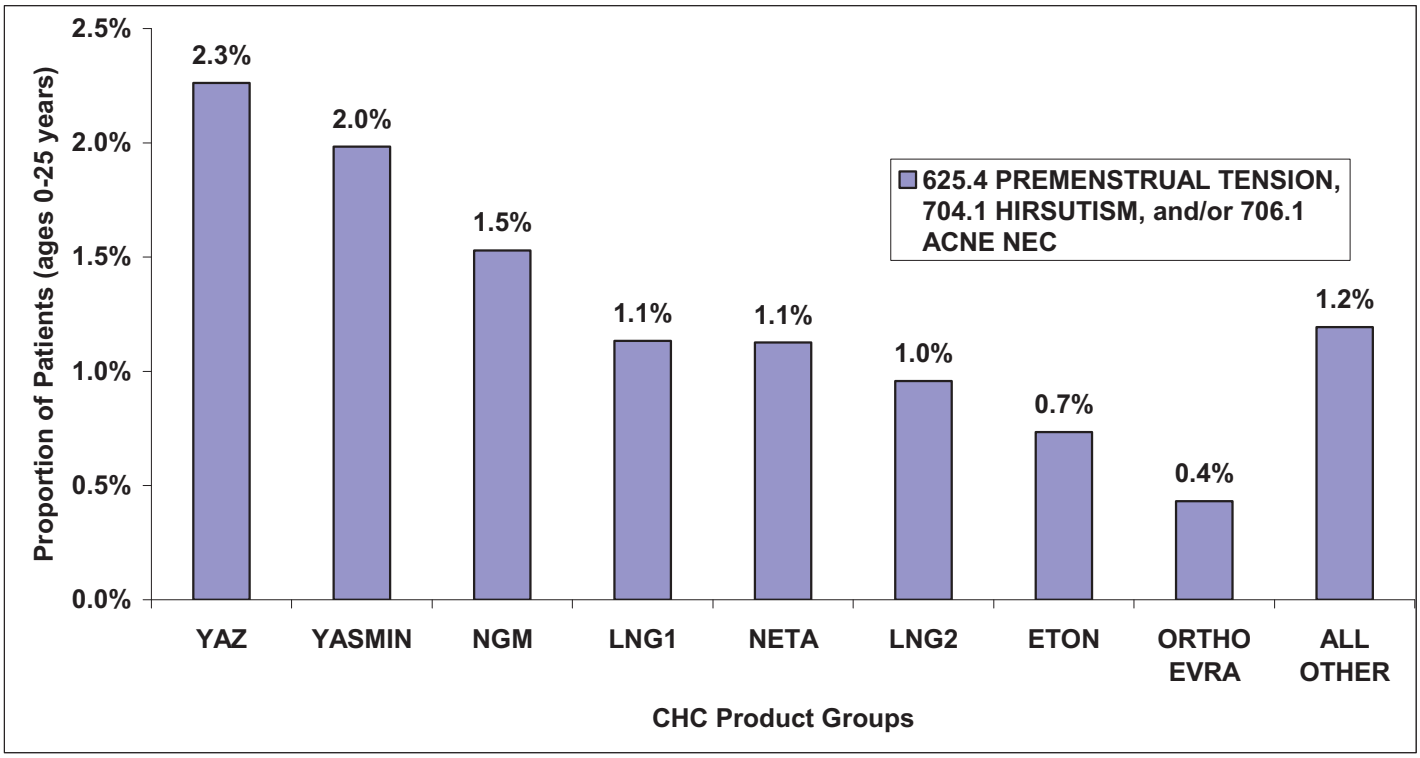


Figure 7: Yasmin®/Yaz® and Combined Hormonal Contraceptive (CHCs) Comparators for One or More Selected Diagnoses (Age 26-34 years), Y2007-2010

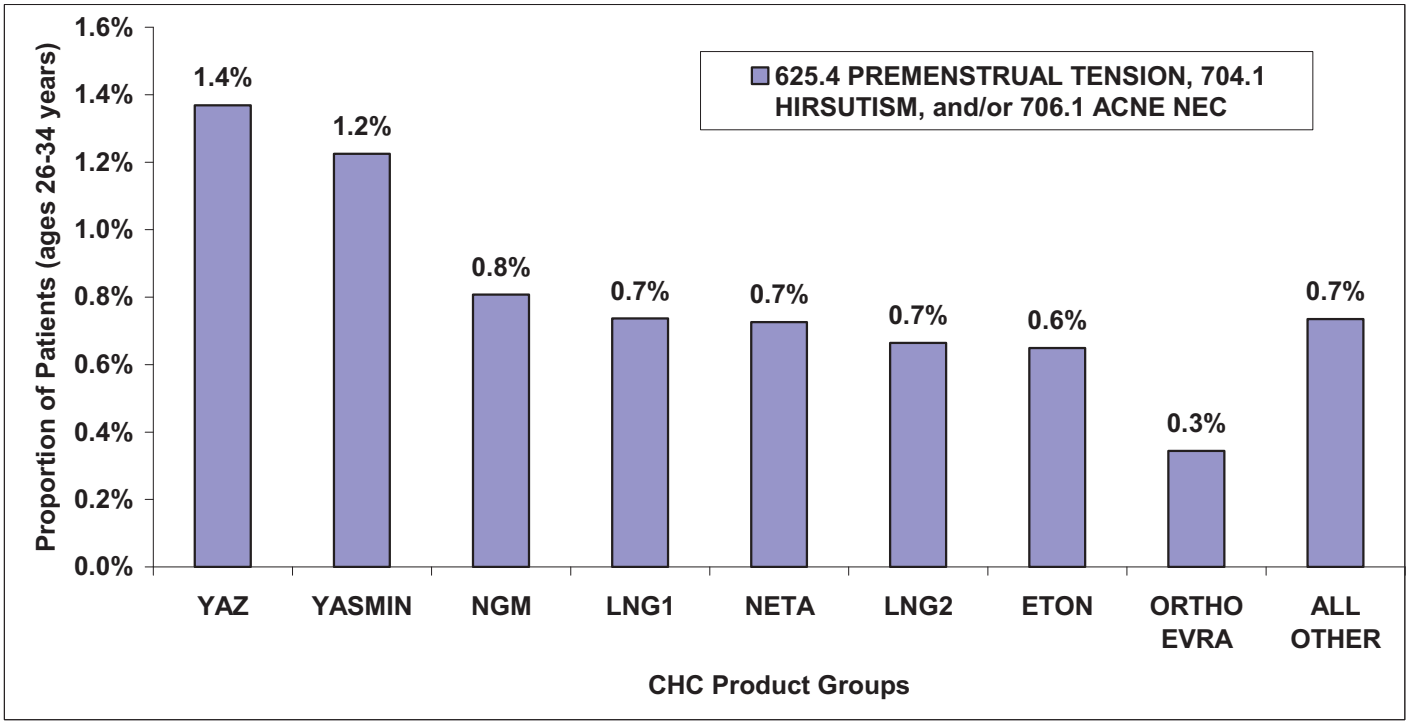
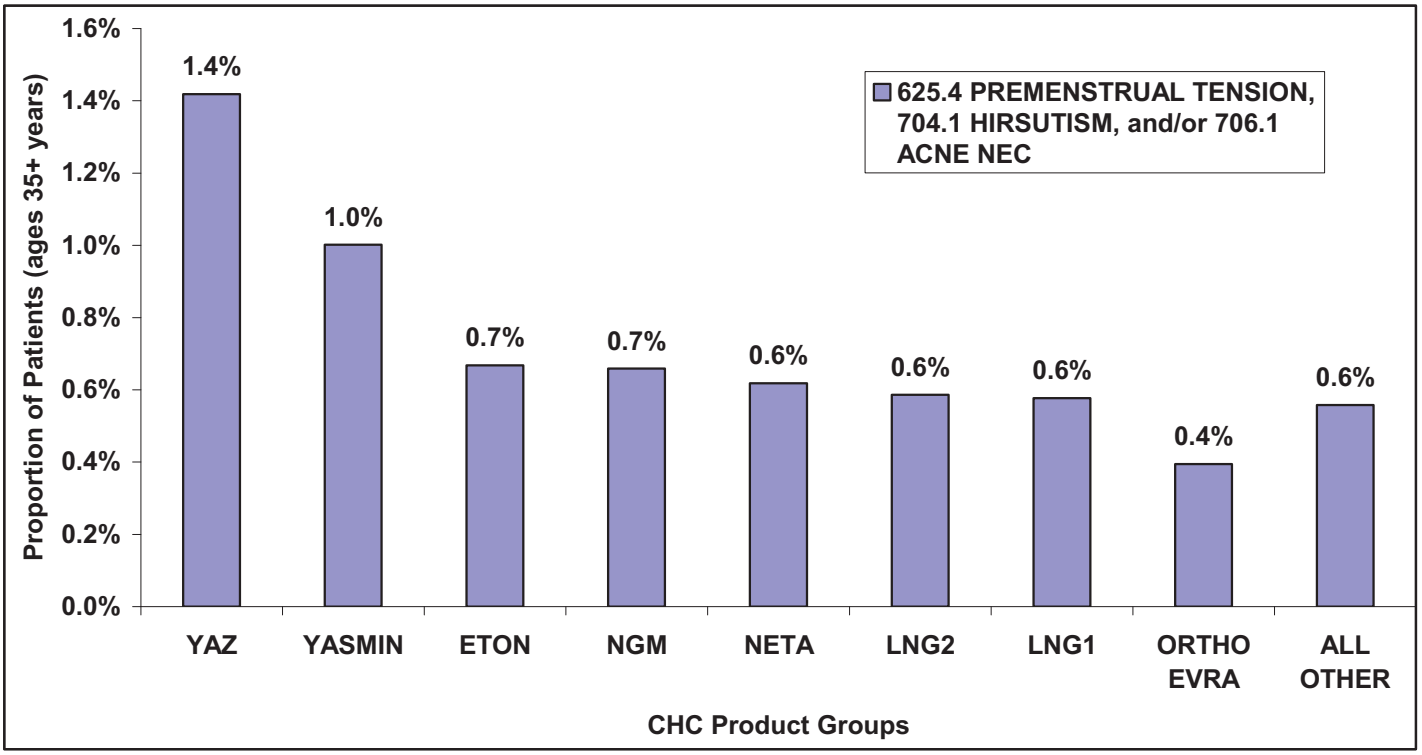


Figure 8: Yasmin®/Yaz® and Combined Hormonal Contraceptive (CHCs) Comparators for One or More Selected Diagnoses (Age 35+ years), Y2007-2010



7 APPENDIX 2: DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

SDI, Vector One®: National (VONA)

The SDI, Vector One®: National (VONA) database measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.4 billion prescription claims per year, representing over 120 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing over 200 million unique patients.

Prescriptions are captured from a sample from the universe of approximately 59,000 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from approximately one-third of stores and a significant sample of prescriptions from many of the remaining stores.

SDI, Vector One®: Total Patient Tracker (TPT)

The SDI, Vector One®: Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time.

TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.4 billion prescription claims per year, representing over 120 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing over 200 million unique patients.

SDI, Physician Drug & Diagnosis Audit (PDDA) with Pain Panel

The SDI, Physician Drug & Diagnosis Audit (PDDA) with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

Wolters Kluwer SOURCE Lx®

The Wolters Kluwer Pharma Solutions Source® Lx database is a longitudinal patient data source which captures adjudicated claims across the United States from a mix of prescription claims from commercial plans, Medicare Part D plans, Cash and Medicaid claims. The database contains approximately 4.8 billion paid, non-reversed prescriptions claims linked to over 172 million unique prescription patients of which approximately 70 million patients have 2 or more years of prescription drug history. Claims from hospital and physician practices include over 190 million patients with CPT/HCPCS medical procedure history as well as ICD-9 diagnosis history of which nearly 91 million prescription drug patients are linked to a diagnosis. The overall sample represents 27,000 pharmacies, 1,000 hospitals, 800 clinics/outpatient facilities, and 80,000 physician practices.

8 APPENDIX 3: STUDY CHCS PRODUCT GROUP

PRODUCT NAME	NDC	STUDY CHC GROUP
0.10 mg of Levonorgesetrel and 20 µg Ethinyl Estradiol		
ALESSE-21	00008091202	LNG 1
ALESSE-28	00008257601	LNG 1
ALESSE-28	00008257602	LNG 1
ALESSE-28	54868395100	LNG 1
LESSINA-28	00555901458	LNG 1
LESSINA-28	00555901467	LNG 1
AVIANE	00555904558	LNG 1
AVIANE	51285001728	LNG 1
AVIANE	54868535600	LNG 1
LEVLITE-28	50419040803	LNG 1
LEVLITE-28	50419040872	LNG 1
LEVLITE-28	54569471000	LNG 1
LEVLITE-28	54868436800	LNG 1
LEVLITE-28	50419040603	LNG 1
LUTERA	52544094928	LNG 1
LUTERA	54569579800	LNG 1
LUTERA	54868621000	LNG 1
ORSYTHIA	00603763417	LNG 1
ORSYTHIA	00603763449	LNG 1
SRONYX	52544096728	LNG 1
0.15 mg of Levonorgesetrel and 30 µg Ethinyl Estradiol		
ALTAVERA	00781558307	LNG 2
ALTAVERA	00781558336	LNG 2
INTROVALE	00781558436	LNG 2
INTROVALE	00781558491	LNG 2
LEVLEN-21	50419041021	LNG 2
LEVLEN-28	50419041112	LNG 2
LEVLEN-28	50419041128	LNG 2
LEVLEN-28	54569384400	LNG 2
LEVLEN-28	54868156400	LNG 2
NORDETTE-21	00008007501	LNG 2
NORDETTE-28	00008007502	LNG 2
NORDETTE-28	00008253301	LNG 2
NORDETTE-28	00008253302	LNG 2
NORDETTE-28	00008253303	LNG 2
NORDETTE-28	51285009158	LNG 2
NORDETTE-28	54569068200	LNG 2
NORDETTE-28	54569068201	LNG 2
NORDETTE-28	54868050700	LNG 2

PORTIA-28	00555902058	LNG 2
JOLESSA	00555912366	LNG 2
LEVORA	00905027721	LNG 2
LEVORA	00905027928	LNG 2
LEVORA	52544027928	LNG 2
LEVORA	54569499700	LNG 2
LEVORA	54868460700	LNG 2
LEVORA	60322014521	LNG 2
LEVORA	60322014728	LNG 2
LEVORA	52544027721	LNG 2
SEASONALE	51285005866	LNG 2
SEASONALE	54868231600	LNG 2
QUASENSE	52544096691	LNG 2
1 mg Norethindrone Acetate and 20 µg Ethinyl Estradiol		
LOESTRIN 1/20	00071091511	NETA
LOESTRIN 1/20	00071091546	NETA
LOESTRIN 1/20	00071091547	NETA
LOESTRIN 1/20	00071091548	NETA
LOESTRIN 1/20	00710091511	NETA
LOESTRIN 1/20	00710091545	NETA
LOESTRIN 1/20	00710091546	NETA
LOESTRIN 1/20	00710091547	NETA
LOESTRIN 1/20	51285007997	NETA
LOESTRIN 24 FE	00430053014	NETA
LOESTRIN 24 FE	35356047605	NETA
LOESTRIN 24 FE	35356047628	NETA
LOESTRIN 24 FE	54868610000	NETA
LOESTRIN FE 1/20	00710091346	NETA
LOESTRIN FE 1/20	00710091347	NETA
LOESTRIN FE 1/20	00071091315	NETA
LOESTRIN FE 1/20	00071091335	NETA
LOESTRIN FE 1/20	00071091336	NETA
LOESTRIN FE 1/20	00071091338	NETA
LOESTRIN FE 1/20	00071091345	NETA
LOESTRIN FE 1/20	00071091347	NETA
LOESTRIN FE 1/20	00071091348	NETA
LOESTRIN FE 1/20	00710091335	NETA
LOESTRIN FE 1/20	00710091336	NETA
LOESTRIN FE 1/20	00710091337	NETA
LOESTRIN FE 1/20	35356036328	NETA
LOESTRIN FE 1/20	51285008070	NETA
LOESTRIN FE 1/20	51285008198	NETA
LOESTRIN FE 1/20	54569325400	NETA
LOESTRIN FE 1/20	54569325401	NETA

LOESTRIN FE 1/20	54868151200	NETA
MICROGESTIN 1/20	52544095021	NETA
MICROGESTIN 1/20	54868621300	NETA
MICROGESTIN FE 1MG-20MCG	52544063028	NETA
MICROGESTIN FE 1MG-20MCG	54868474400	NETA
JUNEL 1/20	00555902542	NETA
JUNEL 1/20	00555902557	NETA
JUNEL 1/20	58016474701	NETA
JUNEL FE 1/20	00555902858	NETA
JUNEL FE 1/20	00555902658	NETA
JUNEL FE 1/20	54868532600	NETA
11.7 mg etonogestrel and 2700 µg Ethinyl Estradiol		
NUVARING	00052027301	ETON
NUVARING	00052027303	ETON
NUVARING	35356041003	ETON
NUVARING	54868483200	ETON
NUVARING	54868483201	ETON
6.0 mg norelgestromin and 750 µg Ethinyl Estradiol		
ORTHO EVRA	00062192001	NGNM
ORTHO EVRA	00062192015	NGNM
ORTHO EVRA	50458019201	NGNM
ORTHO EVRA	50458019215	NGNM
ORTHO EVRA	54569541300	NGNM
ORTHO EVRA	54868467000	NGNM
0.18-0.25 mg norgestimate and 35 µg Ethinyl Estradiol		
ORTHO TRI-CYCLEN	00062190215	NGM
ORTHO TRI-CYCLEN	54868409300	NGM
ORTHO TRI-CYCLEN	00062190315	NGM
ORTHO TRI-CYCLEN	00062191015	NGM
ORTHO TRI-CYCLEN	35356002168	NGM
ORTHO TRI-CYCLEN	50458019115	NGM
ORTHO TRI-CYCLEN	54569426900	NGM
TRI-PREVIFEM	00093531528	NGM
TRI-PREVIFEM	00093531581	NGM
TRI-PREVIFEM	00603766317	NGM
TRI-PREVIFEM	00603766517	NGM
TRI-PREVIFEM	35356001568	NGM
TRI-SPRINTEC	54569555100	NGM
TRI-SPRINTEC	00555901858	NGM
TRI-SPRINTEC	21695077001	NGM
TRI-SPRINTEC	21695077028	NGM
TRI-SPRINTEC	54868502800	NGM
TRI-SPRINTEC	55045378106	NGM

TRINESSA	35356036828	NGM
TRINESSA	52544024828	NGM
TRINESSA	52544093528	NGM
TRINESSA	54569579600	NGM
TRINESSA	54868582600	NGM
3.0 mg Drospirenone and 30 ug Ethinyl Estradiol		
YASMIN 28	50419040203	DRSP
YASMIN 28	54569534900	DRSP
YASMIN 28	54868459000	DRSP
OCELLA	00555913167	DRSP
SYEDA	007815658	DRSP
SAFYRAL	504190407	DRSP
ZARAH	525440981	DRSP
3.0 mg Drospirenone and 20 ug Ethinyl Estradiol		
YAZ	54868582800	DRSP
BEYAZ	504190407	DRSP
GIANVI	000935423	DRSP
LORYNA	007815656	DRSP

9 APPENDIX 4: ICD-9 DIAGNOSIS CODES

Diagnosis Group Name	*Code*
706.1 ACNE NEC	706.1
704.1 HIRSUTISM	704.1
256.4 POLYCYSTIC OVARIES	256.4
625.4 PREMENSTRUAL TENSION	625.4
625.3 DYSMENORRHEA	625.3
627.0 PREMENOPAUSE MENORRHAGIA	627.0
346.4 MENSTRUAL MIGRAINE	346.42 346.43 346.41 346.40
V25.0 CONTRACEPTIVE COUNSELING	V25.0
V25.01 PRESCRIP-ORAL CONTRACEPTION COUNSELING	V25.01
V25.02 INITIATE CONTRACEPTION NEC	V25.02
V25.03 CONTRACEPTION MGMT-EMERGENCY	V25.03
V25.04 COUNSEL NATURAL FAMILY PLANNING	V25.04
V25.09 CONTRACEPTIVE MGMT NEC	V25.09
V25.4 CONTRACEPTIVE SURVELLIANCE	V25.4 V25.40 V25.41 V25.42 V25.43 V25.49
V25.1 INSERTION OF IUD	V25.1 V25.11 V25.12 V25.13
V25.2 STERILIZATION	V25.2
V25.3 MENSTUAL EXTRACTION	V25.3
V25.5 INSERTION OF IMPLANTABLE SUBDERM CONTRACEP	V25.5
V25.8 CONTRACEPTIVE MGMT NEC	V25.8
V25.9 CONTRACEPTIVE MGMT NOS	V25.9

Appendix C

US Approved Labeling for Yasmin (3 mg drospirenone/0.03 mg ethinyl estradiol)

YASMIN 28 TABLETS
(drospirenone and ethinyl estradiol)

PHYSICIAN LABELING

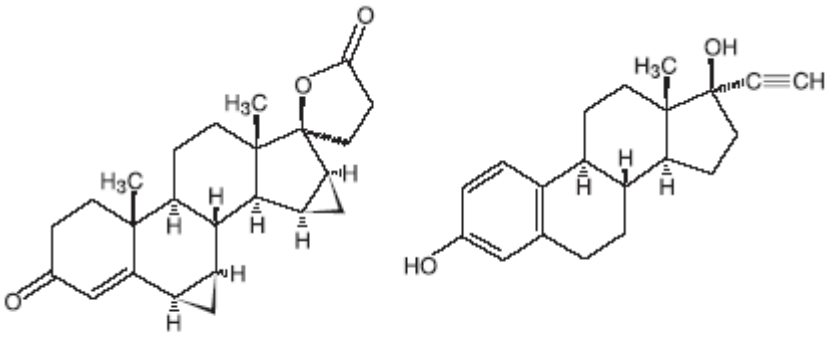
Rx only

PATIENTS SHOULD BE COUNSELED THAT THIS PRODUCT DOES NOT PROTECT AGAINST HIV INFECTION (AIDS) AND OTHER SEXUALLY TRANSMITTED DISEASES.

DESCRIPTION

YASMIN® provides an oral contraceptive regimen consisting of 21 active film coated tablets each containing 3 mg of drospirenone and 0.03 mg of ethinyl estradiol and 7 inert film coated tablets. The inactive ingredients are lactose monohydrate NF, corn starch NF, modified starch NF, povidone 25000 USP, magnesium stearate NF, hydroxylpropylmethyl cellulose USP, macrogol 6000 NF, talc USP, titanium dioxide USP, ferric oxide pigment, yellow NF. The inert film coated tablets contain lactose monohydrate NF, corn starch NF, povidone 25000 USP, magnesium stearate NF, hydroxylpropylmethyl cellulose USP, talc USP, titanium dioxide USP.

Drospirenone (6R,7R,8R,9S,10R,13S,14S,15S,16S,17S)-1,3',4',6,6a,7,8,9,10,11,12,13, 14,15,15a,16-hexadecahydro-10,13-dimethylspiro-[17H-dicyclopropa-6,7:15,16] cyclopenta[a]phenanthrene-17,2'(5H)-furan]-3,5'(2H)-dione) is a synthetic progestational compound and has a molecular weight of 366.5 and a molecular formula of C24H30O3. Ethinyl estradiol (19-nor-17α-pregna 1,3,5(10)-triene-20-yne-3,17-diol) is a synthetic estrogenic compound and has a molecular weight of 296.4 and a molecular formula of C20H24O2. The structural formulas are as follows:



Drospirenone Ethinyl estradiol

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Combination oral contraceptives (COCs) act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increases the difficulty of sperm entry into the uterus) and the endometrium (which reduces the likelihood of implantation).

Drospirenone is a spironolactone analogue with antimineralocorticoid activity. Preclinical studies in animals and *in vitro* have shown that drospirenone has no androgenic, estrogenic, glucocorticoid, and antiglucocorticoid activity. Preclinical studies in animals have also shown that drospirenone has antiandrogenic activity.

PHARMACOKINETICS

Absorption

The absolute bioavailability of drospirenone (DRSP) from a single entity tablet is about 76%. The absolute bioavailability of ethinyl estradiol (EE) is approximately 40% as a result of presystemic conjugation and first-pass metabolism. The absolute bioavailability of **YASMIN** which is a combination tablet of drospirenone and ethinyl estradiol has not been evaluated. Serum concentrations of DRSP and EE reached peak levels within 1–3 hours after administration of **YASMIN**. After single dose administration of **YASMIN**, the relative bioavailability, compared to a suspension, was 107% and 117% for DRSP and EE, respectively.

The pharmacokinetics of DRSP are dose proportional following single doses ranging from 1–10 mg. Following daily dosing of **YASMIN**, steady state DRSP concentrations were observed after 10 days. There was about 2 to 3 fold accumulation in serum C_{max} and AUC (0–24h) values of DRSP following multiple dose administration of **YASMIN** (see TABLE I).

For EE, steady-state conditions are reported during the second half of a treatment cycle. Following daily administration of **YASMIN** serum C_{max} and AUC(0–24h) values of EE accumulate by a factor of about 1.5 to 2.

TABLE I TABLE OF MEAN PHARMACOKINETIC PARAMETERS OF YASMIN (Drospirenone 3 mg and Ethinyl Estradiol 0.03 mg)

Drospirenone
Mean (%CV) Values

Cycle / Day	No. of Subjects	C_{max} (ng/mL)	T_{max} (h)	AUC(0–24h) (ng•h/mL)	$t_{1/2}$ (h)
1/1	12	36.9 (13)	1.7 (47)	288 (25)	NA[a]
1/21	12	87.5 (59)	1.7 (20)	827 (23)	30.9 (44)
6/21	12	84.2 (19)	1.8 (19)	930 (19)	32.5 (38)
9/21	12	81.3 (19)	1.6 (38)	957 (23)	31.4 (39)
13/21	12	78.7 (18)	1.6 (26)	968 (24)	31.1 (36)

Ethinyl Estradiol
Mean (%CV) Values

Cycle / Day	No. of Subjects	C_{max} (pg/mL)	T_{max} (h)	AUC(0–24h) (pg•h/mL)	$t_{1/2}$ (h)
1/1	11	53.5 (43)	1.9 (45)	280.3 (87)	NA[a]
1/21	11	92.1 (35)	1.5 (40)	461.3 (94)	NA[a]
6/21	11	99.1 (45)	1.5 (47)	346.4 (74)	NA[a]
9/21	11	87 (43)	1.5 (42)	485.3 (92)	NA[a]
13/21	10	90.5 (45)	1.6 (38)	469.5 (83)	NA[a]

a) NA = Not available

Effect of Food

The rate of absorption of DRSP and EE following single administration of two YASMIN tablets was slower under fed conditions with the serum Cmax being reduced about 40% for both components. The extent of absorption of DRSP, however, remained unchanged. In contrast the extent of absorption of EE was reduced by about 20% under fed conditions.

Distribution

DRSP and EE serum levels decline in two phases. The apparent volume of distribution of DRSP is approximately 4 L/kg and that of EE is reported to be approximately 4–5 L/kg.

DRSP does not bind to sex hormone binding globulin (SHBG) or corticosteroid binding globulin (CBG) but binds about 97% to other serum proteins. Multiple dosing over 3 cycles resulted in no change in the free fraction (as measured at trough levels). EE is reported to be highly but non-specifically bound to serum albumin (approximately 98.5%) and induces an increase in the serum concentrations of both SHBG and CBG. EE induced effects on SHBG and CBG were not affected by variation of the DRSP dosage in the range of 2 to 3 mg.

Metabolism

The two main metabolites of DRSP found in human plasma were identified to be the acid form of DRSP generated by opening of the lactone ring and the 4,5-dihydrodrospirenone- 3-sulfate. These metabolites were shown not to be pharmacologically active. In in vitro studies with human liver microsomes, DRSP was metabolized only to a minor extent mainly by cytochrome P450 3A4 (CYP3A4).

EE has been reported to be subject to presystemic conjugation in both small bowel mucosa and the liver. Metabolism occurs primarily by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed. These are present as free metabolites and as conjugates with glucuronide and sulfate. CYP3A4 in the liver are responsible for the 2-hydroxylation which is the major oxidative reaction. The 2-hydroxy metabolite is further transformed by methylation and glucuronidation prior to urinary and fecal excretion.

Excretion

DRSP serum levels are characterized by a terminal disposition phase half-life of approximately 30 hours after both single and multiple dose regimens. Excretion of DRSP was nearly complete after ten days and amounts excreted were slightly higher in feces compared to urine. DRSP was extensively metabolized and only trace amounts of unchanged DRSP were excreted in urine and feces. At least 20 different metabolites were observed in urine and feces. About 38–47% of the metabolites in urine were glucuronide and sulfate conjugates. In feces, about 17–20% of the metabolites were excreted as glucuronides and sulfates.

For EE the terminal disposition phase half-life has been reported to be approximately 24 hours. EE is not excreted unchanged. EE is excreted in the urine and feces as glucuronide and sulfate conjugates and undergoes enterohepatic circulation.

Special Populations

Race

The effect of race on the disposition of **YASMIN** has not been evaluated.

Hepatic Dysfunction

YASMIN is contraindicated in patients with hepatic dysfunction (also see **BOLDED WARNINGS**). The mean exposure to DRSP in women with moderate liver impairment is approximately three times the exposure in women with normal liver function.

Renal Insufficiency

YASMIN is contraindicated in patients with renal insufficiency (also see **WARNINGS**).

The effect of renal insufficiency on the pharmacokinetics of DRSP (3 mg daily for 14 days) and the effect of DRSP on serum potassium levels were investigated in female subjects (n=28, age 30–65) with normal renal function and mild and moderate renal impairment. All subjects were on a low potassium diet. During the study 7 subjects continued the use of potassium sparing drugs for the treatment of the underlying illness. On the 14th day (steady-state) of DRSP treatment, the serum DRSP levels in the group with mild renal impairment (creatinine clearance CLcr, 50–80 mL/min) were comparable to those in the group with normal renal function (CLcr, >80 mL/min). The serum DRSP levels were on average 37% higher in the group with moderate renal impairment (CLcr, 30–50 mL/min) compared to those in the group with normal renal function. DRSP treatment was well tolerated by all groups. DRSP treatment did not show any clinically significant effect on serum potassium concentration. Although hyperkalemia was not observed in the study, in five of the seven subjects who continued use of potassium sparing drugs during the study, mean serum potassium levels increased by up to 0.33 mEq/L. Therefore, potential exists for hyperkalemia to occur in subjects with renal impairment whose serum potassium is in the upper reference range, and who are concomitantly using potassium sparing drugs.

INDICATIONS AND USAGE

YASMIN is indicated for the prevention of pregnancy in women who elect to use an oral contraceptive.

Oral contraceptives are highly effective. TABLE II lists the typical accidental pregnancy rates for users of combination oral contraceptives and other methods of contraception. The efficacy of these contraceptive methods, except sterilization, depends upon the reliability with which they are used. Correct and consistent use of methods can result in lower failure rates.

TABLE II Percentage of women experiencing an unintended pregnancy during the first year of typical use and first year of perfect use of contraception and the percentage continuing use at the end of the first year: United States.

	% of Women Experiencing an Accidental Pregnancy Within the First Year of Use		% of Women Continuing Use At One Year[a]
Method	Typical Use[b]	Perfect Use[c]	(4)
(1)	(2)	(3)	
Chance[d]	85	85	
Spermicides[e]	26	6	40
Periodic abstinence	25		63
Calendar		9	
Ovulation method		3	
Sympto-thermal[f]		2	
Post-ovulation		1	
Withdrawal	19	4	
Cap[g]			
Parous women	40	26	42
Nulliparous women	20	9	56
Sponge			
Parous women	40	20	42
Nulliparous women	20	9	56
Diaphragm[g]	20	6	56
Condom[h]			
Female (Reality)	21	5	56
Male	14	3	61
Pill	5		71
progestin only		0.5	
combined		0.1	
IUD			
Progesterone T:	2	1.5	81
Copper T 380A	0.8	0.6	78
Lng 20	0.1	0.1	81
Depo Provera	0.3	0.3	70
Norplant and Norplant-2	0.05	0.05	88
Female Sterilization	0.5	0.5	100
Male Sterilization	0.15	0.1	100

Emergency Contraceptive Pills: Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%[i]

Lactational Amenorrhea Method: LAM is highly effective, *temporary* method of contraception[j]

Source: Trussell J, Contraceptive efficacy. In Hatcher RA, Trussell J, Stewart F, Cates W, Stewart GK, Kowal D, Guest F, Contraceptive Technology: Seventeenth Revised Edition. New York NY: Irvington Publishers, 1998.

a) Among couples attempting to avoid pregnancy, the percentage who continue to use a method for one year.

b) Among *typical* couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

c) Among couples who initiate use of a method (not necessarily for the first time) and who use it *perfectly* (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any reason.

d) The percents becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within one year. This estimate was lowered slightly (to 85%) to represent the percentage who would become pregnant within one year among women now relying on reversible methods of contraception if they abandoned contraception altogether.

e) Foams, creams, gels, vaginal suppositories, and vaginal film.

f) Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phases.

g) With spermicidal cream or jelly.

h) Without spermicides.

i) The treatment schedule is one dose within 72 hours after unprotected intercourse, and a second dose 12 hours after the first dose. The Food and Drug Administration has declared the following brands of oral contraceptives to be safe and effective for emergency contraception: Ovral (1 dose is 2 white pills), Alesse (1 dose is 5 pink pills), Nordette or Levlen (1 dose is 2 light-orange pills), Lo/Ovral (1 dose is 4 white pills), Triphasil or Tri-Levlen (1 dose is 4 yellow pills).

j) However, to maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breastfeeds is reduced, bottle feeds are introduced, or the baby reaches six months of age.

In clinical efficacy studies of **YASMIN** of up to 2 years duration, 2,629 subjects completed 33,160 cycles of use without any other contraception. The mean age of the subjects was 25.5 ± 4.7 years. The age range was 16 to 37 years. The racial demographic was: 83% Caucasian, 1% Hispanic, 1% Black, <1% Asian, <1% other, <1% missing data, 14% not inquired and <1% unspecified. Pregnancy rates in the clinical trials were less than one per 100 woman-years of use.

CONTRAINDICATIONS

YASMIN should not be used in women who have the following:

- Renal insufficiency
- Hepatic dysfunction
- Adrenal insufficiency
- Thrombophlebitis or thromboembolic disorders
- A past history of deep-vein thrombophlebitis or thromboembolic disorders
- Cerebral-vascular or coronary-artery disease
- Valvular heart disease with thrombogenic complications
- Severe hypertension
- Diabetes with vascular involvement
- Headaches with focal neurological symptoms
- Known or suspected carcinoma of the breast
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal genital bleeding

- Cholestatic jaundice of pregnancy or jaundice with prior pill use
- Liver tumor (benign or malignant) or active liver disease
- Known or suspected pregnancy
- Heavy smoking (≥15 cigarettes per day) and over age 35

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

YASMIN contains 3 mg of the progestin drospirenone that has antimineralocorticoid activity, including the potential for hyperkalemia in high-risk patients, comparable to a 25 mg dose of spironolactone. YASMIN should not be used in patients with conditions that predispose to hyperkalemia (i.e. renal insufficiency, hepatic dysfunction and adrenal insufficiency). Women receiving daily, long-term treatment for chronic conditions or diseases with medications that may increase serum potassium, should have their serum potassium level checked during the first treatment cycle. Drugs that may increase serum potassium include ACE inhibitors, angiotensin–II receptor antagonists, potassium-sparing diuretics, heparin, aldosterone antagonists, and NSAIDs.

The use of oral contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, gallbladder disease, and hypertension, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity and diabetes.

Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

The information contained in this package insert is based principally on studies carried out in patients who used oral contraceptives with higher formulations of estrogens and progestogens than those in common use today. The effect of long-term use of the oral contraceptives with lower formulations of both estrogens and progestogens remains to be determined.

Throughout this labeling, epidemiologic studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease, namely, a ratio of the incidence of a disease among oral contraceptive users to that among nonusers. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the difference in the incidence of disease between oral contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population. For further information, the reader is referred to a text on epidemiologic methods.

1. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

a. Myocardial infarction

An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary- artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of

heart attack for current oral contraceptive users has been estimated to be two to six. The risk is very low under the age of 30.

Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women in their mid-thirties or older with smoking accounting for the majority of excess cases. Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over the age of 35 and nonsmokers over the age of 40 (Table III) among women who use oral contraceptives.

TABLE III. (Adapted from P.M. Layde and V. Beral)
CIRCULATORY DISEASE MORTALITY RATES PER 100,000 WOMAN-YEARS BY AGE SMOKING STATUS AND ORAL CONTRACEPTIVE USE

AGE	EVER-USERS NON-SMOKERS	EVER-USERS SMOKERS	CONTROL NON-SMOKERS	CONTROL SMOKERS
15–24	0	10.5	0	0
25–34	4.4	14.2	2.7	4.2
35–44	21.5	63.4	6.4	15.2
45+	52.4	206.7	11.4	27.9

Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity. In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism. Oral contraceptives have been shown to increase blood pressure among users (see **section 9** in **WARNINGS**). Similar effects on risk factors have been associated with an increased risk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

b. Thromboembolism

An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to nonusers to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease. Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization. The risk of thromboembolic disease due to oral contraceptives is not related to length of use and disappears after pill use is stopped.

A two- to four-fold increase in the relative risk of post-operative thromboembolic complications has been reported with the use of oral contraceptives. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions. If feasible, oral contraceptives should be discontinued from at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than four to six weeks after delivery.

Several studies have investigated the relative risks of thromboembolism in women using **YASMIN** compared to those in women using COCs containing other progestins. Two prospective cohort studies, both evaluating the risk of venous and arterial thromboembolism and death, were initiated at the time of **YASMIN** approval.[1, 2] The first (EURAS) showed the risk of

thromboembolism (particularly venous thromboembolism) and death in **YASMIN** users to be comparable to that of other oral contraceptive preparations, including those containing levonorgestrel (a so-called second generation COC). The second prospective cohort study (Ingenix) also showed a comparable risk of thromboembolism in **YASMIN** users compared to users of other COCs, including those containing levonorgestrel. In the second study, COC comparator groups were selected based on their having similar characteristics to those being prescribed **YASMIN**.

Two additional epidemiological studies, one case-control study (van Hylckama Vlieg et al.[3]) and one retrospective cohort study (Lidegaard et al.[4]) suggested that the risk of venous thromboembolism occurring in **YASMIN** users was higher than that for users of levonorgestrel-containing COCs and lower than that for users of desogestrel/gestodene-containing COCs (so-called third generation COCs). In the case-control study, however, the number of **YASMIN** cases was very small (1.2% of all cases) making the risk estimates unreliable. The relative risk for **YASMIN** users in the retrospective cohort study was greater than that for users of other COC products when considering women who used the products for less than one year. However, these one-year estimates may not be reliable because the analysis may include women of varying risk levels. Among women who used the product for 1 to 4 years, the relative risk was similar for users of **YASMIN** to that for users of other COC products.

c. Cerebrovascular diseases

Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor, for both users and nonusers, for both types of strokes, while smoking interacted to increase the risk for hemorrhagic strokes.

In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for nonsmokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users and 25.7 for users with severe hypertension. The attributable risk is also greater in older women.

d. Dose-related risk of vascular disease from oral contraceptives

A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease. A decline in serum high-density lipoproteins (HDL) has been reported with many progestational agents. A decline in serum high-density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the nature and absolute amount of progestogen used in the contraceptive. The amount of both hormones should be considered in the choice of an oral contraceptive.

Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular estrogen/progestogen combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient. New acceptors of oral contraceptive agents should be started on preparations containing the lowest estrogen content which provides satisfactory results in the individual.

e. Persistence of risk of vascular disease

There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women aged 40 to 49 years who had used oral contraceptives for five or more years, but this increased risk was not demonstrated in other age groups. In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small. However, both studies were performed with oral contraceptive formulations containing 50 micrograms or higher of estrogens.

2. ESTIMATES OF MORTALITY FROM CONTRACEPTIVE USE

One study gathered data from a variety of sources which have estimated the mortality rate associated with different methods of contraception at different ages (Table IV). These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is below that associated with childbirth.

The observation of a possible increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970's — but not reported until 1983. However, current clinical practice involves the use of lower estrogen dose formulations combined with careful restriction of oral contraceptive use to women who do not have the various risk factors listed in this labeling.

Because of these changes in practice and, also, because of some limited new data which suggest that the risk of cardiovascular disease with the use of oral contraceptives may now be less than previously observed, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the topic in 1989. The Committee concluded that although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy nonsmoking women (even with the newer low-dose formulations), there are greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if such women do not have access to effective and acceptable means of contraception.

Therefore, the Committee recommended that the benefits of oral contraceptive use by healthy nonsmoking women over 40 may outweigh the possible risks. Of course, women of all ages who take oral contraceptives, should take the lowest possible dose formulation that is effective.

TABLE IV
ANNUAL NUMBER OF BIRTH-RELATED OR METHOD-RELATED DEATHS ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NONSTERILE WOMEN, BY FERTILITY-CONTROL METHOD ACCORDING TO AGE

Method of Control and Outcome	15–19	20–24	25–29	30–34	35–39	40–44
No fertility control methods[a]	7	7.4	9.1	14.8	25.7	28.2
Oral contraceptives non-smoker[b]	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives smoker[b]	2.2	3.4	6.6	13.5	51.1	117.2
lUD[b]	0.8	0.8	1	1	1.4	1.4
Condom[a]	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/spermicide[a]	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence[a]	2.5	1.6	1.6	1.7	2.9	3.6

a) Deaths are birth-related
b) Deaths are method-related

Adapted from H.W. Ory, Family Planning Perspectives, 15:57-63, 1983.

3. CARCINOMA OF THE REPRODUCTIVE ORGANS AND BREASTS

Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian and cervical cancer in women using oral contraceptives.

The risk of having breast cancer diagnosed may be slightly increased among current and recent users of COCs. However, this excess risk appears to decrease over time after COC discontinuation and by 10 years after cessation the increased risk disappears. The risk does not appear to increase with duration of use and no consistent relationships have been found with dose or type of steroid. Most studies show a similar pattern of risk with COC use regardless of a woman's reproductive history or her family breast cancer history. Some studies have found a small increase in risk for women who first use COCs before age 20.

Breast cancers diagnosed in current or previous OC users tend to be less clinically advanced than in nonusers.

Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is a hormonally-sensitive tumor.

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

In spite of many studies of the relationship between oral contraceptive use and breast and cervical cancers, a cause-and-effect relationship has not been established.

4. HEPATIC NEOPLASIA

Benign hepatic adenomas are associated with oral contraceptive use, although the incidence of benign tumors is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after four or more years

of use. Rupture of rare, benign, hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies from Britain have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) oral contraceptive users. However, these cancers are extremely rare in the U.S. and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than one per million users.

5. OCULAR LESIONS

There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

6. ORAL CONTRACEPTIVE USE BEFORE OR DURING EARLY PREGNANCY

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb-reduction defects are concerned, when taken inadvertently during early pregnancy.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion.

It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out. If the patient has not adhered to the prescribed dosing schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral contraceptive use should be discontinued if pregnancy is confirmed.

7. GALLBLADDER DISEASE

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens. More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal. The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens.

8. CARBOHYDRATE AND LIPID METABOLIC EFFECTS

Oral contraceptives have been shown to cause glucose intolerance in a significant percentage of users. Oral contraceptives containing greater than 75 micrograms of estrogens cause hyperinsulinism, while lower doses of estrogen cause less glucose intolerance. Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents. However, in the nondiabetic woman, oral contraceptives appear to have no effect on fasting blood glucose. Because of these demonstrated effects, prediabetic and diabetic women should be carefully observed while taking oral contraceptives.

A small proportion of women will have persistent hypertriglyceridemia while on the pill. As discussed earlier (see **WARNINGS**, **1a** and **1d**), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.

9. ELEVATED BLOOD PRESSURE

An increase in blood pressure has been reported in women taking oral contraceptives and this increase is more likely in older oral contraceptive users and with continued use. Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing concentrations of progestogens.

Women with a history of hypertension or hypertension-related diseases, or renal disease should be encouraged to use another method of contraception. If women with hypertension elect to use oral contraceptives, they should be monitored closely, and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives and there is no difference in the occurrence of hypertension among ever- and never-users.

10. HEADACHE

The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent or severe requires discontinuation of oral contraceptives and evaluation of the cause.

11. BLEEDING IRREGULARITIES

Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first three months of use. Nonhormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out.

Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was pre-existent.

PRECAUTIONS

1. GENERAL

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

2. PHYSICAL EXAMINATION AND FOLLOW-UP

It is good medical practice for all women to have annual history and physical examinations, including women using oral contraceptives. The physical examination, however, may be deferred until after initiation of oral contraceptives if requested by the woman and judged appropriate by the clinician. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

3. LIPID DISORDERS

Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult.

4. LIVER FUNCTION

If jaundice develops in any woman receiving oral contraceptives, the medication should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function.

5. FLUID RETENTION

Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

6. EMOTIONAL DISORDERS

Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

7. CONTACT LENSES

Contact-lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

8. DRUG INTERACTIONS

Effects of Other Drugs on Combined Hormonal Contraceptives

Rifampin

Metabolism of ethinyl estradiol and some progestins (e.g., norethindrone) is increased by rifampin. A reduction in contraceptive effectiveness and an increase in menstrual irregularities have been associated with concomitant use of rifampin.

Anticonvulsants

Anticonvulsants such as phenobarbital, phenytoin, and carbamazepine have been shown to increase the metabolism of ethinyl estradiol and/or some progestins, which could result in a reduction of contraceptive effectiveness.

Antibiotics

Pregnancy while taking combined hormonal contraceptives has been reported when the combined hormonal contraceptives were administered with antimicrobials such as ampicillin, tetracycline, and griseofulvin. However, clinical pharmacokinetic studies have not demonstrated any consistent effects of antibiotics (other than rifampin) on plasma concentrations of synthetic steroids.

Atorvastatin

Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%, respectively.

St. John's Wort

Herbal products containing St. John's Wort (hypericum perforatum) may induce hepatic enzymes (cytochrome P450) and p-glycoprotein transporter and may reduce the effectiveness of oral contraceptives and emergency contraceptive pills. This may also result in breakthrough bleeding.

Other

Ascorbic acid and acetaminophen may increase plasma concentrations of some synthetic estrogens, possibly by inhibition of conjugation. A reduction in contraceptive effectiveness and an increased incidence of menstrual irregularities has been suggested with phenylbutazone.

Effects of Drospirenone on Other Drugs

Metabolic Interactions

Metabolism of DRSP and potential effects of DRSP on hepatic cytochrome P450 (CYP) enzymes have been investigated in *in vitro* and *in vivo* studies (see **Metabolism**). In *in vitro* studies DRSP

did not affect turnover of model substrates of CYP1A2 and CYP2D6, but had an inhibitory influence on the turnover of model substrates of CYP1A1, CYP2C9, CYP2C19 and CYP3A4 with CYP2C19 being the most sensitive enzyme.

The potential effect of DRSP on CYP2C19 activity was investigated in a clinical pharmacokinetic study using omeprazole as a marker substrate. In the study with 24 postmenopausal women [including 12 women with homozygous (wild type) CYP2C19 genotype and 12 women with heterozygous CYP2C19 genotype] the daily oral administration of 3 mg DRSP for 14 days did not affect the oral clearance of omeprazole (40 mg, single oral dose). Based on the available results of *in vivo* and *in vitro* studies it can be concluded that, at clinical dose level, DRSP shows little propensity to interact to a significant extent with cytochrome P450 enzymes.

Interactions With Drugs That Have The Potential To Increase Serum Potassium

There is a potential for an increase in serum potassium in women taking **YASMIN** with other drugs (see **BOLDED WARNINGS**). Of note, occasional or chronic use of NSAID medication was not restricted in any of the **YASMIN** clinical trials.

A drug-drug interaction study of DRSP 3 mg/estradiol (E2) 1 mg versus placebo was performed in 24 mildly hypertensive postmenopausal women taking enalapril maleate 10 mg twice daily. Potassium levels were obtained every other day for a total of 2 weeks in all subjects. Mean serum potassium levels in the DRSP/E2 treatment group relative to baseline were 0.22 mEq/L higher than those in the placebo group. Serum potassium concentrations also were measured at multiple timepoints over 24 hours at baseline and on Day 14. On Day 14, the ratios for serum potassium C_{max} and AUC in the DRSP/E2 group to those in the placebo group were 0.955 (90% CI: 0.914, 0.999) and 1.01 (90% CI: 0.944, 1.08), respectively. No patient in either treatment group developed hyperkalemia (serum potassium concentrations > 5.5 mEq/L).

Effects of Combined Hormonal Contraceptives on Other Drugs

Combined oral contraceptives containing ethinyl estradiol may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporine, prednisolone, and theophylline have been reported with concomitant administration of oral contraceptives. In addition, oral contraceptives may induce the conjugation of other compounds. Decreased plasma concentrations of acetaminophen and increased clearance on temazepam, salicylic acid, morphine, and clofibric acid have been noted when these drugs were administered with oral contraceptives.

9. INTERACTIONS WITH LABORATORY TESTS

Certain endocrine- and liver-function tests and blood components may be affected by oral contraceptives:

a. Increased prothrombin and factors VII, VIII, IX and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

b. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered.

c. Other binding proteins may be elevated in serum.

d. Sex-hormone-binding globulins are increased and result in elevated levels of total circulating sex steroids and corticoids; however, free or biologically active levels remain unchanged.

e. Triglycerides may be increased.

f. Glucose tolerance may be decreased.

g. Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

10. CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

In a 24 month oral carcinogenicity study in mice dosed with 10 mg/kg/day drospirenone alone or 1 + 0.01, 3 + 0.03 and 10 + 0.1 mg/kg/day of drospirenone and ethinyl estradiol, 0.1 to 2 times the exposure (AUC of drospirenone) of women taking a contraceptive dose, there was an increase in carcinomas of the harderian gland in the group that received the high dose of drospirenone alone. In a similar study in rats given 10 mg/kg/day drospirenone alone or 0.3 + 0.003, 3 + 0.03 and 10 + 0.1 mg/kg/day drospirenone and ethinyl estradiol, 0.8 to 10 times the exposure of women taking a contraceptive dose, there was an increased incidence of benign and total (benign and malignant) adrenal gland pheochromocytomas in the group receiving the high dose of drospirenone. Drospirenone was not mutagenic in a number of *in vitro* (Ames, Chinese Hamster Lung gene mutation and chromosomal damage in human lymphocytes) and *in vivo* (mouse micronucleus) genotoxicity tests. Drospirenone increased unscheduled DNA synthesis in rat hepatocytes and formed adducts with rodent liver DNA but not with human liver DNA. See **WARNINGS.**

11. PREGNANCY

Pregnancy category X. See **CONTRAINDICATIONS** and **WARNINGS**.

Estrogens and progestins should not be used during pregnancy. Fourteen pregnancies that occurred with **YASMIN** exposure *in utero* (none with more than a single cycle of exposure) have been identified. One infant was born with esophageal atresia. A causal association with **YASMIN** is unknown.

A teratology study in pregnant rats given drospirenone orally at doses of 5, 15 and 45 mg/kg/day, 6 to 50 times the human exposure based on AUC of drospirenone, resulted in an increased number of fetuses with delayed ossification of bones of the feet in the two higher doses. A similar study in rabbits dosed orally with 1, 30 and 100 mg/kg/day drospirenone, 2 to 27 times the human exposure, resulted in an increase in fetal loss and retardation of fetal development (delayed ossification of small bones, multiple fusions of ribs) at the high dose only. When drospirenone was administered with ethinyl estradiol (100:1) during late pregnancy (the period of genital development) at doses of 5, 15 and 45 mg/kg, there was a dose dependent increase in feminization of male rat fetuses. In a study in 36 cynomolgous monkeys, no teratogenic or feminization effects were observed with orally administered drospirenone and ethinyl estradiol (100:1) at doses up to 10 mg/kg/day drospirenone, 30 times the human exposure.

12. NURSING MOTHERS

Small amounts of oral contraceptive steroids have been identified in the milk of nursing mothers, and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use oral contraceptives but to use other forms of contraception until she has completely weaned her child.

After oral administration of **YASMIN** about 0.02% of the drospirenone dose was excreted into the breast milk of postpartum women within 24 hours. This results in a maximal daily dose of about 3 mcg drospirenone in an infant.

13. PEDIATRIC USAGE

Safety and efficacy of **YASMIN** have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated.

INFORMATION FOR THE PATIENT

See Patient Labeling printed below.

ADVERSE REACTIONS

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see **WARNINGS**).

- Thrombophlebitis
- Arterial thromboembolism
- Pulmonary embolism
- Myocardial infarction
- Cerebral hemorrhage
- Cerebral thrombosis
- Hypertension
- Gallbladder disease
- Hepatic adenomas or benign liver tumors

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed:

- Mesenteric thrombosis
- Retinal thrombosis

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related:

- Nausea
- Vomiting
- Gastrointestinal symptoms (such as abdominal cramps and bloating)
- Breakthrough bleeding
- Spotting
- Change in menstrual flow
- Amenorrhea
- Temporary infertility after discontinuation of treatment
- Edema
- Melasma which may persist
- Breast changes: tenderness, enlargement, secretion
- Change in weight (increase or decrease)
- Change in cervical erosion and secretion
- Diminution in lactation when given immediately postpartum

- Cholestatic jaundice
- Migraine
- Rash (allergic)
- Mental depression
- Reduced tolerance to carbohydrates
- Vaginal candidiasis
- Change in corneal curvature (steepening)
- lntolerance to contact lenses

The following adverse reactions have been reported in users of oral contraceptives and a causal association has been neither confirmed nor refuted:

- Acne
- Budd-Chiari syndrome
- Cataracts
- Changes in appetite
- Changes in libido
- Colitis
- Cystitis-like syndrome
- Dizziness
- Erythema multiforme
- Erythema nodosum
- Headache
- Hemolytic uremic syndrome
- Hemorrhagic eruption
- Hirsutism
- Impaired renal function
- Loss of scalp hair
- Nervousness
- Porphyria
- Pre-menstrual syndrome
- Vaginitis

The following are the most common adverse events reported with use of **YASMIN** during the clinical trials, occurring in > 1% of subjects and which may or may not be drug related: Headache, Menstrual Disorder, Breast Pain, Abdominal Pain, Nausea, Leukorrhea, Flu Syndrome, Acne, Vaginal Moniliasis, Depression, Diarrhea, Asthenia, Dysmenorrhea, Back Pain, Infection, Pharyngitis, Intermenstrual Bleeding, Migraine, Vomiting, Dizziness, Nervousness, Vaginitis, Sinusitis, Cystitis, Bronchitis, Gastroenteritis, Allergic Reaction, Urinary Tract Infection, Pruritus, Emotional Lability, Surgery, Rash, Upper Respiratory Infection.

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of other oral contraceptives by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females. Drospirenone, however, is a spironolactone analogue which has

antimineralocorticoid properties. Serum concentration of potassium and sodium, and evidence of metabolic acidosis, should be monitored in cases of overdose.

NON-CONTRACEPTIVE HEALTH BENEFITS

The following non-contraceptive health benefits related to the use of oral contraceptives are supported by epidemiological studies which largely utilized oral contraceptive formulations containing doses exceeding 0.035 mg of ethinyl estradiol or 0.05 mg mestranol.

Effects on menses

- increased menstrual cycle regularity
- decreased blood loss and decreased incidence of iron-deficiency anemia
- decreased incidence of dysmenorrhea

Effects related to inhibition of ovulation

- decreased incidence of functional ovarian cysts
- decreased incidence of ectopic pregnancies

Effects from long-term use

- decreased incidence of fibroadenomas and fibrocystic disease of the breast
- decreased incidence of acute pelvic inflammatory disease
- decreased incidence of endometrial cancer
- decreased incidence of ovarian cancer

DOSAGE AND ADMINISTRATION

YASMIN

To achieve maximum contraceptive effectiveness, **YASMIN** (drospirenone and ethinyl estradiol) must be taken exactly as directed at intervals not exceeding 24 hours.

YASMIN consists of 21 tablets of a monophasic combined hormonal preparation plus 7 inert tablets. The dosage of **YASMIN** is one yellow tablet daily for 21 consecutive days followed by 7 white inert tablets per menstrual cycle. A patient should begin to take **YASMIN** either on the first day of her menstrual period (Day 1 Start) or on the first Sunday after the onset of her menstrual period (Sunday Start).

Day 1 Start. During the first cycle of **YASMIN** use, the patient should be instructed to take one yellow **YASMIN** daily, beginning on day one (1) of her menstrual cycle. (The first day of menstruation is day one.) She should take one yellow **YASMIN** daily for 21 consecutive days, followed by one white inert tablet daily on menstrual cycle days 22 through 28. It is recommended that **YASMIN** be taken at the same time each day, preferably after the evening meal or at bedtime. If **YASMIN** is first taken later than the first day of the menstrual cycle, **YASMIN** should not be considered effective as a contraceptive until after the first 7 consecutive days of product administration. The possibility of ovulation and conception prior to initiation of medication should be considered.

Sunday Start. During the first cycle of **YASMIN** use, the patient should be instructed to take one yellow **YASMIN** daily, beginning on the first Sunday after the onset of her menstrual period. She should take one yellow **YASMIN** daily for 21 consecutive days, followed by one white inert tablet daily on menstrual cycle days 22 through 28. It is recommended that **YASMIN** be taken at the same time each day, preferably after the evening meal or at bedtime. **YASMIN** should not be considered effective as a contraceptive until after the first 7 consecutive days of product

administration. The possibility of ovulation and conception prior to initiation of medication should be considered.

The patient should begin her next and all subsequent 28-day regimens of **YASMIN** on the same day of the week that she began her first regimen, following the same schedule. She should begin taking her yellow tablets on the next day after ingestion of the last white tablet, regardless of whether or not a menstrual period has occurred or is still in progress. Anytime a subsequent cycle of **YASMIN** is started later than the day following administration of the last white tablet, the patient should use another method of contraception until she has taken a yellow **YASMIN** daily for seven consecutive days.

When switching from another oral contraceptive, **YASMIN** should be started on the same day that a new pack of the previous oral contraceptive would have been started.

Withdrawal bleeding usually occurs within 3 days following the last yellow tablet. If spotting or breakthrough bleeding occurs while taking **YASMIN**, the patient should be instructed to continue taking her **YASMIN** as instructed and by the regimen described above. She should be instructed that this type of bleeding is usually transient and without significance; however, if the bleeding is persistent or prolonged, the patient should be advised to consult her physician.

Although the occurrence of pregnancy is unlikely if **YASMIN** is taken according to directions, if withdrawal bleeding does not occur, the possibility of pregnancy must be considered. If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking them on a day later than she should have), the possibility of pregnancy should be considered at the time of the first missed period and appropriate diagnostic measures taken. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out. Hormonal contraception should be discontinued if pregnancy is confirmed.

The risk of pregnancy increases with each active yellow tablet missed. For additional patient instructions regarding missed pills, see the "WHAT TO DO IF YOU MISS PILLS" section in the DETAILED PATIENT LABELING which follows. If breakthrough bleeding occurs following missed tablets, it will usually be transient and of no consequence. If the patient misses one or more white tablets, she should still be protected against pregnancy provided she begins taking yellow tablets again on the proper day.

In the nonlactating mother, **YASMIN** may be initiated 4 weeks postpartum, for contraception. When the tablets are administered in the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered. (See **CONTRAINDICATIONS**, **WARNINGS**, and **PRECAUTIONS** concerning thromboembolic disease.)

HOW SUPPLIED

YASMIN 28 Tablets (drospirenone and ethinyl estradiol) are available in packages of 3 BLISTER packs (NDC 50419-402-03).

Each pack contains 21 active yellow round, unscored, film coated tablets each containing 3 mg drospirenone and 0.03 mg ethinyl estradiol, and 7 inert white round, unscored, film coated tablets.

Store at 25° C (77°F); excursions permitted to 15–30°C (59–86°F). [See USP Controlled Room Temperature.]

REFERENCES

1. Dinger JC, Heinemann LAJ, et al: The safety of a drospirenone-containing oral contraceptive: final results from the European active surveillance study on oral contraceptives based on 142,475 women-years of observation. *Contraception* 2007;75:344-354.

2. Seeger JD, Loughlin J, Eng PM, et al: Risk of thromboembolism in women taking ethinylestradiol/drospirenone and other oral contraceptives. *Obstetrics & Gynecology* 2007;110(3):587-593.

3. van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, et al: The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. *BMJ* 2009;339:b2921.

4. Lidegaard O, Lokkegaard E, Svendsen AL, et al: Hormonal contraception and risk of venous thromboembolism: national follow-up study. *BMJ* 2009; 339:b2890.

Manufactured for: Bayer HealthCare Pharmaceuticals Inc.

Manufactured in: Germany

BRIEF SUMMARY PATIENT PACKAGE INSERT

YASMIN ® 28 Tablets
(drospirenone and ethinyl estradiol)

28 tablets containing the following:
21 yellow – “active" tablets
7 white – "inert" tablets

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

YASMIN is different from other birth-control pills because it contains the progestin drospirenone. Drospirenone may increase potassium. Therefore, you should not take YASMIN if you have kidney, liver or adrenal disease because this could cause serious heart and health problems. Other drugs may also increase potassium. If you are currently on daily, long-term treatment for a chronic condition with any of the medications below, you should consult your healthcare provider about whether YASMIN is right for you, and during the first month that you take YASMIN, you should have a blood test to check your potassium level.

- **NSAIDs (ibuprofen [Motrin®, Advil®], naproxen [Naprosyn®, Aleve® and others] when taken long-term and for treatment of arthritis or other problems)**
- **Potassium-sparing diuretics (spironolactone and others)**
- **Potassium supplementation**
- **ACE inhibitors (Capoten®, Vasotec®, Zestril® and others)**
- **Angiotensin-II receptor antagonists (Cozaar®, Diovan®, Avapro® and others)**
- **Heparin**

Oral contraceptives, also known as "birth-control pills" or "the pill," are taken to prevent pregnancy, and when taken correctly, have a failure rate of less than 1% per year when used without missing any pills. The typical failure rate of large numbers of pill users is less than 5% per year when women who miss pills are included. However, forgetting to take pills considerably increases the chances of pregnancy.

For the majority of women, oral contraceptives can be taken safely. But there are some women who are at high risk of developing certain serious diseases that can be life–threatening or may cause temporary or permanent disability or death. The risks associated with taking oral contraceptives increase significantly if you:

- smoke
- have high blood pressure, diabetes, high cholesterol
- have or have had clotting disorders, heart attack, stroke, angina pectoris, cancer of the breast or sex organs, jaundice, or malignant or benign liver tumors.

You should not take the pill if you suspect you are pregnant or have unexplained vaginal bleeding.

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should not smoke.

Most side effects of the pill are not serious. The most common such effects are nausea, vomiting, bleeding between menstrual periods, weight gain, breast tenderness, and difficulty wearing contact lenses. These side effects, especially nausea and vomiting may subside within the first three months of use.

The serious side effects of the pill occur very infrequently, especially if you are in good health and are young. However, you should know that the following medical conditions have been associated with or made worse by the pill:

1. Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), blockage or rupture of a blood vessel in the brain (stroke), blockage of blood vessels in the heart (heart attack and angina pectoris) or other organs of the body. As mentioned above, smoking increases the risk of heart attacks and strokes and subsequent serious medical consequences.

2. Liver tumors, which may rupture and cause severe bleeding. A possible but not definite association has been found with the pill and liver cancer. However, liver cancers are extremely rare. The chance of developing liver cancer from using the pill is thus even rarer.

3. High blood pressure, although blood pressure usually returns to normal when the pill is stopped.

4. Cancer of the breast. Various studies give conflicting reports on the relationship between breast cancer and oral contraceptive use. Oral contraceptive use may slightly increase your chance of having breast cancer diagnosed, particularly after using hormonal contraceptives at a younger age. After you stop using hormonal contraceptives, the chances of getting breast cancer begin to go back down. You should have regular breast examinations by a healthcare provider and examine your own breasts monthly. Tell your healthcare provider if you have a family history of breast cancer or if you have had breast nodules or an abnormal mammogram. Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is a hormone-sensitive tumor.

The symptoms associated with these serious side effects are discussed in the detailed leaflet given to you with your supply of pills. Notify your doctor or healthcare provider if you notice any unusual physical disturbances while taking the pill. ln addition, drugs such as rifampin, as well as some anticonvulsants, some antibiotics and some herbal products such as St. John's Wort, may decrease oral contraceptive effectiveness.

Taking the pill provides some important non-contraceptive benefits. These include less painful menstruation, less menstrual blood loss and anemia, fewer pelvic infections, and fewer cancers of the ovary and the lining of the uterus.

Be sure to discuss any medical condition you may have with your healthcare provider. Your healthcare provider will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the healthcare provider believes that it is appropriate to postpone it. You should be reexamined at least once a year while taking oral contraceptives. The detailed patient information booklet gives you further information which you should read and discuss with your healthcare provider.

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

INSTRUCTIONS TO PATIENTS

HOW TO TAKE THE PILL

IMPORTANT POINTS TO REMEMBER

***BEFORE* YOU START TAKING YOUR PILLS**

1. BE SURE TO READ THESE DIRECTIONS:
   Before you start taking your pills. Anytime you are not sure what to do.
2. THE RIGHT WAY TO TAKE THE PILL IS TO TAKE ONE PILL EVERY DAY AT THE SAME TIME.
   If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant.
3. MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST 1–3 PACKS OF PILLS.
   If you do have spotting or light bleeding or feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it does not go away, check with your doctor or healthcare provider.
4. MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up these missed pills.
   On the days you take two pills, to make up for missed pills, you could also feel a little sick to your stomach.
5. IF YOU HAVE VOMITING OR DIARRHEA, or IF YOU TAKE SOME MEDICINES, including some antibiotics and some herbal products such as St. John's Wort, your pills may not work as well.
   Use a back-up method (such as condoms or spermicides) until you check with your doctor or healthcare provider.
6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your doctor or healthcare provider about how to make pill-taking easier or about using another method of birth control.
7. IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your doctor or healthcare provider.

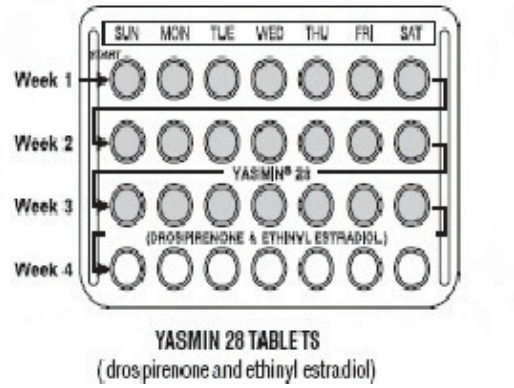
***BEFORE* YOU START TAKING YOUR PILLS**

1. DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL.
   It is important to take it at about the same time every day.
2. LOOK AT YOUR PILL PACK - IT HAS 28 PILLS:
   The YASMIN pill pack has 21 yellow "active" pills (with hormones) to be taken for three weeks, followed by 7 white "reminder" pills (without hormones) to be taken for one week.
3. ALSO FIND:

   1) where on the pack to start taking pills,

   2) in what order to take the pills (follow the arrows)

   3) the week numbers as shown in the diagram below



YASMIN 28 TABLETS
(drospirenone and ethinyl estradiol)

4. BE SURE YOU HAVE READY AT ALL TIMES:
   ANOTHER KIND OF BIRTH CONTROL (such as condoms or spermicides) to use as a back-up in case you miss pills.

   AN EXTRA, FULL PILL PACK.

WHEN TO START THE FIRST PACK OF PILLS

You have a choice for which day to start taking your first pack of pills. Decide with your doctor or healthcare provider which is the best day for you. Pick a time of day which will be easy to remember.

DAY 1 START:

1. Take the first yellow "active" pill of the first pack during the *first 24 hours of your period.*
2. You will not need to use a back-up method of birth control, since you are starting the pill at the beginning of your period.

SUNDAY START:

1. Take the first yellow "active" pill of the first pack on the *Sunday after your period starts,* even if you are still bleeding. If your period begins on Sunday, start the pack that same day.
2. *Use another method of birth control* (such as condoms or spermicides) as a back-up method if you have sex any time from the Sunday you start your first pack until the next Sunday (7 days).

WHAT TO DO DURING THE MONTH

1. **TAKE ONE PILL AT THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY**
   Do not skip pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea).
   Do not skip pills even if you do not have sex very often.
2. **WHEN YOU FINISH A PACK OR SWITCH YOUR BRAND OF PILLS:**
   Start the next pack on the day after your last white "reminder" pill. Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS

If you **MISS 1** yellow "active" pill:

1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take two pills in one day.
2. You do not need to use a back-up birth control method if you have sex.

If you **MISS 2** yellow "active" pills in a row in **WEEK 1 OR WEEK 2** of your pack:

1. Take two pills on the day you remember and two pills the next day.
2. Then take one pill a day until you finish the pack.
3. You MAY BECOME PREGNANT if you have sex in the *7 days* after you miss pills. You MUST use another birth control method (such as condoms or spermicides) as a back-up for those 7 days.

If you **MISS 2** yellow "active" pills in a row in the **3RD WEEK**:

1. ***If you are a Day 1 Starter:***
   THROW OUT the rest of the pill pack and start a new pack that same day.
   If you are a Sunday Starter*:*
   Keep taking one pill every day until Sunday. On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected. However, if you miss your period two months in a row, call your doctor or healthcare provider because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the *7 days* after you miss pills. You MUST use another birth control method (such as condoms or spermicides) as a back-up for those 7 days.

If you **MISS 3 OR MORE** yellow "active" pills in a row (during the first 3 weeks).

1. **If you are a Day 1 Starter:**
   THROW OUT the rest of the pill pack and start a new pack that same day.
   If you are a Sunday Starter:
   Keep taking 1 pill every day until Sunday. On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected. However, if you miss your period two months in a row, call your doctor or healthcare provider because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms or spermicides) as a back-up for those 7 days.

If you forget any of the 7 white "reminder" pills in Week 4:

THROW AWAY the pills you missed.

Keep taking one pill each day until the pack is empty.

You do not need a back-up method.

FINALLY, IF YOU ARE STILL NOT SURE WHAT TO DO ABOUT THE PILLS YOU HAVE MISSED:

Use a BACK-UP METHOD (such as condoms or spermicides) anytime you have sex.

KEEP TAKING ONE ACTIVE PILL EACH DAY until you can reach your doctor or healthcare provider.

For additional information see Detailed Patient Labeling

DETAILED PATIENT PACKAGE INSERT

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

YASMIN is different from other birth-control pills because it contains the progestin drospirenone. Drospirenone may increase potassium. Therefore, you should not take YASMIN if you have kidney, liver or adrenal disease because this could cause serious heart and health problems. Other drugs may also increase potassium. If you are currently on daily, long-term treatment for a chronic condition with any of the medications below, you should consult your healthcare provider about whether YASMIN is right for you, and during the first month that you take YASMIN, you should have a blood test to check your potassium level.

- NSAIDs (ibuprofen [Motrin®, Advil®], naproxen [Naprosyn®, Aleve® and others] when taken long-term and for treatment of arthritis or other problems)
- Potassium-sparing diuretics (spironolactone and others)
- Potassium supplementation
- ACE inhibitors (Capoten®, Vasotec®, Zestril® and others)
- Angiotensin-II receptor antagonists (Cozaar®, Diovan®, Avapro® and others)
- Heparin

INTRODUCTION

Any woman who considers using oral contraceptives (the birth-control pill or "the pill") should understand the benefits and risks of using this form of birth control. This leaflet will give you much of the information you will need to make this decision and will also help you determine if you are at risk of developing any of the serious side effects of the pill. It will tell you how to use the pill properly so that it will be as effective as possible. However, this leaflet is not a replacement for a careful discussion between you and your healthcare provider. You should discuss the information provided in this leaflet with him or her, both when you first start taking the pill and during your revisits. You should also follow your healthcare provider's advice with regard to regular check-ups while you are on the pill.

EFFECTIVENESS OF ORAL CONTRACEPTIVES

Oral contraceptives or "birth-control pills" or "the pill" are used to prevent pregnancy and are more effective than other nonsurgical methods of birth control. When they are taken correctly, the chance of becoming pregnant is less than 1% (one pregnancy per 100 women per year of use)

when used perfectly, without missing any pills. Typical failure rates, including women who don't always follow the instructions exactly, are about 5% per year. The chance of becoming pregnant increases with each missed pill during a menstrual cycle.

In comparison, typical failure rates for other nonsurgical methods of birth control during the first year of use are as follows:

Percentage of women experiencing an unintended pregnancy during the first year of typical use and first year of perfect use of contraception and the percentage continuing use at the end of the first year: United States.

	% of Women Experiencing an Accidental Pregnancy Within the First Year of Use		% of Women Continuing Use At One Year[a]
Method	Typical Use[b]	Perfect Use[c]	(4)
(1)	(2)	(3)	
Chance[d]	85	85	
Spermicides[e]	26	6	40
Periodic abstinence	25		63
Calendar		9	
Ovulation method		3	
Sympto-thermal[f]		2	
Post-ovulation		1	
Withdrawal	19	4	
Cap[g]			
Parous women	40	26	42
Nulliparous women	20	9	56
Sponge			
Parous women	40	20	42
Nulliparous women	20	9	56
Diaphragm[g]	20	6	56
Condom[h]			
Female (Reality)	21	5	56
Male	14	3	61
Pill	5		71
progestin only		0.5	
combined		0.1	
IUD			
Progesterone T:	2	1.5	81
Copper T 380A	0.8	0.6	78
Lng 20	0.1	0.1	81
Depo Provera	0.3	0.3	70
Norplant and Norplant-2	0.05	0.05	88
Female Sterilization	0.5	0.5	100
Male Sterilization	0.15	0.1	100

Emergency Contraceptive Pills: Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%[i]

Lactational Amenorrhea Method: LAM is highly effective, *temporary* method of contraception[j]

Source: Trussell J, Contraceptive efficacy. In Hatcher RA, Trussell J, Stewart F, Cates W, Stewart GK, Kowal D, Guest F, Contraceptive Technology: Seventeenth Revised Edition. New York NY: Irvington Publishers, 1998.

a) Among *typical* couples attempting to avoid pregnancy, the percentage who continue to use a method for one year.

b) Among couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

c) Among couples who initiate use of a method (not necessarily for the first time) and who use it *perfectly* (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any reason.

d) The percents becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within one year. This estimate was lowered slightly (to 85%) to represent the percentage who would become pregnant within one year among women now relying on reversible methods of contraception if they abandoned contraception altogether.

e) Foams, creams, gels, vaginal suppositories, and vaginal film.

f) Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phases.

g) With spermicidal cream or jelly.

h) Without spermicides.

i) The treatment schedule is one dose within 72 hours after unprotected intercourse, and a second dose 12 hours after the first dose. The Food and Drug Administration has declared the following brands of oral contraceptives to be safe and effective for emergency contraception: Ovral (1 dose is 2 white pills), Alesse (1 dose is 5 pink pills), Nordette or Levlen (1 dose is 2 light-orange pills), Lo/Ovral (1 dose is 4 white pills), Triphasil or Tri-Levlen (1 dose is 4 yellow pills).

j) However, to maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breastfeeds is reduced, bottle feeds are introduced, or the baby reaches six months of age.

WHO SHOULD NOT TAKE ORAL CONTRACEPTIVES

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use YASMIN should not smoke.

Some women should not use the pill. For example, you should not take **YASMIN** if you are pregnant or think you may be pregnant. You should also not use **YASMIN** if you have had any of the following conditions:

- A history of heart attack or stroke
- Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), brain (stroke) or eyes
- A history of blood clots in the deep veins of your legs
- Chest pain (angina pectoris)
- Known or suspected breast cancer or cancer of the lining of the uterus, cervix or vagina
- Unexplained vaginal bleeding (until a diagnosis is reached by your doctor)

- Yellowing of the whites of the eyes or of the skin (jaundice) during pregnancy or during previous use of the pill
- Liver tumor (benign or cancerous)
- Known or suspected pregnancy

In addition, you should not use YASMIN if you have any of the following conditions:

- Kidney Disease
- Liver Disease
- Adrenal Disease

Tell your healthcare provider if you have ever had any of the above conditions (Your healthcare provider can recommend another method of birth control). If you are currently on daily, long-term treatment for a chronic condition with any of the following medications, you should consult your healthcare provider before taking **YASMIN:**

- NSAIDs (ibuprofen, naproxen and others)
- Potassium-sparing diuretics (spironolactone and others)
- Potassium supplementation
- ACE inhibitors (captopril, enalapril, lisinopril and others)
- Angiotensin-II receptor antagonists (Cozaar®, Diovan®, Avapro® and others)
- Heparin

OTHER CONSIDERATIONS BEFORE TAKING ORAL CONTRACEPTIVES

Tell your healthcare provider if you or any family member has ever had:

- Breast nodules, fibrocystic disease of the breast, an abnormal breast X-ray or mammogram
- Diabetes
- Elevated cholesterol or triglycerides
- High blood pressure
- Migraine or other headaches or epilepsy
- Mental depression
- Gallbladder, heart or kidney disease
- History of scanty or irregular menstrual periods

Women with any of these conditions should be checked often by their healthcare provider if they choose to use oral contraceptives.

Also, be sure to inform your doctor or healthcare provider if you smoke or take any medications.

RISKS OF TAKING ORAL CONTRACEPTIVES

1. RISK OF DEVELOPING BLOOD CLOTS

Blood clots and blockage of blood vessels are the most serious side effects of taking oral contraceptives and can be fatal. In particular, a clot in the legs can cause thrombophlebitis and a clot that travels to the lungs can cause sudden blocking of the vessel carrying blood to the lungs. Rarely, clots occur in the blood vessels of the eye and may cause blindness, double vision, or impaired vision.

If you take oral contraceptives and need elective surgery, need to stay in bed for a prolonged illness or have recently delivered a baby, you may be at risk of developing blood clots. You should consult your doctor about stopping oral contraceptives three to four weeks before surgery and not taking oral contraceptives for two weeks after surgery or during bed rest. You should also not take oral contraceptives soon after delivery of a baby or a mid-trimester pregnancy loss or termination. It is advisable to wait for at least four weeks after delivery if you are not breast-feeding. If you are breast-feeding, you should wait until you have weaned your child before using the pill. (See also the section on breast-feeding in **GENERAL PRECAUTIONS**.)

2. HEART ATTACKS AND STROKES

Oral contraceptives may increase the tendency to develop strokes (stoppage or rupture of blood vessels in the brain) and angina pectoris and heart attacks (blockage of blood vessels in the heart). Any of these conditions can cause death or serious disability.

Smoking greatly increases the possibility of suffering heart attacks and strokes. Furthermore, smoking and the use of oral contraceptives greatly increase the chances of developing and dying of heart disease.

3. GALLBLADDER DISEASE

Oral contraceptive users probably have a greater risk than nonusers of having gallbladder disease, although this risk may be related to pills containing high doses of estrogens.

4. LIVER TUMORS

In rare cases, oral contraceptives can cause benign but dangerous liver tumors. These benign liver tumors can rupture and cause fatal internal bleeding. In addition, a possible but not definite association has been found with the pill and liver cancers in two studies, in which a few women who developed these very rare cancers were found to have used oral contraceptives for long periods. However, liver cancers are extremely rare. The chance of developing liver cancer from using the pill is thus even rarer.

5. CANCER OF THE REPRODUCTIVE ORGANS AND BREASTS

Various studies give conflicting reports on the relationship between breast cancer and oral contraceptive use. Oral contraceptive use may slightly increase your chance of having breast cancer diagnosed, particularly after using hormonal contraceptives at a younger age. After you stop using hormonal contraceptives, the chances of getting breast cancer begin to go back down. You should have regular breast examinations by a healthcare provider and examine your own breasts monthly. Tell your healthcare provider if you have a family history of breast cancer or if you have had breast nodules or an abnormal mammogram. Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is a hormone-sensitive tumor.

Some studies have found an increase in the incidence of cancer of the cervix in women who use oral contraceptives. However, this finding may be related to factors other than the use of oral contraceptives.

ESTIMATED RISK OF DEATH FROM A BIRTH CONTROL METHOD OR PREGNANCY

All methods of birth control and pregnancy are associated with a risk of developing certain diseases which may lead to disability or death. An estimate of the number of deaths associated with different methods of birth control and pregnancy has been calculated and is shown in the following table.

ANNUAL NUMBER OF BIRTH-RELATED OR METHOD-RELATED DEATHS ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NONSTERILE WOMEN, BY FERTILITY-CONTROL METHOD ACCORDING TO AGE

Method of Control and Outcome	15–19	20–24	25–29	30–34	35–39	40–44
No fertility control methods[a]	7	7.4	9.1	14.8	25.7	28.2
Oral contraceptives non-smoker[b]	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives smoker[b]	2.2	3.4	6.6	13.5	51.1	117.2
lUD[b]	0.8	0.8	1	1	1.4	1.4
Condom[a]	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/spermicide[a]	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence[a]	2.5	1.6	1.6	1.7	2.9	3.6

a) Deaths are birth-related

b) Deaths are method-related

Adapted from H.W. Ory, Family Planning Perspectives, 15:57-63, 1983.

In the above table, the risk of death from any birth-control method is less than the risk of childbirth, except for oral contraceptive users over the age of 35 who smoke and pill users over the age of 40 even if they do not smoke. It can be seen in the table that for women aged 15 to 39, the risk of death was highest with pregnancy (7–26 deaths per 100,000 women, depending on age). Among pill users who do not smoke, the risk of death was always lower than that associated with pregnancy for any age group, except for those women over the age of 40, when the risk increases to 32 deaths per 100,000 women, compared to 28 associated with pregnancy at that age. However, for pill users who smoke and are over the age of 35, the estimated number of deaths exceeds those for other methods of birth control. If a woman is over the age of 40 and smokes, her estimated risk of death is four times higher (117/100,000 women) than the estimated risk associated with pregnancy (28/100,000 women) in that age group.

The suggestion that women over 40 who do not smoke should not take oral contraceptives is based on information from older high-dose pills and on less-selective use of pills than is practiced today. An Advisory Committee of the FDA discussed this issue in 1989 and recommended that the benefits of oral contraceptive use by healthy, non-smoking women over 40 years of age may outweigh the possible risks. However, all women, especially older women, are cautioned to use the lowest-dose pill that is effective.

WARNING SIGNALS

If any of these adverse effects occur while you are taking oral contraceptives, call your doctor immediately:

- Sharp chest pain, coughing of blood, or sudden shortness of breath (indicating a possible clot in the lung)
- Pain in the calf (indicating a possible clot in the leg)
- Crushing chest pain or heaviness in the chest (indicating a possible heart attack)
- Sudden severe headache or vomiting, dizziness or fainting, disturbances of vision or speech, weakness, or numbness in an arm or leg (indicating a possible stroke)

- Sudden partial or complete loss of vision (indicating a possible clot in the eye)
- Breast lumps (indicating possible breast cancer or fibrocystic disease of the breast; ask your doctor or healthcare provider to show you how to examine your breasts)
- Severe pain or tenderness in the stomach area (indicating a possibly ruptured liver tumor)
- Difficulty in sleeping, weakness, lack of energy, fatigue, or change in mood (possibly indicating severe depression)
- Jaundice or a yellowing of the skin or eyeballs, accompanied frequently by fever, fatigue, loss of appetite, dark-colored urine, or light-colored bowel movements (indicating possible liver problems)

SIDE EFFECTS OF ORAL CONTRACEPTIVES

1. VAGINAL BLEEDING

Irregular vaginal bleeding or spotting may occur while you are taking the pills. Irregular bleeding may vary from slight staining between menstrual periods to breakthrough bleeding, which is a flow much like a regular period. Irregular bleeding occurs most often during the first few months of oral contraceptive use, but may also occur after you have been taking the pill for some time. Such bleeding may be temporary and usually does not indicate any serious problems. It is important to continue taking your pills on schedule. If the bleeding occurs in more than one cycle or lasts for more than a few days, talk to your doctor or healthcare provider.

2. CONTACT LENSES

If you wear contact lenses and notice a change in vision or an inability to wear your lenses, contact your doctor or healthcare provider.

3. FLUID RETENTION

Oral contraceptives may cause edema (fluid retention) with swelling of the fingers or ankles and may raise your blood pressure. If you experience fluid retention, contact your doctor or healthcare provider.

4. MELASMA

A spotty darkening of the skin is possible, particularly of the face.

5. OTHER SIDE EFFECTS

Other side effects may include nausea, vomiting, change in appetite, headache, nervousness, depression, dizziness, loss of scalp hair, rash, and vaginal infections.

If any of these side effects occur, call your doctor or healthcare provider.

GENERAL PRECAUTIONS

1. Missed periods and use of oral contraceptives before or during early pregnancy.

There may be times when you may not menstruate regularly after you have completed taking a cycle of pills. If you have taken your pills regularly and miss one menstrual period, continue taking your pills for the next cycle but be sure to inform your healthcare provider before doing so. If you have not taken the pills daily as instructed and missed a menstrual period, or if you missed two consecutive menstrual periods, you may be pregnant. Check with your healthcare provider immediately to determine whether you are pregnant. Stop taking oral contraceptives if pregnancy is confirmed.

There is no conclusive evidence that oral contraceptive use is associated with an increase in birth defects when taken inadvertently during early pregnancy. Previously, a few studies had reported that oral contraceptives might be associated with birth defects, but these studies have not been confirmed. Nevertheless, oral contraceptives should not be used during pregnancy. You should check with your doctor about risks to your unborn child of any medication taken during pregnancy.

2. While Breast-Feeding

If you are breast-feeding, consult your doctor before starting oral contraceptives. Some of the drug will be passed on to the child in the milk. A few adverse effects on the child have been reported, including yellowing of the skin (jaundice) and breast enlargement. In addition, oral contraceptives may decrease the amount and quality of your milk. If possible, do not use oral contraceptives while breast-feeding. You should use another method of contraception since breast-feeding provides only partial protection from becoming pregnant, and this partial protection decreases significantly as you breast-feed for longer periods of time. You should consider starting oral contraceptives only after you have weaned your child completely.

3. Laboratory Tests

If you are scheduled for any laboratory tests, tell your doctor you are taking birth-control pills. Certain blood tests may be affected by birth-control pills.

4. Drug Interactions

Certain drugs may interact with birth-control pills to make them less effective in preventing pregnancy or cause an increase in breakthrough bleeding. Such drugs include rifampin, drugs used for epilepsy such as barbiturates (for example, phenobarbital) and phenytoin (Dilantin is one brand of this drug), phenylbutazone (Butazolidin is one brand) and possibly certain antibiotics. Herbal products containing St. John's Wort (hypericum perforatum) may reduce the effectiveness of oral contraceptives. This may also result in breakthrough bleeding. You may need to use an additional method of contraception during any cycle in which you take drugs that can make oral contraceptives less effective **(also See BOLDED TEXT AT BEGINNING).**

5. Sexually Transmitted Diseases

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

HOW TO TAKE THE PILL

IMPORTANT POINTS TO REMEMBER
BEFORE YOU START TAKING YOUR PILLS

1. BE SURE TO READ THESE DIRECTIONS:
   Before you start taking your pills.
   Any time you are not sure what to do.
2. THE RIGHT WAY TO TAKE THE PILL IS TO TAKE ONE PILL EVERY DAY AT THE SAME TIME.
   If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant.
3. MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST 1–3 PACKS OF PILLS.
   If you do have spotting or light bleeding or feel sick to your stomach, do not stop taking the

pill. The problem will usually go away. If it does not go away, check with your doctor or healthcare provider.

4. MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up these missed pills.

On the days you take two pills, to make up for missed pills, you could also feel a little sick to your stomach.

5. IF YOU HAVE VOMITING OR DIARRHEA, for any reason, or IF YOU TAKE SOME MEDICINES, including some antibiotics and some herbal products such as St. John's Wort, your pills may not work as well.
   Use a back-up method (such as condoms or spermicides) until you check with your doctor or healthcare provider.
6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your doctor or healthcare provider about how to make pill-taking easier or about using another method of birth control.
7. IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your doctor or healthcare provider.

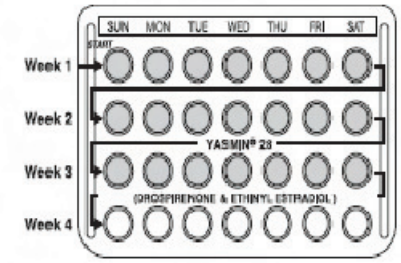
BEFORE YOU START TAKING YOUR PILLS

1. DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL.
   It is important to take it at about the same time every day.
2. LOOK AT YOUR PILL PACK - IT HAS 28 PILLS: The YASMIN pill pack has 21 yellow "active" pills (with hormones) to be taken for three weeks, followed by 7 white "reminder" pills (without hormones) to be taken for one week.
3. ALSO FIND:

   1) where on the pack to start taking pills,

   2) in what order to take the pills (follow the arrows)

   3) the week numbers as shown in the diagram below



YASMIN 28 TABLETS
(drospirenone and ethinyl estradiol)

4. BE SURE YOU HAVE READY AT ALL TIMES:
   ANOTHER KIND OF BIRTH CONTROL (such as condoms or spermicides) to use as a back-up in case you miss pills.
   AN EXTRA, FULL PILL PACK.

WHEN TO START THE *FIRST* PACK OF PILLS

You have a choice for which day to start taking your first pack of pills. Decide with your doctor or healthcare provider which is the best day for you. Pick a time of day which will be easy to remember.

DAY 1 START:

1. Take the first yellow "active" pill of the first pack during the *first 24 hours of your period.*
2. You will not need to use a back-up method of birth control, since you are starting the pill at the beginning of your period.

SUNDAY START:

1. Take the first yellow "active" pill of the first pack on the *Sunday after your period starts*, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.
2. *Use another method of birth control* (such as condoms or spermicides) as a back-up method if you have sex any time from the Sunday you start your first pack until the next Sunday (7 days).

WHAT TO DO DURING THE MONTH

1. **TAKE ONE PILL AT THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY** Do not skip pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea).
2. Do not skip pills even if you do not have sex very often.
3. **WHEN YOU FINISH A PACK OR SWITCH YOUR BRAND OF PILLS:** Start the next pack on the day after your last white "reminder" pill. Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS

If you **MISS 1** yellow "active" pill:

1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take two pills in one day.
2. You do not need to use a back-up birth control method if you have sex.

If you **MISS 2** yellow "active" pills in a row in **WEEK 1 OR WEEK 2** of your pack:

1. Take two pills on the day you remember and two pills the next day.
2. Then take one pill a day until you finish the pack.
3. You MAY BECOME PREGNANT if you have sex in the 7 *days* after you miss pills. You MUST use another birth control method (such as condoms or spermicides) as a back-up for those 7 days.

If you **MISS 2** yellow "active" pills in a row in the **3RD WEEK:**

1. **If you are a Day 1 Starter:**
   THROW OUT the rest of the pill pack and start a new pack that same day.
   If you are a Sunday Starter:
   Keep taking one pill every day until Sunday. On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected. However, if you miss your period two months in a row, call your doctor or healthcare provider because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms or spermicides) as a back-up for those 7 days.

If you **MISS 3 OR MORE** yellow "active" pills in a row (during the first 3 weeks).

1. **If you are a Day 1 Starter:**
   THROW OUT the rest of the pill pack and start a new pack that same day.
   If you are a Sunday Starter:
   Keep taking 1 pill every day until Sunday. On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected. However, if you miss your period two months in a row, call your doctor or healthcare provider because you might be pregnant.

You MAY BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms or spermicides) as a back-up for those 7 days.

If you forget any of the 7 white "reminder" pills in Week 4:

THROW AWAY the pills you missed.

Keep taking one pill each day until the pack is empty.

You do not need a back-up method.

FINALLY, IF YOU ARE STILL NOT SURE WHAT TO DO ABOUT THE PILLS YOU HAVE MISSED:

Use a BACK-UP METHOD (such as condoms or spermicides) any time you have sex.

KEEP TAKING ONE ACTIVE PILL EACH DAY until you can reach your doctor or healthcare provider.

PREGNANCY DUE TO PILL FAILURE

The incidence of pill failure resulting in pregnancy is approximately less than 1% (one pregnancy per 100 women per year of use) if taken every day as directed, but more typical failure rates are about 5%. If failure does occur with **YASMIN** use, the risk to the fetus is unknown.

PREGNANCY AFTER STOPPING THE PILL

There may be some delay in becoming pregnant after you stop using oral contraceptives, especially if you had irregular menstrual cycles before you used oral contraceptives. It may be advisable to postpone conception until you begin menstruating regularly once you have stopped taking the pill and desire pregnancy.

There does not appear to be any increase in birth defects in newborn babies when pregnancy occurs soon after stopping the pill.

OVERDOSAGE

Serious ill effects have not been reported following ingestion of large doses of other oral contraceptives by young children. Overdosage of **YASMIN** may cause nausea and withdrawal bleeding in females and may increase blood levels of potassium or decrease blood levels of sodium, which could be dangerous. In case of overdosage, contact your healthcare provider.

OTHER INFORMATION

Your healthcare provider will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the healthcare provider believes that it is appropriate to postpone it. You should be re-examined at least once a year. Be sure to inform your healthcare provider if there is a family history of any of the conditions listed previously in this leaflet. Be sure to keep all appointments

with your healthcare provider, because this is a time to determine if there are early signs of side effects of oral contraceptive use.

Do not use the drug for any condition other than the one for which it was prescribed. This drug has been prescribed specifically for you; do not give it to others who may want birth-control pills.

HEALTH BENEFITS FROM ORAL CONTRACEPTIVES

In addition to preventing pregnancy, use of oral contraceptives may provide certain benefits. They are:

- Menstrual cycles may become more regular
- Blood flow during menstruation may be lighter and less iron may be lost. Therefore, anemia due to iron deficiency is less likely to occur.
- Pain or other symptoms during menstruation may be encountered less frequently
- Ovarian cysts may occur less frequently
- Ectopic (tubal) pregnancy may occur less frequently
- Noncancerous cysts or lumps in the breast may occur less frequently
- Acute pelvic inflammatory disease may occur less frequently
- Oral contraceptive use may provide some protection against developing two forms of cancer: cancer of the ovaries and cancer of the lining of the uterus

If you want more information about birth-control pills, ask your doctor or pharmacist. They have a more technical leaflet called the Prescribing Information which you may wish to read.

Manufactured by

Bayer HealthCare Pharmacueticals Inc.
Wayne, NJ 07470

Manufactured in Germany

US April 2010

Appendix D

US Approved Labeling for YAZ (3 mg drospirenone/0.02 mg ethinyl estradiol)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use YAZ safely and effectively. See full prescribing information for YAZ.

YAZ (drospirenone/ethinyl estradiol tablets)

Initial U.S. Approval: 2001

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

See full prescribing information for complete boxed warning

- **Women over 35 years old who smoke should not use Yaz (4).**
- **Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. (4)**

----------RECENT MAJOR CHANGES----------

Warnings and Precautions (5.1, 5.7) 3/2011

----------INDICATIONS AND USAGE----------

Yaz is an estrogen/progestin COC, indicated for use by women to:

- Prevent pregnancy. (1.1)
- Treat symptoms of premenstrual dysphoric disorder (PMDD) for women who choose to use an oral contraceptive for contraception. (1.2)
- Treat moderate acne for women at least 14 years old only if the patient desires an oral contraceptive for birth control. (1.3)

----------DOSAGE AND ADMINISTRATION----------

- Take one tablet daily by mouth at the same time every day. (2.1)
- Tablets must be taken in the order directed on the blister pack. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Yaz consists of 28 film-coated, biconvex tablets in the following order (3):

- 24 light pink tablets, each containing 3 mg drospirenone (DRSP) and 0.02 mg ethinyl estradiol (EE) as betadex clathrate
- 4 white inert tablets

----------CONTRAINDICATIONS----------

- Renal impairment or adrenal insufficiency (4)
- A high risk of arterial or venous thrombotic diseases (4)
- Undiagnosed abnormal uterine bleeding (4)
- Breast cancer or other estrogen- or progestin-sensitive cancer (4)
- Liver tumors or liver disease (4)
- Pregnancy (4)

----------WARNINGS AND PRECAUTIONS----------

- Vascular risks: Stop Yaz if a thrombotic event occurs. Stop at least 4 weeks before and through 2 weeks after major surgery. Start no earlier than 4 weeks after delivery, in women who are not breastfeeding. (5.1)
- Hyperkalemia: DRSP has antimineralocorticoid activity. Do not use in patients predisposed to hyperkalemia. Check serum potassium level during the first treatment cycle in women on long-term treatment with medications that may increase serum potassium. (5.2, 7.3)
- Liver disease: Discontinue Yaz if jaundice occurs. (5.4)
- High blood pressure: Do not prescribe Yaz for women with uncontrolled hypertension or hypertension with vascular disease. (5.5)
- Carbohydrate and lipid metabolic effects: Monitor prediabetic and diabetic women taking Yaz. Consider an alternate contraceptive method for women with uncontrolled dyslipidemia. (5.7)
- Headache: Evaluate significant change in headaches and discontinue Yaz if indicated. (5.8)
- Uterine bleeding: Evaluate irregular bleeding or amenorrhea. (5.9)

----------ADVERSE REACTIONS----------

- The most frequent (≥ 2%) adverse reactions in contraception and acne clinical trials were: headache/migraine (6.7%), menstrual irregularities (4.7%), nausea/vomiting (4.2%), breast pain/tenderness (4.0%) and mood changes (2.2%).
- The most frequent (≥ 2%) adverse reactions in PMDD clinical trials were: menstrual irregularities (24.9%), nausea (15.8%), headache (13.0%), breast tenderness (10.5%), fatigue (4.2%), irritability (2.8%), decreased libido (2.8%), increased weight (2.5%), and affect lability (2.1%).

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals Inc. at 1-888-842-2937 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

Drugs or herbal products that induce certain enzymes (for example, CYP3A4) may decrease the effectiveness of COCs or increase breakthrough bleeding. Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with COCs. (7.1)

----------USE IN SPECIFIC POPULATIONS----------

Nursing Mothers: Not recommended; can decrease milk production. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 3/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

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1.2 Premenstrual Dysphoric Disorder (PMDD)
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2 DOSAGE AND ADMINISTRATION
2.1 How to Take Yaz
2.2 How to Start Yaz
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FULL PRESCRIBING INFORMATION

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptives (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs should not be used by women who are over 35 years of age and smoke. *[See Contraindications (4)]*.

1 INDICATIONS AND USAGE

1.1 Oral Contraceptive

Yaz is indicated for use by women to prevent pregnancy.

1.2 Premenstrual Dysphoric Disorder (PMDD)

Yaz is also indicated for the treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive as their method of contraception. The effectiveness of Yaz for PMDD when used for more than three menstrual cycles has not been evaluated.

The essential features of PMDD according to the Diagnostic and Statistical Manual-4th edition (DSM-IV) include markedly depressed mood, anxiety or tension, affective lability, and persistent anger or irritability. Other features include decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite or sleep, and feeling out of control. Physical symptoms associated with PMDD include breast tenderness, headache, joint and muscle pain, bloating and weight gain. In this disorder, these symptoms occur regularly during the luteal phase and remit within a few days following onset of menses; the disturbance markedly interferes with work or school, or with usual social activities and relationships with others. Diagnosis is made by healthcare providers according to DSM-IV criteria, with symptomatology assessed prospectively over at least two menstrual cycles. In making the diagnosis, care should be taken to rule out other cyclical mood disorders.

Yaz has not been evaluated for the treatment of premenstrual syndrome (PMS).

1.3 Acne

Yaz is indicated for the treatment of moderate acne vulgaris in women at least 14 years of age, who have no known contraindications to oral contraceptive therapy and have achieved menarche. Yaz should be used for the treatment of acne only if the patient desires an oral contraceptive for birth control.

2 DOSAGE AND ADMINISTRATION

2.1 How to Take Yaz

Take one tablet by mouth at the same time every day. The failure rate may increase when pills are missed or taken incorrectly.

To achieve maximum contraceptive and PMDD effectiveness, Yaz must be taken exactly as directed. Single missed pills should be taken as soon as remembered.

2.2 How to Start Yaz

Instruct the patient to begin taking Yaz either on the first day of her menstrual period (Day 1 Start) or on the first Sunday after the onset of her menstrual period (Sunday Start).

Day 1 Start

During the first cycle of Yaz use, instruct the patient to take one light pink Yaz daily, beginning on Day one (1) of her menstrual cycle. (The first day of menstruation is Day one.) She should take one light pink Yaz daily for 24 consecutive days, followed by one white inert tablet daily on days 25 through 28. Yaz should be taken in the order directed on the package at the same time each day, preferably after the evening meal or at bedtime with some liquid, as needed. Yaz can be taken without regard to meals. If Yaz is first taken later than the first day of the menstrual cycle, Yaz should not be considered effective as a contraceptive until after the first 7 consecutive days of product administration. Instruct the patient to use a non-hormonal contraceptive as back-up during the first 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered.

Sunday Start

During the first cycle of Yaz use, instruct the patient to take one light pink Yaz daily, beginning on the first Sunday after the onset of her menstrual period. She should take one light pink Yaz daily for 24 consecutive days, followed by one white inert tablet daily on days 25 through 28. Yaz should be taken in the order directed on the package at the same time each day, preferably after the evening meal or at bedtime with some liquid, as needed. Yaz can be taken without regard to meals. Yaz should not be considered effective as a contraceptive until after the first 7 consecutive days of product administration. Instruct the patient to use a non-hormonal contraceptive as back-up during the first 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered.

The patient should begin her next and all subsequent 28-day regimens of Yaz on the same day of the week that she began her first regimen, following the same schedule. She should begin taking her light pink tablets on the next day after ingestion of the last white tablet, regardless of whether or not a menstrual period has occurred or is still in progress. Anytime a subsequent cycle of Yaz is started later than the day following administration of the last white tablet, the patient should use another method of contraception until she has taken a light pink Yaz daily for seven consecutive days.

When switching from a different birth control pill

When switching from another birth control pill, Yaz should be started on the same day that a new pack of the previous oral contraceptive would have been started.

When switching from a method other than a birth control pill

When switching from a transdermal patch or vaginal ring, Yaz should be started when the next application would have been due. When switching from an injection, Yaz should be started when the next dose would have been due. When switching from an intrauterine contraceptive or an implant, Yaz should be started on the day of removal.

Withdrawal bleeding usually occurs within 3 days following the last light pink tablet. If spotting or breakthrough bleeding occurs while taking Yaz, instruct the patient to continue taking her Yaz by the regimen described above. Counsel her that this type of bleeding is usually transient and without significance; however, advise her that if the bleeding is persistent or prolonged, she should consult her healthcare provider.

Although the occurrence of pregnancy is low if Yaz is taken according to directions, if withdrawal bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking them on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy. Discontinue Yaz if pregnancy is confirmed.

The risk of pregnancy increases with each active light pink tablet missed. For additional patient instructions regarding missed pills, see the "**WHAT TO DO IF YOU MISS PILLS**" section in the **FDA Approved Patient Labeling** which follows. If breakthrough bleeding occurs following missed tablets, it will usually be transient and of no consequence. If the patient misses one or more white tablets, she should still be protected against pregnancy provided she begins taking a new cycle of light pink tablets on the proper day.

For postpartum women who do not breastfeed or after a second trimester abortion, start Yaz no earlier than 4 weeks postpartum due to the increased risk of thromboembolism. If the patient starts on Yaz postpartum and has not yet had a period, evaluate for possible pregnancy, and instruct her to use an additional method of contraception until she has taken Yaz for 7 consecutive days.

2.3 Advice in case of Gastrointestinal Disturbances

In case of severe vomiting or diarrhea, absorption may not be complete and additional contraceptive measures should be taken. If vomiting occurs within 3–4 hours after tablet-taking, this can be regarded as a missed tablet.

3 DOSAGE FORMS AND STRENGTHS

Yaz (drospirenone/ethinyl estradiol tablets) is available in blister packs.

Each blister pack (28 film-coated tablets) contains in the following order:

- 24 light pink tablets each containing 3 mg drospirenone (DRSP) and 0.02 mg ethinyl estradiol (EE) as betadex clathrate
- 4 white inert tablets

4 CONTRAINDICATIONS

Do not prescribe Yaz to women who are known to have the following:

- Renal impairment
- Adrenal insufficiency
- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
  - Smoke, if over age 35 *[see Boxed Warning and Warnings and Precautions (5.1)]*
  - Have deep vein thrombosis or pulmonary embolism, now or in the past *[see Warnings and Precautions (5.1)]*
  - Have cerebrovascular disease *[see Warnings and Precautions (5.1)]*
  - Have coronary artery disease *[see Warnings and Precautions (5.1)]*
  - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) *[see Warnings and Precautions (5.1)]*
  - Have inherited or acquired hypercoagulopathies *[see Warnings and Precautions (5.1)]*
  - Have uncontrolled hypertension *[see Warnings and Precautions (5.5)]*
  - Have diabetes mellitus with vascular disease *[see Warnings and Precautions (5.7)]*
  - Have headaches with focal neurological symptoms or have migraine headaches with or without aura if over age 35 *[see Warnings and Precautions (5.8)]*
- Undiagnosed abnormal uterine bleeding *[see Warnings and Precautions (5.9)]*
- Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past *[see Warnings and Precautions (5.3)]*
- Liver tumors, benign or malignant, or liver disease *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.7)]*
- Pregnancy, because there is no reason to use COCs during pregnancy *[see Warnings and Precautions (5.10) and Use in Specific Populations (8.1)]*

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders and Other Vascular Problems

Stop Yaz if an arterial or venous thrombotic (VTE) event occurs.

The use of COCs increases the risk of venous thromboembolism. However, pregnancy increases the risk of venous thromboembolism as much or more than the use of COCs. The risk of venous thromboembolism in women using COCs has been estimated to be 3 to 9 per 10,000 woman-years. The risk of VTE is highest during the first year of use. Interim data from a large, prospective cohort safety study of various COCs suggest that this increased risk, as compared to that in non-COC users, is greatest during the first 6 months of COC use. Interim data from this safety study indicate that the greatest risk of VTE is present after initially starting a COC or restarting (following a 4 week or greater pill-free interval) the same or a different COC.

Use of COCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions, especially in women with other risk factors for these events.

The risk of thromboembolic disease due to oral contraceptives gradually disappears after COC use is discontinued.

If feasible, stop Yaz at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of thromboembolism.

Start Yaz no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum thromboembolism decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.

COCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years of age), hypertensive women who also smoke. COCs also increase the risk for stroke in women with other underlying risk factors.

Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

Stop Yaz if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately. *[See Adverse Reactions (6).]*

Epidemiologic studies including a DRSP-containing COC

Several studies have investigated the relative risks of thromboembolism in women using a different DRSP-containing COC (Yasmin, which contains 0.03 mg of EE and 3 mg of DRSP) compared to those in women using COCs containing other progestins. Two prospective cohort studies, both evaluating the risk of venous and arterial thromboembolism and death, were initiated at the time of Yasmin approval.[1,2] The first (EURAS) showed the risk of thromboembolism (particularly venous thromboembolism) and death in Yasmin users to be comparable to that of other oral contraceptive preparations, including those containing levonorgestrel (a so-called second generation COC). The second prospective cohort study (Ingenix) also showed a comparable risk of thromboembolism in Yasmin users compared to users of other COCs, including those containing levonorgestrel. In the second study, COC comparator groups were selected based on their having similar characteristics to those being prescribed Yasmin.

Two additional epidemiological studies, one case-control study (van Hylckama Vlieg et al.[3]) and one retrospective cohort study (Lidegaard et al.[4]) suggested that the risk of venous thromboembolism occurring in Yasmin users was higher than that for users of levonorgestrel-containing COCs and lower than that for users of desogestrel/gestodene-containing COCs (so-called third generation COCs). In the case-control study, however, the number of Yasmin cases was very small (1.2% of all cases) making the risk estimates unreliable. The relative risk for Yasmin users in the retrospective cohort study was greater than that for users of other COC products when considering women who used the products for less than one year. However, these one-year estimates may not be reliable because the analysis may include women of varying risk levels. Among women who used the product for 1 to 4 years, the relative risk was similar for users of Yasmin to that for users of other COC products.

5.2 Hyperkalemia

Yaz contains 3 mg of the progestin DRSP which has antimineralocorticoid activity, including the potential for hyperkalemia in high-risk patients, comparable to a 25 mg dose of spironolactone. Yaz should not be used in patients with conditions that predispose to hyperkalemia (that is, renal impairment, hepatic dysfunction and adrenal insufficiency). Women receiving daily, long-term treatment for chronic conditions or diseases with medications that may increase serum potassium should have their serum potassium level checked during the first treatment cycle. Medications that may increase serum potassium include ACE inhibitors, angiotensin-II receptor antagonists, potassium-sparing diuretics, potassium supplementation, heparin, aldosterone antagonists, and NSAIDS.

5.3 Carcinoma of the Breasts and Reproductive Organs

Women who currently have or have had breast cancer should not use Yaz because breast cancer is a hormonally-sensitive tumor.

There is substantial evidence that COCs do not increase the incidence of breast cancer. Although some past studies have suggested that COCs might increase the incidence of breast cancer, more recent studies have not confirmed such findings.

Some studies suggest that COCs are associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there is controversy about the extent to which these findings may be due to differences in sexual behavior and other factors.

5.4 Liver Disease

Discontinue Yaz if jaundice develops. Steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded.

Hepatic adenomas are associated with COC use. An estimate of the attributable risk is 3.3 cases/100,000 COC users. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) COC users. However, the attributable risk of liver cancers in COC users is less than one case per million users.

Oral contraceptive-related cholestasis may occur in women with a history of pregnancy-related cholestasis. Women with a history of COC-related cholestasis may have the condition recur with subsequent COC use.

5.5 High Blood Pressure

For women with well-controlled hypertension, monitor blood pressure and stop Yaz if blood pressure rises significantly. Women with uncontrolled hypertension or hypertension with vascular disease should not use COCs.

An increase in blood pressure has been reported in women taking COCs, and this increase is more likely in older women and with extended duration of use. The incidence of hypertension increases with increasing concentration of progestin.

5.6 Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among COC users.

5.7 Carbohydrate and Lipid Metabolic Effects

Carefully monitor prediabetic and diabetic women who are taking Yaz. COCs may decrease glucose intolerance in a dose-related fashion.

Consider alternative contraception for women with uncontrolled dyslipidemias. A small proportion of women will have adverse lipid changes while on COC's.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

5.8 Headache

If a woman taking Yaz develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Yaz if indicated.

An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC.

5.9 Bleeding Irregularities

Unscheduled (breakthrough or intracyclic) bleeding and spotting sometimes occur in patients on COCs, especially during the first three months of use. If bleeding persists or occurs after previously regular cycles, check for causes such as pregnancy or malignancy. If pathology and pregnancy are excluded, bleeding irregularities may resolve over time or with a change to a different COC.

Based on patient diaries from two contraceptive clinical trials of Yaz, 8 to 25% of women experienced unscheduled bleeding per 28-day cycle. A total of 12 subjects out of 1,056 (1.1%) discontinued due to menstrual disorders including intermenstrual bleeding, menorrhagia, and metrorrhagia.

Women who use Yaz may experience absence of withdrawal bleeding, even if they are not pregnant. Based on subject diaries from contraception trials for up to 13 cycles, 6 to 10% of women experienced cycles with no withdrawal bleeding. Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was pre-existent.

If withdrawal bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking them on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

5.10 COC Use Before or During Early Pregnancy

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb-reduction defects are concerned, when taken inadvertently during early pregnancy.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy [see Use in Specific Populations (8.1)].

5.11 Depression

Women with a history of depression should be carefully observed and Yaz discontinued if depression recurs to a serious degree.

5.12 Interference with Laboratory Tests

The use of COCs may change the results of some laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins. Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentrations of thyroid-binding globulin increase with use of COCs. DRSP causes an increase in plasma renin activity and plasma aldosterone induced by its mild antimineralocorticoid activity.

5.13 Monitoring

A woman who is taking COCs should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated healthcare.

5.14 Other Conditions

In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema. Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking COCs.

6 ADVERSE REACTIONS

The following serious adverse reactions with the use of COCs are discussed elsewhere in the labeling:

- Serious cardiovascular events and smoking *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Vascular events *[see Warnings and Precautions (5.1)]*
- Liver disease *[see Warnings and Precautions (5.3)]*

Adverse reactions commonly reported by COC users are:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Contraception and Acne Clinical Trials

The data provided reflect the experience with the use of Yaz in the adequate and well-controlled studies for contraception (N=1,056) and for moderate acne vulgaris (N=536).

For contraception, a Phase 3, multicenter, multinational, open-label study was conducted to evaluate safety and efficacy up to one year in 1,027 women aged 17 – 36 who took at least one dose of Yaz. A second Phase 3 study was a single center, open-label, active-controlled study to evaluate the effect of 7 28-day cycles of Yaz on carbohydrate metabolism, lipids and hemostasis in 29 women aged 18–35. For acne, two multicenter, double-blind, randomized, placebo-controlled studies, in 536 women aged 14–45 with moderate acne vulgaris who took at least one dose of Yaz, evaluated the safety and efficacy during up to 6 cycles.

The adverse reactions seen across the 2 indications overlapped, and are reported using the frequencies from the pooled dataset. The most common adverse reactions (≥ 2% of users) were: headache/migraine (6.7%), menstrual irregularities (including vaginal hemorrhage [primarily spotting] and metrorrhagia (4.7%), nausea/vomiting (4.2%), breast pain/tenderness (4%) and mood changes (mood swings, depression, depressed mood and affect lability) (2.2%).

PMDD Clinical Trials

Safety data from trials for the indication of PMDD are reported separately due to differences in study design and setting in the Contraception and Acne studies as compared to the PMDD clinical program.

Two (one parallel and one crossover designed) multicenter, double-blind, randomized, placebo-controlled trials for the secondary indication of treating the symptoms of PMDD evaluated safety and efficacy of Yaz during up to 3 cycles among 285 women aged 18–42, diagnosed with PMDD and who took at least one dose of Yaz.

Common adverse reactions (≥ 2% of users) were: menstrual irregularities (including vaginal hemorrhage [primarily spotting] and metrorrhagia) (24.9%), nausea (15.8%), headache (13%), breast tenderness (10.5%), fatigue (4.2%), irritability (2.8%), decreased libido (2.8%), increased weight (2.5%), and affect lability (2.1%).

Adverse Reactions (≥1%) Leading to Study Discontinuation:

Contraception Clinical Trials

Of 1,056 women, 6.6% discontinued from the clinical trials due to an adverse reaction; the most frequent adverse reactions leading to discontinuation were headache/migraine (1.6%) and nausea/vomiting (1%).

Acne Clinical Trials

Of 536 women, 5.4% discontinued from the clinical trials due to an adverse reaction; the most frequent adverse reaction leading to discontinuation was menstrual irregularities (including menometrorrhagia, menorrhagia, metrorrhagia and vaginal hemorrhage) (2.2%) .

PMDD Clinical Trials

Of 285 women, 11.6% discontinued from the clinical trials due to an adverse reaction; the most frequent adverse reactions leading to discontinuation were: nausea/vomiting (4.6%), menstrual irregularity (including vaginal hemorrhage, menorrhagia, menstrual disorder, menstruation irregular and metrorrhagia) (4.2%), fatigue (1.8%), breast tenderness (1.4%), depression (1.4%), headache (1.1%), and irritability (1.1%).

Serious Adverse Reactions:

Contraception Clinical Trials: migraine and cervical dysplasia

Acne Clinical Trials: none reported in the clinical trials

PMDD Clinical Trials: cervical dysplasia

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Yaz. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions are grouped into System Organ Classes, and ordered by frequency.

Vascular disorders: Venous and arterial thromboembolic events (including pulmonary emboli, deep vein thrombosis, cerebral thrombosis, retinal thrombosis, myocardial infarction and stroke), hypertension (including hypertensive crisis)

Hepatobiliary disorders: Gallbladder disease, liver function disturbances, liver tumors

Immune system disorders: Hypersensitivity (including anaphylactic reaction)

Metabolism and nutrition disorders: Hyperkalemia, hypertriglyceridemia, changes in glucose tolerance or effect on peripheral insulin resistance (including diabetes mellitus)

Skin and subcutaneous tissue disorders: Chloasma, angioedema, erythema nodosum, erythema multiforme

Gastrointestinal disorders: Inflammatory bowel disease

Musculoskeletal and connective tissue disorders: Systemic lupus erythematosus

7 DRUG INTERACTIONS

Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations**.**

7.1 Effects of Other Drugs on Combined Hormonal Contraceptives

Substances diminishing the efficacy of COCs: Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of COCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate and products containing St. John's wort. Interactions between oral contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Substances increasing the plasma levels of COCs: Co-administration of atorvastatin and certain COCs containing EE increase AUC values for EE by approximately 20%. Ascorbic acid and acetaminophen may increase plasma EE levels, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels.

*HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors***:** Significant changes (increase and decrease) in plasma levels of estrogen and progestin have been noted in some cases of co-administration with HIV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors.

Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids.

Effect on DRSP: The main metabolites of DRSP in human plasma are generated without involvement of the cytochrome P450 system. Inhibitors of this enzyme system are therefore unlikely to influence the metabolism of DRSP.

7.2 Effects of Combined Oral Contraceptives on Other Drugs

COCs containing EE may inhibit the metabolism of other compounds. COCs have been shown to significantly decrease plasma concentrations of lamotrigine, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary. Consult the labeling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations.

In vitro and clinical studies did not indicate an inhibitory potential of DRSP towards human CYP450 enzymes at clinically relevant concentrations *[see Clinical Pharmacology (12.3)*].

7.3 Interactions that Have the Potential to Increase Serum Potassium

There is a potential for an increase in serum potassium in women taking Yaz with other drugs that may increase serum potassium *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There is little or no increased risk of birth defects in women who inadvertently use COCs during early pregnancy. Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to low dose COCs prior to conception or during early pregnancy.

The administration of COCs to induce withdrawal bleeding should not be used as a test for pregnancy. COCs should not be used during pregnancy to treat threatened or habitual abortion.

Women who do not breastfeed may start COCs no earlier than four weeks postpartum.

8.3 Nursing Mothers

When possible, advise the nursing mother to use other forms of contraception until she has weaned her child. Estrogen-containing COCs can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. Small amounts of oral contraceptive steroids and/or metabolites are present in breast milk.

After oral administration of 3 mg DRSP/0.03 mg EE (Yasmin) tablets, about 0.02% of the DRSP dose was excreted into the breast milk of postpartum women within 24 hours. This results in a maximal daily dose of about 0.003 mg DRSP in an infant.

8.4 Pediatric Use

Safety and efficacy of Yaz has been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 18 and for users 18 years and older. Use of this product before menarche is not indicated.

8.5 Geriatric Use

Yaz has not been studied in postmenopausal women and is not indicated in this population.

8.6 Patients with Renal Impairment

Yaz is contraindicated in patients with renal impairment [*see Contraindications (4) and Warnings and Precautions (5.2)*].

In subjects with mild renal impairment (creatinine clearance CLcr, 50–80 mL/min), serum DRSP levels were comparable to those in subjects with normal renal function (CLcr, >80 mL/min). In subjects with moderate renal impairment (CLcr, 30–50 mL/min), serum DRSP levels were on average 37% higher than those in the group with normal renal function. In addition, there is a potential to develop hyperkalemia in subjects with renal impairment whose serum potassium is in the upper reference range, and who are concomitantly using potassium sparing drugs *[see Clinical Pharmacology (12.3)]*.

8.7 Patients with Hepatic Impairment

Yaz is contraindicated in patients with hepatic disease [*see Contraindications (4) and Warnings and Precautions (5.4)]*. The mean exposure to DRSP in women with moderate liver impairment is approximately three times higher than the exposure in women with normal liver function. Yaz has not been studied in women with severe hepatic impairment.

10 OVERDOSAGE

There have been no reports of serious ill effects from overdose, including ingestion by children. Overdosage may cause withdrawal bleeding in females and nausea.

DRSP is a spironolactone analogue which has antimineralocorticoid properties. Serum concentration of potassium and sodium, and evidence of metabolic acidosis, should be monitored in cases of overdose.

11 DESCRIPTION

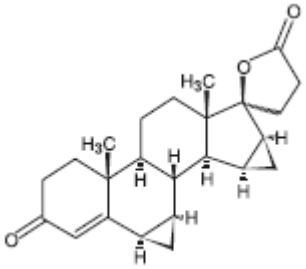
Yaz (drospirenone/ethinyl estradiol tablets) provides an oral contraceptive regimen consisting of 24 light pink active film-coated tablets each containing 3 mg of drospirenone and 0.02 mg of ethinyl estradiol stabilized by betadex as a clathrate (molecular inclusion complex) and 4 white inert film coated tablets.

The inactive ingredients in the light pink tablets are lactose monohydrate NF, corn starch NF, magnesium stearate NF, hypromellose USP, talc USP, titanium dioxide USP, ferric oxide pigment, red NF. The white inert film-coated tablets contain lactose monohydrate NF, corn starch NF, povidone 25000 USP, magnesium stearate NF, hypromellose USP, talc USP, titanium dioxide USP.

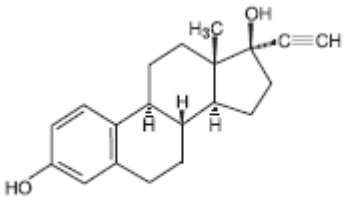
Drospirenone (6R,7R,8R,9S,10R,13S,14S,15S,16S,17S)-1,3',4',6,6a,7,8,9,10,11, 12,13,14,15,15a,16-hexadecahydro-10,13-dimethylspiro-[17H-dicyclopropa- [6,7:15,16]cyclopenta[a]phenanthrene-17,2'(5H)-furan]-3,5'(2H)-dione) is a synthetic progestational compound and has a molecular weight of 366.5 and a molecular formula of $C_{24}H_{30}O_3$.

Ethinyl estradiol (19-nor-17α-pregna 1,3,5(10)-triene-20-yne-3, 17-diol) is a synthetic estrogenic compound and has a molecular weight of 296.4 and a molecular formula of $C_{20}H_{24}O_2$.

The structural formulas are as follows:



Drospirenone



Ethinyl estradiol

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

COCs lower the risk of becoming pregnant primarily by suppressing ovulation. Other possible mechanisms may include cervical mucus changes that inhibit sperm penetration and the endometrial changes that reduce the likelihood of implantation.

12.2 Pharmacodynamics

Drospirenone is a spironolactone analogue with antimineralocorticoid and antiandrogenic activity**.** The estrogen in Yaz is ethinyl estradiol.

Contraception

Two studies evaluated the effect of 3 mg DRSP / 0.02 mg EE combinations on the suppression of ovarian activity as assessed by measurement of follicle size via transvaginal ultrasound and serum hormone (progesterone and estradiol) analyses during two treatment cycles (21-day active tablet period plus 7-day pill-free period). More than 90% of subjects in these studies demonstrated ovulation inhibition. One study compared the effect of 3 mg DRSP/0.02 mg EE combinations with two different regimens (24-day active tablet period plus 4-day pill-free period vs. 21-day active tablet period plus 7-day pill-free period) on the suppression of ovarian activity during two treatment cycles. During the first treatment cycle, there were no subjects (0/49, 0%) taking the 24-day regimen who ovulated compared to 1 subject (1/50, 2%) using the 21-day regimen. After intentionally introduced dosing errors (3 missed active tablets on Days 1 to 3) during the second treatment cycle, there was 1 subject (1/49, 2%) taking the 24-day regimen who ovulated compared to 4 subjects (4/50, 8%) using the 21-day regimen.

Acne

Acne vulgaris is a skin condition with a multifactorial etiology including androgen stimulation of sebum production. While the combination of EE and DRSP increases sex hormone binding globulin (SHBG) and decreases free testosterone, the relationship between these changes and a decrease in the severity of facial acne in otherwise healthy women with this skin condition has not been established. The impact of the antiandrogenic activity of DRSP on acne is not known.

12.3 Pharmacokinetics

Absorption

The absolute bioavailability of DRSP from a single entity tablet is about 76%. The absolute bioavailability of EE is approximately 40% as a result of presystemic conjugation and first-pass metabolism**.** The absolute bioavailability of Yaz**,** which is a combination tablet of DRSP and EE stabilized by betadex as a clathrate (molecular inclusion complex), has not been evaluated. The bioavailability of EE is similar when dosed via a betadex clathrate formulation compared to when it is dosed as a free steroid. Serum concentrations of DRSP and EE reached peak levels within 1–2 hours after administration of Yaz.

The pharmacokinetics of DRSP are dose proportional following single doses ranging from 1–10 mg. Following daily dosing of Yaz, steady state DRSP concentrations were observed after 8 days. There was about 2 to 3 fold accumulation in serum C_{max} and AUC (0–24h) values of DRSP following multiple dose administration of Yaz (see Table I).

For EE, steady-state conditions are reported during the second half of a treatment cycle. Following daily administration of Yaz, serum C_{max} and AUC (0–24h) values of EE accumulate by a factor of about 1.5 to 2 (see Table I).

TABLE I: TABLE OF PHARMACOKINETIC PARAMETERS OF YAZ (DRSP 3 mg and EE 0.02 mg)

DRSP					
Cycle / Day	**No. of Subjects**	**Cmax[a] (ng/mL)**	**Tmax[b] (h)**	**AUC(0–24h)[a] (ng•h/mL)**	**$t_{1/2}$ [a] (h)**
1/1	23	38.4 (25)	1.5 (1–2)	268 (19)	NA[c]
1/21	23	70.3 (15)	1.5 (1–2)	763 (17)	30.8 (22)
EE					
Cycle / Day	**No. of Subjects**	**Cmax[a] (pg/mL)**	**Tmax[b] (h)**	**AUC(0–24h)[a] (pg•h/mL)**	**$t_{1/2}$ [a] (h)**
1/1	23	32.8 (45)	1.5 (1–2)	108 (52)	NA[c]
1/21	23	45.1 (35)	1.5 (1–2)	220 (57)	NA[c]

a) geometric mean (geometric coefficient of variation)

b) median (range)

c) NA = Not available

Food Effect

The rate of absorption of DRSP and EE following single administration of a formulation similar to Yaz was slower under fed (high fat meal) conditions with the serum C_{max} being reduced about 40% for both components. The extent of absorption of DRSP, however, remained unchanged. In contrast, the extent of absorption of EE was reduced by about 20% under fed conditions.

Distribution

DRSP and EE serum levels decline in two phases. The apparent volume of distribution of DRSP is approximately 4 L/kg and that of EE is reported to be approximately 4-5 L/kg.

DRSP does not bind to SHBG or corticosteroid binding globulin (CBG) but binds about 97% to other serum proteins. Multiple dosing over 3 cycles resulted in no change in the free fraction (as measured at trough levels). EE is reported to be highly but non-specifically bound to serum albumin (approximately 98.5 %) and induces an increase in the serum concentrations of both SHBG and CBG. EE induced effects on SHBG and CBG were not affected by variation of the DRSP dosage in the range of 2 to 3 mg.

Metabolism

The two main metabolites of DRSP found in human plasma were identified to be the acid form of DRSP generated by opening of the lactone ring and the 4,5-dihydrodrospirenone-3-sulfate. These metabolites were shown not to be pharmacologically active. In *in vitro* studies with human liver microsomes, DRSP was metabolized only to a minor extent mainly by Cytochrome P450 3A4 (CYP3A4).

EE has been reported to be subject to presystemic conjugation in both small bowel mucosa and the liver. Metabolism occurs primarily by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed. These are present as free metabolites and as conjugates with glucuronide and sulfate. CYP3A4 in the liver is responsible for the 2-hydroxylation which is the major oxidative reaction. The 2-hydroxy metabolite is further transformed by methylation and glucuronidation prior to urinary and fecal excretion.

Excretion

DRSP serum levels are characterized by a terminal disposition phase half-life of approximately 30 hours after both single and multiple dose regimens. Excretion of DRSP was nearly complete after ten days and amounts excreted were slightly higher in feces compared to urine. DRSP was extensively metabolized and only trace amounts of unchanged DRSP were excreted in urine and feces. At least 20 different metabolites were observed in urine and feces. About 38–47% of the metabolites in urine were glucuronide and sulfate conjugates. In feces, about 17–20% of the metabolites were excreted as glucuronides and sulfates.

For EE the terminal disposition phase half-life has been reported to be approximately 24 hours. EE is not excreted unchanged. EE is excreted in the urine and feces as glucuronide and sulfate conjugates and undergoes enterohepatic circulation.

Specific Populations

Pediatric Use: Safety and efficacy of Yaz has been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 18 and for users 18 years and older. Use of this product before menarche is not indicated. *[See Use in Specific Populations (8.4)]*

Geriatric Use: Yaz has not been studied in postmenopausal women and is not indicated in this population. *[See Use in Specific Populations (8.5)]*

Race: No clinically significant difference was observed between the pharmacokinetics of DRSP or EE in Japanese versus Caucasian women (age 25–35) when 3mg DRSP/0.02 mg EE was administered daily for 21 days. Other ethnic groups have not been specifically studied.

Renal Impairment*:* Yaz is contraindicated in patients with renal impairment.

The effect of renal impairment on the pharmacokinetics of DRSP (3 mg daily for 14 days) and the effect of DRSP on serum potassium levels were investigated in female subjects (n=28, age 30–65) with normal renal function and mild and moderate renal impairment. All subjects were on a low potassium diet. During the study, 7 subjects continued the use of potassium sparing drugs for the treatment of their underlying illness. On the 14th day (steady-state) of DRSP treatment, the serum DRSP levels in the group with mild renal impairment (creatinine clearance CLcr, 50–80 mL/min) were comparable to those in the group with normal renal function (CLcr, >80 mL/min). The serum DRSP levels were on average 37% higher in the group with moderate renal impairment (CLcr, 30–50 mL/min) compared to those in the group with normal renal function. DRSP treatment did not show any clinically significant effect on serum potassium concentration. Although hyperkalemia was not observed in the study, in five of the seven subjects who continued use of potassium sparing drugs during the study, mean serum potassium levels increased by up to 0.33 mEq/L. *[See Contraindications (4), Warnings and Precautions (5.2) and Use in Specific Populations (8.6).]*

Hepatic Impairment: Yaz is contraindicated in patients with hepatic disease.

The mean exposure to DRSP in women with moderate liver impairment is approximately three times higher than the exposure in women with normal liver function. Yaz has not been studied in women with severe hepatic impairment. *[see Contraindications (4), Warnings and Precautions (5.4) and Use in Specific Populations (8.7)]*

Drug Interactions

Effects of Other Drugs on Combined Hormonal Contraceptives

Substances diminishing the efficacy of COCs: Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of COCs or increase breakthrough bleeding. *[See Drug Interactions (7.1).]*

Substances increasing the plasma levels of COCs: Co-administration of atorvastatin and certain COCs containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20%. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels. *[See Drug Interactions (7.1).]*

HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma levels of estrogen and progestin have been noted in some cases of co-administration with HIV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors. *[See Drug Interactions (7.1).]*

Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids. *[See Drug Interactions (7.1).]*

Effects of Combined Oral Contraceptives on Other Drugs

COCs containing ethinyl estradiol may inhibit the metabolism of other compounds. COCs have been shown to significantly decrease plasma concentrations of lamotrigine, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary. Consult the labeling of the

concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations. *[See Drug Interactions (7.2) .]*

Metabolism of DRSP and potential effects of DRSP on hepatic cytochrome P450 (CYP) enzymes have been investigated in *in vitro* and *in vivo* studies. In *in vitro* studies DRSP did not affect turnover of model substrates of CYP1A2 and CYP2D6, but had an inhibitory influence on the turnover of model substrates of CYP1A1, CYP2C9, CYP2C19 and CYP3A4, with CYP2C19 being the most sensitive enzyme. The potential effect of DRSP on CYP2C19 activity was investigated in a clinical pharmacokinetic study using omeprazole as a marker substrate. In the study with 24 postmenopausal women [including 12 women with homozygous (wild type) CYP2C19 genotype and 12 women with heterozygous CYP2C19 genotype] the daily oral administration of 3 mg DRSP for 14 days did not affect the oral clearance of omeprazole (40 mg, single oral dose) and the CYP2C19 product 5-hydroxy omeprazole. Furthermore, no significant effect of DRSP on the systemic clearance of the CYP3A4 product omeprazole sulfone was found. These results demonstrate that DRSP did not inhibit CYP2C19 and CYP3A4 *in vivo*. *[See Drug Interactions (7.2) .]*

Two additional clinical drug-drug interaction studies using simvastatin and midazolam as marker substrates for CYP3A4 were each performed in 24 healthy postmenopausal women. The results of these studies demonstrated that pharmacokinetics of the CYP3A4 substrates were not influenced by steady state DRSP concentrations achieved after administration of 3 mg DRSP/day. *[See Drug Interactions (7.2) .]*

Interactions With Drugs That Have the Potential to Increase Serum Potassium

There is a potential for an increase in serum potassium in women taking Yaz with other drugs that may increase serum potassium *[see Warnings and Precautions (5.2)]*.

A drug-drug interaction study of DRSP 3 mg/estradiol (E2) 1 mg versus placebo was performed in 24 mildly hypertensive postmenopausal women taking enalapril maleate 10 mg twice daily. Potassium levels were obtained every other day for a total of 2 weeks in all subjects. Mean serum potassium levels in the DRSP/E2 treatment group relative to baseline were 0.22 mEq/L higher that those in the placebo group. Serum potassium concentrations also were measured at multiple time points over 24 hours at baseline and on Day 14. On Day 14, the ratios for serum potassium C_{max} and AUC in the DRSP/E2 group to those in the placebo group were 0.955 (90% CI: 0.914, 0.999) and 1.010 (90% CI: 0.944, 1.08), respectively. No patient in either treatment group developed hyperkalemia (serum potassium concentrations >5.5 mEq/L).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24 month oral carcinogenicity study in mice dosed with 10 mg/kg/day DRSP alone or 1 + 0.01, 3 + 0.03 and 10 + 0.1 mg/kg/day of DRSP and EE, 0.1 to 2 times the exposure (AUC of DRSP) of women taking a contraceptive dose, there was an increase in carcinomas of the harderian gland in the group that received the high dose of DRSP alone. In a similar study in rats given 10 mg/kg/day DRSP alone or 0.3 + 0.003, 3 + 0.03 and 10 + 0.1 mg/kg/day DRSP and EE, 0.8 to 10 times the exposure of women taking a contraceptive dose, there was an increased incidence of benign and malignant adrenal gland pheochromocytomas in the group receiving the high dose of DRSP. Mutagenesis studies for DRSP were conducted *in vivo* and *in vitro* and no evidence of mutagenic activity was observed.

14 CLINICAL STUDIES

14.1 Oral Contraceptive Clinical Trial

In the primary contraceptive efficacy study of Yaz (3 mg DRSP/0.02 mg EE) of up to 1 year duration, 1,027 subjects were enrolled and completed 11,480 28-day cycles of use. The age range was 17 to 36 years. The racial demographic was: 87.8% Caucasian, 4.6% Hispanic, 4.3% Black, 1.2% Asian, and 2.1% other. Women with a BMI greater than 35 were excluded from the trial. The pregnancy rate (Pearl Index) was 1.41 (95% CI [0.73, 2.47]) per 100 woman-years of use based on 12 pregnancies that occurred after the onset of treatment and within 14 days after the last dose of Yaz in women 35 years of age or younger during cycles in which no other form of contraception was used.

14.2 Premenstrual Dysphoric Disorder Clinical Trials

Two multicenter, double-blind, randomized, placebo-controlled studies were conducted to evaluate the effectiveness of Yaz in treating the symptoms of PMDD. Women aged 18–42 who met DSM-IV criteria for PMDD, confirmed by

prospective daily ratings of their symptoms, were enrolled. Both studies measured the treatment effect of Yaz using the Daily Record of Severity of Problems scale, a patient-rated instrument that assesses the symptoms that constitute the DSM-IV diagnostic criteria. The primary study was a parallel group design that included 384 evaluable reproductive-aged women with PMDD who were randomly assigned to receive Yaz or placebo treatment for 3 menstrual cycles. The supportive study, a crossover design, was terminated prematurely prior to achieving recruitment goals due to enrollment difficulties. A total of 64 women of reproductive age with PMDD were treated initially with Yaz or placebo for up to 3 cycles followed by a washout cycle and then crossed over to the alternate medication for 3 cycles.

Efficacy was assessed in both studies by the change from baseline during treatment using a scoring system based on the first 21 items of the Daily Record of Severity of Problems. Each of the 21 items was rated on a scale from 1 (not at all) to 6 (extreme); thus a maximum score of 126 was possible. In both trials, women who received Yaz had statistically significantly greater improvement in their Daily Record of Severity of Problems scores. In the primary study, the average decrease (improvement) from baseline was 37.5 points in women taking Yaz, compared to 30.0 points in women taking placebo.

14.3 Acne Clinical Trials

In two multicenter, double-blind, randomized, placebo-controlled studies, 889 subjects, ages 14 to 45 years, with moderate acne received Yaz or placebo for six 28-day cycles. The primary efficacy endpoints were the percent change in inflammatory lesions, non-inflammatory lesions, total lesions, and the percentage of subjects with a "clear" or "almost clear" rating on the Investigator's Static Global Assessment (ISGA) scale on day 15 of cycle 6, as presented in Table II:

Table II: Efficacy Results for Acne Trials*

	Study 1		Study 2	
	YAZ N=228	Placebo N=230	YAZ N=218	Placebo N=213
ISGA Success Rate	35 (15%)	10 (4%)	46 (21%)	19 (9%)
Inflammatory Lesions				
Mean Baseline Count	33	33	32	32
Mean Absolute (%) Reduction	15 (48%)	11 (32%)	16 (51%)	11 (34%)
Non-inflammatory Lesions				
Mean Baseline Count	47	47	44	44
Mean Absolute (%) Reduction	18 (39%)	10 (18%)	17 (42%)	11 (26%)
Total lesions				
Mean Baseline Count	80	80	76	76
Mean Absolute (%) Reduction	33 (42%)	21 (25%)	33 (46%)	22 (31%)

* Evaluated at day 15 of cycle 6, last observation carried forward for the Intent to treat population

15 REFERENCES

1. Dinger JC, Heinemann LAJ, et al: The safety of a drospirenone-containing oral contraceptive: final results from the European active surveillance study on oral contraceptives based on 142,475 women-years of observation. *Contraception* 2007;75:344-354.

2. Seeger JD, Loughlin J, Eng PM, et al: Risk of thromboembolism in women taking ethinyl estradiol/drospirenone and other oral contraceptives. *Obstetrics & Gynecology* 2007;110(3):587-593.

3. van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, et al: The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. *BMJ* 2009;339:b2921.

4. Lidegaard O, Lokkegaard E, Svendsen AL, et al: Hormonal contraception and risk of venous thromboembolism: national follow-up study. *BMJ* 2009; 339:b2890.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Yaz (drospirenone/ethinyl estradiol tablets) are available in packages of three blister packs (NDC 50419-405-03).

The film-coated tablets are rounded with biconvex faces, one side is embossed with DS or DP in a regular hexagon.

Each blister pack (28 film-coated tablets) contains in the following order:

- 24 active light pink round, unscored, film-coated tablets debossed with a "DS" in a regular hexagon on one side, each containing 3 mg drospirenone and 0.02 mg ethinyl estradiol
- 4 inert white round, unscored, film-coated tablets debossed with a "DP" in a regular hexagon on one side.

16.2 Storage Conditions

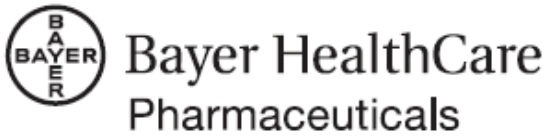
Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling.

- Counsel patients that cigarette smoking increases the risk of serious cardiovascular events from COC use, and that women who are over 35 years old and smoke should not use COCs.
- Counsel patients that the increased risk of VTE compared to non-users of COCs is greatest after initially starting a COC or restarting (following a 4 week or greater pill-free interval) the same or a different COC.
- Counsel patients that Yaz does not protect against HIV-infection (AIDS) and other sexually transmitted diseases.
- Counsel patients on Warnings and Precautions associated with COCs.
- Counsel patients that Yaz contains DRSP. Drospirenone may increase potassium. Patients should be advised to inform their healthcare provider if they have kidney, liver or adrenal disease because the use of Yaz in the presence of these conditions could cause serious heart and health problems. They should also inform their healthcare provider if they are currently on daily, long-term treatment (NSAIDs, potassium-sparing diuretics, potassium supplementation, ACE inhibitors, angiotensin-II receptor antagonists, heparin or aldosterone antagonists) for a chronic condition.
- Yaz is not indicated during pregnancy. If pregnancy is planned or occurs during treatment with Yaz, further intake must be stopped.
- Counsel patients to take one tablet daily by mouth at the same time every day. Instruct patients what to do in the event pills are missed. *See* ***"WHAT TO DO IF YOU MISS PILLS"*** *section in* ***FDA-APPROVED PATIENT LABELING.***
- Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with COCs.
- Counsel patients who are breastfeeding or who desire to breastfeed that COCs may reduce breast milk production. This is less likely to occur if breastfeeding is well established.
- Counsel any patient who starts COCs postpartum, and who have not yet had a period, to use an additional method of contraception until she has taken a light pink tablet for 7 consecutive days.
- Counsel patients that amenorrhea may occur. Rule out pregnancy in the event of amenorrhea in two or more consecutive cycles.

Manufactured for



Bayer HealthCare Pharmaceuticals Inc.
Wayne, NJ 07470

Manufactured in Germany

FDA Approved Patient Labeling

Guide for Using Yaz

WARNING TO WOMEN WHO SMOKE

Do not use Yaz if you smoke cigarettes and are over 35 years old. Smoking increases your risk of serious cardiovascular side effects (heart and blood vessel problems) from birth control pills, including death from heart attack, blood clots or stroke. This risk increases with age and the number of cigarettes you smoke.

Birth control pills help to lower the chances of becoming pregnant when taken as directed. They do not protect against HIV infection (AIDS) and other sexually transmitted diseases.

What Is Yaz?

Yaz is a birth control pill. It contains two female hormones, a synthetic estrogen called ethinyl estradiol and a progestin called drospirenone.

The progestin drospirenone may increase potassium. Therefore, you should not take Yaz if you have kidney, liver or adrenal disease because this could cause serious heart and health problems. Other drugs may also increase potassium. If you are currently on daily, long-term treatment for a chronic condition with any of the medications below, you should consult your healthcare provider about whether Yaz is right for you, and during the first month that you take Yaz, you should have a blood test to check your potassium level.

- NSAIDs (ibuprofen [Motrin, Advil], naproxen [Aleve and others] when taken long-term and daily for treatment of arthritis or other problems)
- Potassium-sparing diuretics (spironolactone and others)
- Potassium supplementation
- ACE inhibitors (Capoten, Vasotec, Zestril and others)
- Angiotensin-II receptor antagonists (Cozaar, Diovan, Avapro and others)
- Heparin
- Aldosterone antagonists

Yaz may also be taken to treat premenstrual dysphoric disorder (PMDD) if you choose to use the Pill for birth control. Unless you have already decided to use the Pill for birth control, you should not start Yaz to treat your PMDD because there are other medical therapies for PMDD that do not have the same risks as the Pill. PMDD is a mood disorder related to the menstrual cycle. PMDD significantly interferes with work or school, or with usual social activities and relationships with others. Symptoms include markedly depressed mood, anxiety or tension, mood swings, and persistent anger or irritability. Other features include decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite or sleep, and feeling out of control. Physical symptoms associated with PMDD may include breast tenderness, headache, joint and muscle pain, bloating and weight gain. These symptoms occur regularly before menstruation starts and go away within a few days following the start of the period. Diagnosis of PMDD should be made by healthcare providers.

You should only use Yaz for treatment of PMDD if you:

- Have already decided to use oral contraceptives for birth control, and
- Have been diagnosed with PMDD by your healthcare provider.

Yaz has not been shown to be effective for the treatment of premenstrual syndrome (PMS), a less serious set of symptoms occurring before menstruation. If you or your healthcare provider believe you have PMS, you should take Yaz only if you want to prevent pregnancy; and not for the treatment of PMS.

Yaz may also be taken to treat moderate acne if all of the following are true:

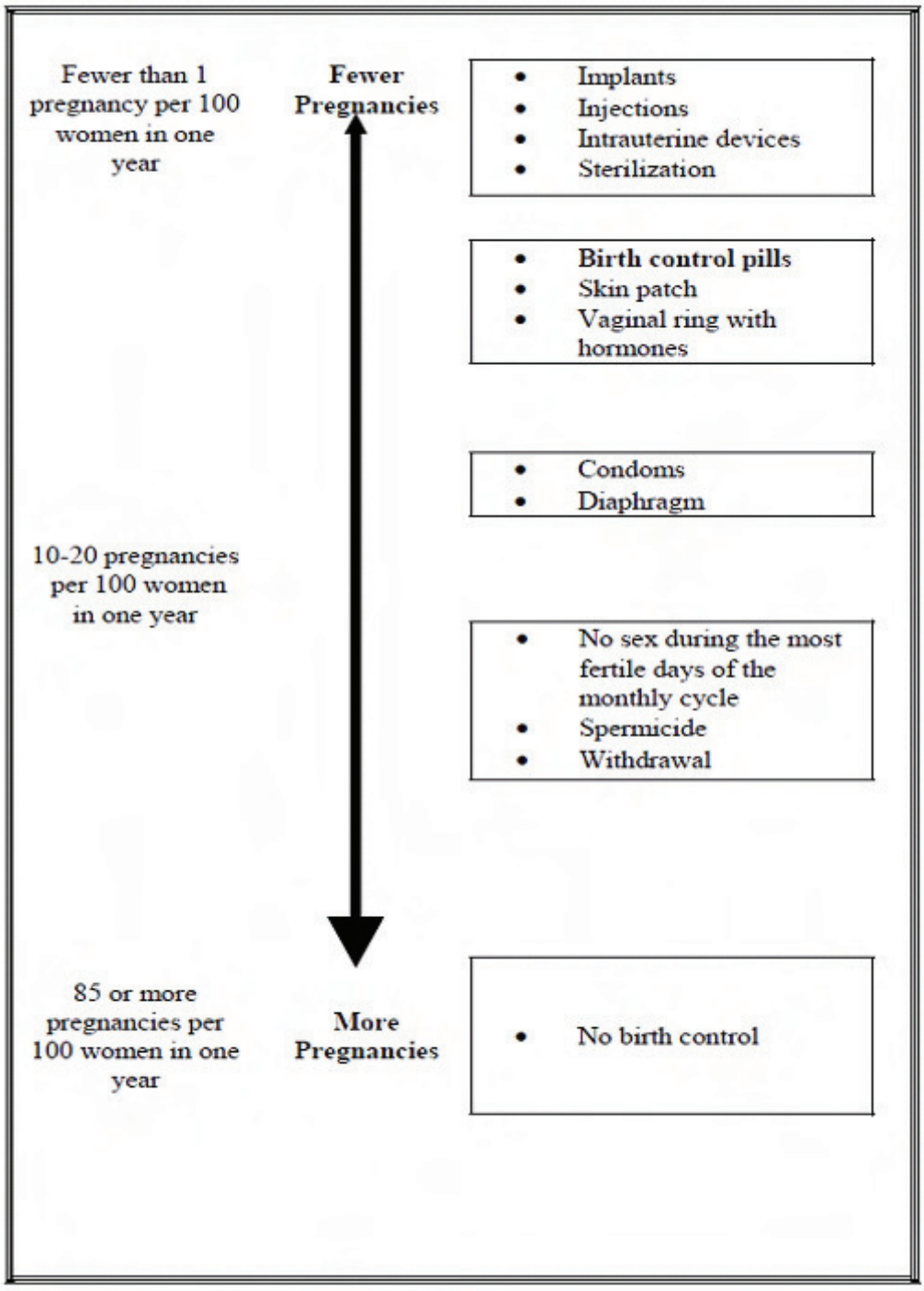
- Your healthcare provider says it is safe for you to use Yaz.
- You are at least 14 years old.
- You have started having menstrual periods.
- You want to use a birth control pill to prevent pregnancy.

How Well Does Yaz Work?

Your chance of getting pregnant depends on how well you follow the directions for taking your birth control pills. The better you follow the directions, the less chance you have of getting pregnant.

Based on the results of one clinical study, 1 to 2 women out of 100 women, may get pregnant during the first year they use Yaz.

The following chart shows the chance of getting pregnant for women who use different methods of birth control. Each box on the chart contains a list of birth control methods that are similar in effectiveness. The most effective methods are at the top of the chart. The box on the bottom of the chart shows the chance of getting pregnant for women who do not use birth control and are trying to get pregnant.



How Do I Take Yaz?

1. **Be sure to read these directions** before you start taking your pills or anytime you are not sure what to do.

2. The right way to take the pill is to take one pill every day at the same time in the order directed on the package. Preferably, take the pill after the evening meal or at bedtime, with some liquid, as needed. Yaz can be taken without regard to meals.

If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant. See "WHAT TO DO IF YOU MISS PILLS" below.

Reference ID: 2917017

3. Many women have spotting or light bleeding at unexpected times, or may feel sick to their stomach during the first 1-3 packs of pills.

If you do have spotting or light bleeding or feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it does not go away, check with your healthcare provider.

4. Missing pills can also cause spotting or light bleeding, even when you make up these missed pills.

On the days you take two pills, to make up for missed pills, you could also feel a little sick to your stomach.

5. If you have vomiting (within 3 to 4 hours after you take your pill), you should follow the instructions for "WHAT TO DO IF YOU MISS PILLS." If you have diarrhea or if you take certain medicines, including some antibiotics and some herbal products such as St. John's Wort, your pills may not work as well.

Use a back-up method (such as condoms and spermicides) until you check with your healthcare provider.

6. If you have trouble remembering to take the pill, talk to your healthcare provider about how to make pill-taking easier or about using another method of birth control.

7. **If you have any questions or are unsure about the information in this leaflet, call your healthcare provider.**

Before You Start Taking Your Pills

1. Decide What Time of Day You Want to Take Your Pill

It is important to take Yaz in the order directed on the package at the same time every day, preferably after the evening meal or at bedtime, with some liquid, as needed. Yaz can be taken without regard to meals.

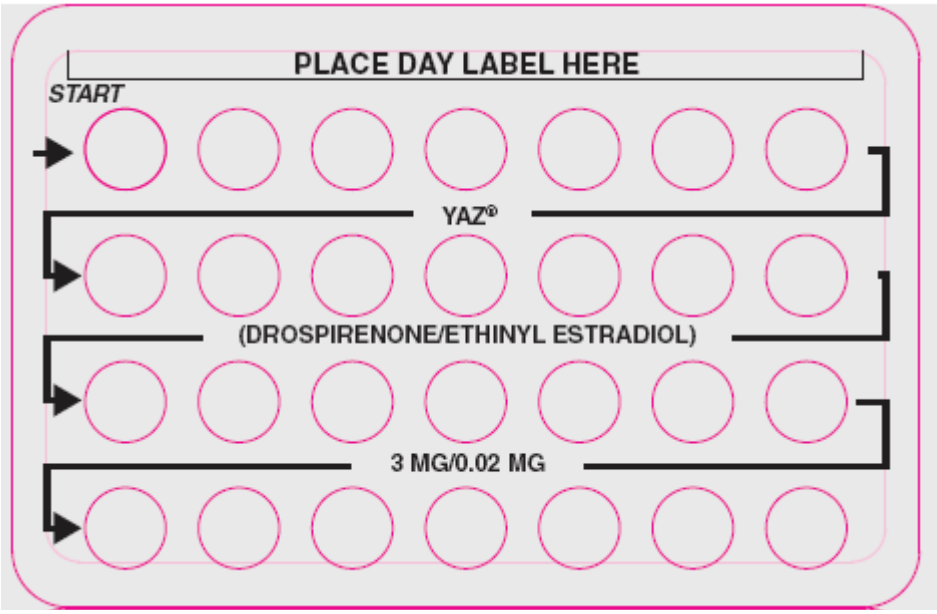
2. Look at Your Pill Pack – It has 28 Pills

The Yaz-pill pack has 24 light pink pills (with hormones) to be taken for 24 days, followed by 4 white pills (without hormones) to be taken for the next four days.

3. Also look for:

a) Where on the pack to start taking pills,

b) In what order to take the pills (follow the arrows)



4. Be sure you have ready at all times (a) another kind of birth control (such as condoms and spermicides) to use as a back-up in case you miss pills, and (b) an extra, full pill pack.

When To Start the First Pack of Pills

You have a choice for which day to start taking your first pack of pills. Decide with your healthcare provider which is the best day for you. Pick a time of day which will be easy to remember.

Day 1 Start:

1. Take the first light pink pill of the pack during the first 24 hours of your period.

2. You will not need to use a back-up method of birth control, since you are starting the Pill at the beginning of your period. However, if you start Yaz later than the first day of your period, you should use another method of birth control (such as a condom and spermicide) as a back-up method until you have taken 7 light pink pills.

Sunday Start:

1. Take the first light pink pill of the pack on the Sunday after your period starts, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.

2. Use another method of birth control (such as a condom and spermicide) as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days). This also applies if you start Yaz after having been pregnant, and you have not had a period since your pregnancy.

When You Switch From a Different Birth Control Pill

When switching from another birth control pill, Yaz should be started on the same day that a new pack of the previous birth control pill would have been started.

When You Switch From Another Type of Birth Control Method

When switching from a transdermal patch or vaginal ring, Yaz should be started when the next application would have been due. When switching from an injection, Yaz should be started when the next dose would have been due. When switching from an intrauterine contraceptive or an implant, Yaz should be started on the day of removal.

What to Do During the Month

1. Take one pill at the same time every day until the pack is empty.

Do not skip pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea).

Do not skip pills even if you do not have sex very often.

2. When you finish a pack of pills, start the next pack on the day after your last white pill. Do not wait any days between packs.

What to Do if You Miss Pills

If you miss 1 light pink pill of your pack:

1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take two pills in one day.

2. You do not need to use a back-up birth control method if you have sex.

If you miss 2 light pink pills in a row in Week 1 or Week 2 of your pack:

1. Take two pills on the day you remember and two pills the next day.

2. Then take one pill a day until you finish the pack.

3. **You could become pregnant** if you have sex in the 7 days after you restart your pills. You must use another birth control method (such as a condom and spermicide) as a back-up for those 7 days.

If you miss 2 light pink pills in a row in Week 3 or Week 4 of your pack:

1. **If you are a Day 1 Starter**:

Throw out the rest of the pill pack and start a new pack that same day.

If you are a Sunday Starter:

Keep taking one pill every day until Sunday. On Sunday, throw out the rest of the pack and start a new pack of pills that same day.

2. **You could become pregnant** if you have sex in the 7 days after you restart your pills. You must use another birth control method (such as a condom and spermicide) as a back-up for those 7 days.

3. You may not have your period this month but this is expected. **However, if you miss your period two months in a row, call your healthcare provider because you might be pregnant.**

If you miss 3 or more light pink pills in a row during any week:

1. **If you are a Day 1 Starter:**

Throw out the rest of the pill pack and start a new pack that same day.

If you are a Sunday Starter:

Keep taking 1 pill every day until Sunday. On Sunday, throw out the rest of the pack and start a new pack of pills that same day.

2. **You could become pregnant** if you have sex in the 7 days after you restart your pills. You must use another birth control method (such as condoms and spermicides) as a back-up for those 7 days.

3. **Call your healthcare provider if you miss your period, because you might be pregnant.**

If you miss any of the 4 white pills in Week 4:

Throw away the pills you missed.

Keep taking one pill each day until the pack is empty.

You do not need a back-up method.

Finally, if you are still not sure what to do about the pills you have missed:

Use a back-up method (such as condoms and spermicides) anytime you have sex.

Contact your healthcare provider and continue taking one active light pink pill each day until otherwise directed.

WHO SHOULD NOT TAKE Yaz?

Your healthcare provider will not give you Yaz if you:

• Ever had blood clots in your legs (deep vein thrombosis), lungs (pulmonary embolism), or eyes (retinal thrombosis)

• Ever had a stroke

• Ever had a heart attack

• Have certain heart valve problems or heart rhythm abnormalities that can cause blood clots to form in the heart

• Have an inherited problem with your blood that makes it clot more than normal

• Have high blood pressure that medicine can't control

• Have diabetes with kidney, eye, nerve, or blood vessel damage

• Ever had certain kinds of severe migraine headaches with aura, numbness, weakness or changes in vision

• Ever had breast cancer or any cancer that is sensitive to female hormones

• Have liver disease, including liver tumors

• Have kidney disease

• Have adrenal disease

Also, do not take birth control pills if you:

• Smoke and are over 35 years old

• Are or suspect you are pregnant

Birth control pills may not be a good choice for you if you have ever had jaundice (yellowing of the skin or eyes) caused by pregnancy (also called cholestasis of pregnancy).

Tell your healthcare provider if you have ever had any of the above conditions (your healthcare provider can recommend another method of birth control).

What Else Should I Know about Taking Yaz?

Birth control pills do not protect you against any sexually transmitted disease, including HIV, the virus that causes AIDS.

Do not skip any pills, even if you do not have sex often.

If you miss a period, you could be pregnant. However, some women miss periods or have light periods on birth control pills, even when they are not pregnant. Contact your healthcare provider for advice if you:

- Think you are pregnant

- Miss one period and have not taken your birth control pills every day
- Miss two periods in a row

Birth control pills should not be taken during pregnancy. However, birth control pills taken by accident during pregnancy are not known to cause birth defects.

You should stop Yaz at least four weeks before you have major surgery and not restart it until at least two weeks after the surgery due to an increased risk of blood clots.

If you are breastfeeding, consider another birth control method until you are ready to stop breastfeeding. Birth control pills that contain estrogen, like Yaz, may decrease the amount of milk you make. A small amount of the pill's hormones pass into breast milk.

If you are currently on daily, long-term treatment for a chronic condition with any of the following medications, you should consult your healthcare provider before taking Yaz:

- NSAIDs (ibuprofen, naproxen and others)
- Potassium-sparing diuretics (spironolactone and others)
- Potassium supplementation
- ACE inhibitors (captopril, enalapril, lisinopril and others)
- Angiotensin-II receptor antagonists (Cozaar, Diovan, Avapro and others)
- Heparin
- Aldosterone antagonists

Tell your healthcare provider about all medicines and herbal products that you take. Some other medicines and herbal products may make birth control pills less effective, including:

- Barbiturates
- Bosentan
- Carbamazepine
- Felbamate
- Griseofulvin
- Oxcarbazepine
- Phenytoin
- Rifampin
- St. John’s wort
- Topiramate

Consider using another birth control method when you take medicines that may make birth control pills less effective.

Birth control pills may interact with lamotrigine, an anticonvulsant used for epilepsy. This may increase the risk of seizures, so your healthcare provider may need to adjust the dose of lamotrigine.

If you have vomiting or diarrhea, your birth control pills may not work as well. Use another birth control method, like condoms and a spermicide, until you check with your healthcare provider.

If you are scheduled for any laboratory tests, tell your doctor you are taking birth-control pills. Certain blood tests may be affected by birth-control pills.

What are the Most Serious Risks of Taking Birth Control Pills?

Like pregnancy, birth control pills increase the risk of serious blood clots, especially in women who have other risk factors, such as smoking, obesity, or age greater than 35. This increased risk is highest when you first start taking birth control pills and when you restart the same or different birth control pills after not using them for a month or more.

It is possible to die from a problem caused by a blood clot, such as a heart attack or a stroke. Some examples of serious clots are blood clots in the:

- Legs (thrombophlebitis)
- Lungs (pulmonary embolus)
- Eyes (loss of eyesight)
- Heart (heart attack)
- Brain (stroke)

A few women who take birth control pills may get:

- High blood pressure
- Gallbladder problems
- Rare cancerous or noncancerous liver tumors

All of these events are uncommon in healthy women.

Call your healthcare provider right away if you have:

- Persistent leg pain
- Sudden shortness of breath
- Sudden blindness, partial or complete
- Severe pain in your chest
- Sudden, severe headache unlike your usual headaches
- Weakness or numbness in an arm or leg, or trouble speaking
- Yellowing of the skin or eyeballs

What are the Common Side Effects of Birth Control Pills?

The most common side effects of birth control pills are:

- Spotting or bleeding between menstrual periods
- Nausea
- Breast tenderness
- Headache

These side effects are usually mild and usually disappear with time.

Less common side effects are:

- Acne
- Less sexual desire
- Bloating or fluid retention
- Blotchy darkening of the skin, especially on the face
- High blood sugar, especially in women who already have diabetes
- High fat (cholesterol; triglyceride) levels in the blood
- Depression, especially if you have had depression in the past. Call your healthcare provider immediately if you have any thoughts of harming yourself.
- Problems tolerating contact lenses
- Weight changes

This is not a complete list of possible side effects. Talk to your healthcare provider if you develop any side effects that concern you. You may report side effects to the FDA at 1-800-FDA-1088.

No serious problems have been reported from a birth control pill overdose, even when accidentally taken by children.

Do Birth Control Pills Cause Cancer?

Birth control pills do not seem to cause breast cancer. However, if you have breast cancer now, or have had it in the past, do not use birth control pills because some breast cancers are sensitive to hormones.

Women who use birth control pills may have a slightly higher chance of getting cervical cancer. However, this may be due to other reasons such as having more sexual partners.

What Should I Know about My Period when Taking Yaz?

Irregular vaginal bleeding or spotting may occur while you are taking Yaz. Irregular bleeding may vary from slight staining between menstrual periods to breakthrough bleeding, which is a flow much like a regular period. Irregular bleeding occurs most often during the first few months of oral contraceptive use, but may also occur after you have been taking the pill for some time. Such bleeding may be temporary and usually does not indicate any serious problems. It is important to continue taking your pills on schedule. If the bleeding occurs in more than one cycle, is unusually heavy, or lasts for more than a few days, call your healthcare provider.

Some women may not have a menstrual period but this should not be cause for alarm as long has you have taken the pills according to direction.

What if I Miss My Scheduled Period when Taking Yaz?

It is not uncommon to miss your period. However, if you miss two periods in a row or miss one period when you have not taken your birth control pills according to directions, call your healthcare provider. Also notify your healthcare provider if you have symptoms of pregnancy such as morning sickness or unusual breast tenderness. It is important that your healthcare provider checks you to find out if you are pregnant. Stop taking Yaz if you are pregnant.

What If I Want to Become Pregnant?

You may stop taking the pill whenever you wish. Consider a visit with your healthcare provider for a pre-pregnancy checkup before you stop taking the pill.

General Advice about Yaz

Your healthcare provider prescribed Yaz for you. Please do not share Yaz with anyone else. Keep Yaz out of the reach of children.

If you have concerns or questions, ask your healthcare provider. You may also ask your healthcare provider for a more detailed label written for medical professionals.

Bayer HealthCare Pharmaceuticals Inc.

Reference ID: 2917017

Appendix E

List of Selected References for Epidemiologic Studies for Drospirenone-containing Combination Oral Contraceptives

1. Dinger J, Heinemann L, Kühl-Habich D. 2007. The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance Study on oral contraceptives based on 142,475 women-years of observation. Contraception, 75(5): 344-54.
2. Seeger J, Loughlin J, Eng P, Clifford C, Cutone J, Walker A. 2007. Risk of thromboembolism in women taking ethinylestradiol /drospirenone and other oral contraceptives. Obstet Gynecol,110(3): 587-93.
3. Lidegaard Ø, Løkkegaard E, Svendsen AL, Agger C. 2009. Hormonal contraception and risk of venous thromboembolism: national follow-up study. Br Med J, 339: b2890.
4. van Hylckama Vlieg A, Helmerhorst F, Vandenbroucke J, Doggen C, Rosendaal F. 2009. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. BMJ, 339: b2921 doi:10.1136/bmj.b2921.
5. Dinger J, Assmann A, Mőhner S, Minh T. 2010. Risk of venous thromboembolism and the use of dienogest- and drospirenone-containing oral contraceptives: results from a German case-control study. J Fam Plann Reprod Health Care; 36(3): 123–9.
6. Jick S, Hernandez R. 2011. Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data. BMJ, 342: d2151 doi:10.1136/bmj.d2151.
7. Parkin L, Sharples K, Hernandez R, Jick S. 2011. Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested case-control study based on UK General Practice Research Database. BMJ, 342: d2139 doi:10.1136/bmj.d2139.
8. Lidegaard Ø, Nielsen L, Skovlund C, Skjeldestad F, Løkkegaard E. 2011. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9. BMJ, 343: d6423 doi: 10.1136/bmj.d6423.