CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-098

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE SENT: January 7, 2000	**DUE DATE:** January 17, 2000	**OPDRA CONSULT #:** 99-061

TO (Divisions):

Susan Allen, MD
Acting Director, Division of Reproductive and Urologic Drug Products
HFD-580

PRODUCT NAME:	**MANUFACTURER:**
Yasmin™ (Drospirenone 3 mg and Ethinyl Estradiol 0.03 mg Tablets) 21 and 28 day **NDA #:** 21-098	Berlex Laboratories, Inc.

CASE REPORT NUMBER(S): N/A

SUMMARY:

response to a consult from the Division of Reproductive and Urologic Drug Products (HFD-580), PDRA conducted a review of the proposed proprietary name Yasmin™, to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION:

OPDRA has no objections to the use of the proprietary name Yasmin™.

/S/

Jerry Phillips
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 480-8173

/S/ 1/6/00

Peter Honig, MD
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: January 3, 1999

NDA# 21-098

NAME OF DRUG: Yasmin™

NDA HOLDER: Berlex Laboratories, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products (HFD-580) to review the proposed proprietary drug name, Yasmin™, regarding potential name confusion with existing proprietary/generic drug names.

According to the Labeling and Nomenclature Committee (LNC) database, Yasmin™ was reviewed and found acceptable.

PRODUCT INFORMATION

Yasmin™ is a combination oral contraceptive indicated for the prevention of pregnancy in women who elect to use this product as a method of contraception. Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus and the endometrium. Yasmin™ is rapidly and extensively absorbed. Peak serum concentrations were reached 1 to 2 hours after single dose administration of two yasmin tablets. The terminal disposition phases half life for ethinyl estradiol and drospirenone have been reported to be approximately 24 and 30 hours, respectively. Yasmin™ will be available in cartons of 3 blister dispensers, each dispenser containing either a 21 day cycle or a 28 day cycle.

II. RISK ASSESSMENT:

In order to predict the potential for medication errors and to determine the degree of confusion associated with the proposed name, Yasmin™, with other approved and unapproved drug names, the medication error staff of OPDRA searched ALTMEDDEX Intranet Series, 1999, which includes the following published texts: DrugDex, Poisindex, Martindale, RPS Herbal Medicines, Index Nominum, and Physicians' Desk Reference (1999). Additional publications utilized to search for potential sound-alike or look-alike names to approved drugs were the American Drug Index (43rd Edition), Drug Facts and Comparisons (Updated Monthly), the Electronic Orange Book, CDER's New Approvals, and the US Patent and Trademark Office online database. OPDRA also searched several FDA databases for potential sound-alike or look-alike names to unapproved/approved drugs (Establishment Evaluation System (EES), Drug Product Reference File (DPR), Decision Support System (DSS) and the LNC database. In addition, OPDRA conducted an internal study of written and verbal analysis of the proposed proprietary name, involving health care practitioners within OPDRA,

to evaluate potential errors in handwriting and verbal communication of the name. This exercise was conducted to simulate an actual practice setting.

A) STUDY CONDUCTED WITHIN OPDRA

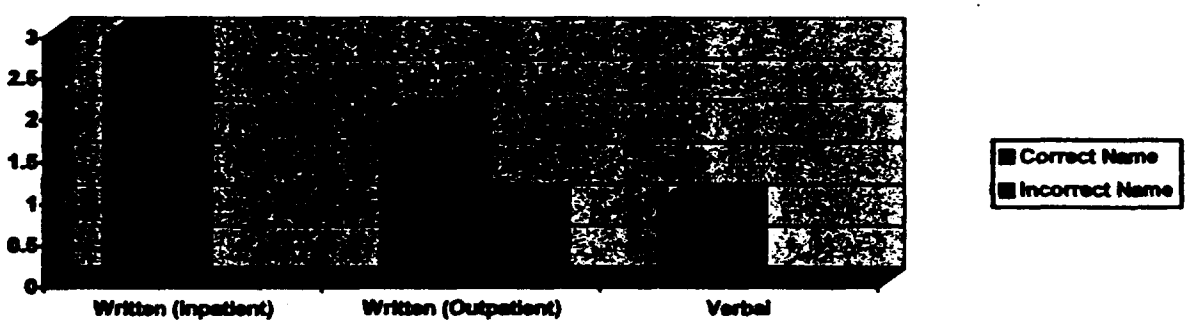
Methodology:

This study involved 19 health professionals comprised of pharmacists, physicians, and nurses within OPDRA to determine the degree of confusion of this name with other drug names due to the similarity in handwriting and verbal pronunciation of the name. OPDRA staff members wrote one inpatient order and three outpatient prescriptions, each consisting of known drug products and a prescription for Yasmin™ (See below). These prescriptions were scanned into the computer and a random sample of the written orders, were then delivered to the participating health professionals via e-mail. In addition, one pharmacist recorded an outpatient prescription order on voice mail. The voice mail messages were then sent to the participating health professionals for their review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Yasmin-28 1 PO QD no refills.	Yasmin-28, Take one table daily, with no refills.
Inpatient RX: Yasmin-28 1 PO QD	

Results:

We received responses from seven out of nineteen participants, six of which interpreted the name correctly. Three participants interpreted outpatient prescription orders, three interpreted inpatient orders, and one interpreted a verbal order. The results are as follows:



Eighty-six percent of the participants who responded interpreted the name correctly. The only incorrect response was "Yazmin". A low response rate to the verbal survey occurred, which makes interpretation of this data difficult.

B) FOCUS GROUP FINDINGS

The group discussed the following sound-alike/look-alike name that was uncovered in our searches:

[redacted]			
Jasmine	Herbal Tea	No medicinal use	S/A (look-alike) per OPDRA.

Although both names contain seven characters, five of which are common, the group did not consider this product to have significant potential for confusion since it is an herbal tea.

C) DISCUSSION:

The results of the verbal and written analysis studies demonstrate six out of seven participants interpreted the proprietary name Yasmin™ correctly. This study was completed prior to OPDRA expanding the number of our study participants by involving CDER in the evaluation of prescriptions. OPDRA did not repeat the study due to the limited amount of review time remaining and the low potential for concern with the proposed name. The only incorrect response provided was a phonetic variation of the name. The inaccurate interpretation of the proposed name did not overlap with any existing approved drug products.

In addition, the proprietary name does not contain any USAN stems.

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

In reviewing the draft product package insert, container labels, and carton labeling for YASMIN™, OPDRA has attempted to focus on safety issues relating to potential medication errors. Many of the items discussed in this consult involve issues normally reviewed by the chemist and medical officer.

A) BLISTER LABEL

The strength of both active ingredients should appear on the front side of the blister label, as is done with other oral contraceptives.

B) POUCH LABELING

The terminal zero in "3.0 mg" and "0.030 mg" should be deleted to avoid a tenfold confusion on strengths. In addition, the carton and insert labeling should be revised accordingly.

IV. RECOMMENDATIONS:

1. OPDRA has no objections to the use of the proprietary name Yasmin™.

2. OPDRA recommends the above labeling revisions to encourage the safest possible use of this product.

3. OPDRA considers this a final review due to the primary goal date of 17 March 2000, and will not request re-evaluation 60 days prior to the NDA approval.

If you have further questions or need clarifications, please contact Carol Holquist at 301-827-3244.

/S/ 1-5-2000

Carol Holquist, RPh
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

/S/ 1/6/2000

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

CC:

NDA 21-098
Office Files
HFD-580; DivFiles; Jeanine Best, Project Manager
HFD-580; Susan Allen, Acting Division Director
HFD-440; Denise Toyer, Safety Evaluator, DDREII, OPDRA
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-400; Peter Honig, Deputy Director, OPDRA
HFD-002; Murray Lumpkin, Acting Director, OPDRA

NDA 21-098
Yasmin® 28 Tablets (drospirenone/ethinyl estradiol)
Berlex Laboratories, Inc.

This Application is not on the Application Integrity Policy.

/S/ 4/13/01

/S/

Douglas C. Throckmorton, M.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20816
Tel (301) 594-5327, FAX (301) 594-5494

Memorandum

DATE: 10.10.00

FROM: Douglas C. Throckmorton, M.D., Deputy Director /S/
Division of Cardio-Renal Drug Products, HFD-110

THROUGH: Ray Lipicky, M.D., Ph.D., Division Director /S/
Division of Cardio-Renal Drug Products, HFD-110

TO: Janine Best, Project Manager
Scott E. Monroe, M.D., Medical Officer
Susan Allen, M.D. Division Director
Division of Reproductive and Urologic Drug Products (HFD-580)

SUBJECT: Clinical consequences of anti-mineralocorticoid effects of Yasmin
NAME OF DRUG: Drosperinone/ ethinyl estradiol
TRADE NAME: Yasmin
FORMULATION: PO

RELATED APPLICATIONS: N/A
APPROVED INDICATIONS: N/A
SPONSOR: Berlex Laboratories, Inc.

DOCUMENTS USED FOR REVIEW:

1. Memos dated 3.17.00 and 7.10.00 from Dr. Houn.
2. Memos dated 7.10.00 from Dr. Allen.
3. Memos dated 2.23.00 and 7.6.00 from Dr. Mann.
4. Memos dated 6.16.00 from Dr. Monroe.
5. Medical Review dated 2.15.00.
6. Statistical Review of NDA 21-098 from Dr. Kammerman.
7. Individual data listings from renal impairment study (section 14.2.1 of submission).
8. Draft Yasmin labeling (sent 9.20.00).
9. NDA 21-098 submissions dated 9.11.00 and 9.25.00.
   --analysis of changes in serum K+ and adverse events potentially related to hyperkalemia, submitted 9.11.00.
   --overheads for meeting with HFD-580 on 9.25.00.

ISSUES AND COMMENTS

Yasmin (Drosperinone, DSP) is an oral contraceptive under consideration by HFD-580. Per the sponsor, in pre-clinical evaluation it was found to have anti-mineralocorticoid effects equivalent to 25 milligrams of spironolactone. The issue is the clinical implications of this blockade. The kidney plays the primary role of regulating serum and total body potassium levels (the colon and sweating also play minor roles in the process). Within the kidney, potassium excretion is regulated by several mechanisms, including mineralocorticoids (especially aldosterone), which stimulate potassium secretion in the distal nephron, increasing K+ excretion into the urine. In individuals with normal kidneys, these other mechanisms (*e.g.*, sodium delivery to the distal part of the nephron, changes in cell transporters) compensate for a loss of the mineralocorticoid effect, such that individuals with normal kidneys should not be at risk for hyperkalemia under normal circumstances. This ability to compensate for acute and chronic changes in serum K+ can be seen as a kind of 'potassium excretory reserve'. Patients with damaged kidneys progressively lose this 'reserve, such that minor changes in dietary intake (*e.g.*, increased orange juice consumption) or other pathways used by the body to excrete potassium (*e.g.*, dehydration, constipation) can lead to life-threatening hyperkalemia. This 'potassium excretory reserve' can also be diminished by the concomitant use of drugs that block the mechanisms of K+ excretion: ACE Inhibitors (ACEIs), beta-blockers, heparin, digoxin, etc. Obviously, the more of these risk factors present in a given patient, the higher the risk of hyperkalemia when stressed. Based on this calculus, there are two groups that need consideration with regard to chronic Yasmin use: normal individuals and individuals who have impaired 'K+ excretory reserve.'

1. Does Yasmin (DSP) affect serum potassium levels and/or increase the risk of hyperkalemia in patients with normal renal function?

2. Does Yasmin (DSP) affect serum potassium levels and/or increase the risk of hyperkalemia in patients with diminished 'potassium excretory reserve' including patients taking ACE-inhibitors, NSAIDs, and those with renal insufficiency?

3. Based on the answers to these first two questions, what additional information is needed to understand the risk of hyperkalemia in patients taking Yasmin?

The remainder of this consultation will address these three questions in turn. There is a fourth issue, raised by the sponsor in their briefing package for the 10.25.00 meeting with the FDA: the potential 'benefits' of mineralocorticoid blockade. The idea put forward is that these benefits (*e.g.*, lowered blood pressure, decreased fluid retention, less hypokalemia) could offset the concerns about hyperkalemia. This issue will not be addressed further in this consultation as Drs. Allen and Houn appropriately pointed out that these potential 'benefits' are attractive but unproven. As such, they could not offset safety concerns based on Yasmin's capacity to impair potassium excretion.

1. Does Yasmin affect serum potassium levels and/or increase the risk of hyperkalemia in patients with normal renal function?

This discussion will be based primarily on the data submitted by the sponsor in the 10.11.00 Briefing Package. These data excluded two studies due to excessive hemolysis (92052, 93044) but included two studies whose results have not been individually submitted to the FDA for analysis (97036, 96097). In total, data on 1892 younger women who received DSP were submitted (plus 334 women given ethinyl estradiol or placebo as controls). Additional materials come from the briefing package provided for the sponsor for their meeting with HFD-580 on 10.25.00.

Mean Changes in Serum K+

The first analysis looked at the mean changes in serum K+ among the DSP and control populations in the trials that enrolled apparently healthy women. Text Table 6 from the package submitted 10.11.00 provides two useful points in this regard. First, the mean maximum K+ after baseline was higher in the DSP group than in the controls. This is easiest to see in results from 96097, where the maximum values for all of the 4 doses of DSP +estradiol groups are about twice that of the control (estradiol alone). Second, this increase in the maximum K+ during therapy is obscured when the postbaseline mean is evaluated (again, Text Table 6).

Individual Changes in Serum K+

The next analysis looked at the incidence of elevated K+ levels among the individuals in the trials. Using table 4 from the sponsor's 10.11.00 submission (page 23 of 118) the incidence of serum K+≥5.5 meq/L was 20/1892 (1.1%) in the DSP group and 5/334 (1.5%) in the control groups. One subject in the DSP group had a serum K+ >6.0 meq/L. The sponsor reported similar numbers looking only at those subjects who had post-baseline values.

Issues and Comments (cont)

Literature on Use of Mineralocorticoid-Antagonists in Women

In the 10.25.00 submission, the sponsor cited literature from the gynecological literature, where the use of spironolactone at doses up to 200 mg per day is apparently common. From a review of 56 publications on hyperandrogenic conditions, they identified two reported cases of hyperkalemia, and concluded that this supports the safe use of very high doses of spironolactone (with higher degrees of anti-mineralocorticoid activity) in the otherwise healthy female population. These results are quite difficult to interpret, as the reporting of hyperkalemia in this population is likely limited by infrequent testing of serum electrolytes and infrequent reporting of hyperkalemia as an adverse event (like all lab findings in general).

Effects of High Doses of DSP

In study 89092, the sponsor looked at the effect of 5 days of DSP (10mg) of DSP in healthy 6 women.Per Dr. Monroe's review, this short-term treatment had little effect on the renin-aldosterone axis in the women.

In study 89015, the sponsor administered single doses of DSP (10 to 100 mg) to healthy males. Renin levels rose only in the highest dose group, and no hyperkalemia was reported.

Conclusions of Reviewer

What can be concluded from the available data on the effects of DSP in young women? That the administration of DSP in this group is associated with a small mean increase in serum K+ (reflected in the increased 'maximum' K+) that is compensated for by the 'reserve' capacity of the kidney, such that hyperkalemia (however defined) occurs rarely and at a similar frequency as the controls. The one individual whose serum K+ rose on DSP fits this pattern (that is, short-term rise in K+, followed by increased K+ excretion and return of serum K+ to normal). This is also the pattern described for the time-course of spironolactone's effects on K+ (in its approved label).

The information from the literature and the small short-term studies of DSP is of little utility in determining the effects of DSP in its target population.

2. Does Yasmin (DSP) affect serum potassium levels and/or increase the risk of hyperkalemia in patients with diminished 'potassium excretory reserve' including patients taking ACE-inhibitors, NSAIDs, and those with renal failure?

NSAIDs

The sponsor collected information on the use of NSAIDs in addition to DSP from the population of healthy women examined in question one above (517 patients on DSP, 133 on control). Within this small group, the incidence of serum K+≥5.5 meq/L was similar in the two groups (0.8% and 2.2% respectively). Given the small numbers available and the broad confidence intervals around any means, these results allow us to say little except that the concomitant use of DSP and NSAIDs does not appear to increase the risk of elevated K+ by a factor of, say, 10X or more.

Angiotensin-Converting Enzyme Inhibitors (ACEIs)

The potential interaction between DSP and ACEIs was examined in study 98106, that enrolled 24 hypertensive women (12 on estradiol/ DSP +enalapril, 12 on enalapril). The results (see Dr. Monroe's review dated 6.21.00, table 4 and Dr. Kammerman's statistical review, page 3) suggest that the change from baseline was greater in the DSP +enalapril group than in the enalapril-alone group. Dr. Monroe correctly points out that ACEIs can increase serum K+. The sponsor's use of bioequivalence definitions of 'equivalent' are creative, but demonstrating that the mean changes are 'equivalent' in this sense does not exclude a significant effect on individuals. The best interpretation of this study, then, is that there is weak evidence of an effect of DSP to increase K+ when administered on a background of ACEI therapy.

Renal Failure

The sponsor conducted a trial in 28 women with renal impairment (trial 303063). Three groups, formed according to their calculated creatinine clearance (normal, mild, and moderate renal impairment) were given DSP 3 mg daily for 14 days.

Issues and Comments (cont)

Mean Changes in Serum K+ and H+ in Renal Failure

Each of the serum K+ levels measured throughout the study are reported in the clinical study report for the study (section 14.2.1) along with the mean changes. The patients with the worst renal function started with a higher mean K+, but there was no trend towards higher mean K+ evident during this short study. There were, however, relevant changes in serum acid-base parameters (see Dr. Monroe's review, table 10). In the group with the worst renal function, a decrease in the mean pH and serum HCO3 were seen from baseline through the end of therapy. While not conclusive, it is tempting to attribute this change in acid-base balance to an impaired ability of the kidney to excrete H+. This would be consistent with the anti-mineralocorticoid effects of DSP in the distal tubule of the kidney.

Individual Changes in Serum K+ in Renal Failure

Per Dr. Monroe's review, there were 5 individuals with serum K+ >5 meq/L during treatment orwithin 48 hours of treatment with DSP: 2 were in the 'mild' renal impairment group (creatinine clearance 50 to 80 ml/min) and 3 were in the 'moderate' renal impairment group (creatinine clearance30 to 50 ml/min). Interpretation of this finding is limited by the higher baseline serum K+ in the two groups with renal impairment.

Conclusions Regarding Renal Failure

Dr. Monroe raised two points limitations of the trial, both of them relevant:

- The small size of the trial relative to the anticipated frequency of hyperkalemia (drawing from the ACEI data).
- The use of a low-K+ diet during the study.

With these limitations, it is difficult to use this trial to either assert or exclude an interaction between renal function and DSP with regard to K+ homeostasis. The sponsor appropriately examined the potential additional interaction between DSP and concomitant ACE/Beta-blocker therapy in this population. Unfortunately, the numbers of patients exposed were simply inadequate to expect to detect an effect on K+ unless it were overwhelming (it was not).

RALES Trial Data

There is one additional set of data that can shed some light on the risk of hyperkalemia in patients with impaired 'potassium excretory reserve' who receive a drug with anti-mineralocorticoid activity. First, recall that the sponsor asserts that the level of anti-mineralocorticoid activity found in DSP is equivalent to 25 mg of spironolactone. In the RALES trial, 25 mg of spironolactone was administered to patients with advanced congestive heart failure (CHF). These patients were at increased risk for hyperkalemia for two major reasons:

1) Advanced CHF. In CHF, the kidneys are often receiving inadequate blood flow, making them retain sodium and water. As a consequence, potassium excretion is impaired. The patients in these trials were in advanced stages of CHF.

2) Concomitant use of drugs that impair potassium excretion in the subjects: ACEIs in 95%, blockers in 10%, and digoxin in 70+%.

In the RALES trial results presented by the sponsor, there was an increase in the mean serum K+ for patients treated with 25 mg of spironolactone for 24 weeks (4.21 meq/L at baseline, 4.57 meq/L at week 24). Hyperkalemia (K+≥6.0 meq/L developed in 1.2% of the placebo and 1.7% of the spironolactone group. These results suggest that chronic administration of spironolactone 25 mg (the amount of anti-mineralocorticoid activity present in DSP per the sponsor) is associated with significant (but still small) incidence of increased serum K+ in a population at very high risk for hyperkalemia. Extrapolating these data to the population taking DSP is obviously fraught with uncertainty. These data do suggest that patients with marginal 'reserve' for excreting potassium (similar to those in the RALES trial) have an increased risk of hyperkalemia during chronic use of a medication with relatively small amounts of anti-mineralocorticoid activity (such as DSP).

Issues and Comments (cont)

3. Based on the answers to the two questions above, what additional information is needed to understand the risk of hyperkalemia in patients taking Yasmin?

The database for Yasmin (drosperinone, DSP) has two components of relevance to the issue of hyperkalemia: a relatively large database in younger women without impaired renal function; and a series of very small trials in patients at increased risk of hyperkalemia due to either drugs or renal injury.

First, the database from young women using DSP chronically did not reveal any increase in the incidence of hyperkalemia during chronic administration of DSP. The size of the database (1892 patients given DSP), our ability to detect hyperkalemia is limited to around 1:600, and our ability to detect relative incidence obviously more limited than that. With the addition of the post-marketing data provided by the sponsor and our knowledge of the kidneys ability to handle potassium under other circumstances, these data provide some reassurance that the risk of hyperkalemia in individuals with normal renal function who are not taking other drugs that impair potassium excretion is quite low. Importantly, this analysis depends on the results of trials not yet submitted to the FDA (97036, 96097).

The next issue concerns the use of DSP by the population with impaired 'potassium excretory reserve'. In this population, I concur with the reviewers from HFD-580, who concluded that the trials in renal failure and following the use of ACEIs were too small to determine anything regarding the risk of hyperkalemia following DSP in these populations. The trial using ACEIs, in addition, lacks appropriate controls to even allow us to interpret the effects of DSP in that trial separately from the effects of ACEIs. Similarly, the post-hoc analysis of the women who used NSAIDs is underpowered to detect hyperkalemia of clinical significance.

The result then, is that with the addition of the trials yet to be submitted to the FDA, the database in DSP use in normal female subjects is sufficient to conclude that the risk of hyperkalemia in this population will be rare (<1:1000 individuals taking DSP). For the individuals with impairment of renal potassium excretory capacity, the data are insufficient to adequately describe the risk of hyperkalemia with chronic DSP use. Does this mean that additional trials are called for to better define the risk? In the end, I believe that such a trial would add little to our current understanding of the consequences of DSP use in patients with impaired renal clearance of potassium. The best interpretation of the available data is that a small fraction of these patients will develop hyperkalemia, a fraction nonetheless greater than those who do not use DSP. Performing a trial to provide further information on the rate of hyperkalemia in patients with impaired ability to excrete K+ would require large numbers of subjects. For illustration, the RALES trial enrolled 1600+ individuals at high risk of hyperkalemia, and found that the incidence of hyperkalemia was increased 30% in the spironolactone group compared with placebo. Delineating the risk of significant hyperkalemia with DSP would likely need similar numbers.

In lieu of such a trial, the contraindication of DSP use by patients at risk for hyperkalemia due to renal injury or concomitant medications may be sufficient to lower the populational risk. With such warnings and physician monitoring, I believe hyperkalemia can be reduced substantially in the population at risk. The sponsor should additionally be encouraged to rigorously define the 'benefits' they hypothesize for chronic mineralocorticoid blockade.

cc:
ORIG: Division File

HFD-110/Deputy Division Director	Douglas Throckmorton
HFD-110/ Division Director	Raymond Lipicky
HFD-580/Project Manager	Jeanine Best
HFD-580/ Medical Officer	Scott Monroe
HFD-580/Division Director	Susan Allen

NDA 21-098
Yasmin® 28 *Tablets* (drospirenone/ethinyl estradiol)
Berlex Laboratories, Inc.

OPDRA Consult regarding thromboembolic events reported in the postmarketing period for approved oral contraceptives.

/S/

4/27/04

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**OPDRA POSTMARKETING SAFETY REVIEW**	
TO: Dr. Susan Allen, M.D., Director, Division of Reproductive and Urologic Drug Products (DRUDP) HFD-580	**FROM:** Denise Toyer, Pharm.D Safety Evaluator, Division of Drug Risk Evaluation II (DDREII) HFD-440	**OPDRA PID #** D010190 April 30, 2001
DATE REQUESTED: As Soon As Possible **DATE RECEIVED:** April 2, 2001	**REQUESTOR/Phone #:** Dena Hixon, M.D., Team Leader Division of Reproductive and Urologic Drug Products	
DRUG (Est): drospirenone and ethinyl estradiol	**NDA #** 21-098	**SPONSOR:** Berlex Laboratories
DRUG NAME (Trade): Yasmin	**THERAPEUTIC CLASSIFICATION:** Oral Contraceptive	
EVENT: Thromboembolic Event		

Executive Summary: Yasmin (drospirenone and ethinyl estradiol), an oral contraceptive, is currently under review in DRUDP. A recent submission from the applicant contained information pertaining to one case involving a serious adverse event (thromboembolic event with death as the outcome) that occurred within the first six months of European marketing. OPDRA agreed to provide WHO data on the newly marketed product. Additionally, DRUDP requested a review of the most recently approved oral contraceptives to determine if any cases of thromboembolic events were reported within the first year of marketing in the United States. A search of the World Health Organization's database for all reports associated with the combination product of drospirenone and ethinyl estradiol (including the trademarks Yasmin and Petibelle) did not identify any adverse event reports. A search of the AERS database for thromboembolic events associated with the eight most recently approved oral contraceptives (Alesse, Cyclessa, Desogen, Estrostep, Micro-Levlen, Mircette, Ortho-Cept, and Ortho-Tri-Cyclen) identified eight reports of thromboembolic events. These reports occurred within the first year of approval and were associated with Mircette (3), Estrostep (1), and Alesse (4). The individual reports were not reviewed and may include duplicates. Two of the eight reports occurred within six months of approval (Mircette-4 months and Alesse-5 months). Drospirenone/ethinyl estradiol has only been on the European market for approximately 6 months, which may account for the lack of adverse event reports in the WHO database. Thromboembolic adverse events have been reported, in the past, within six months of marketing of new oral contraceptives.

Reason for Request/Review: Yasmin (drospirenone and ethinyl estradiol) is currently under review in DRUDP. A recent submission from the applicant contained information pertaining to a serious adverse event that occurred within the first six months of European marketing. Information pertaining to the adverse event is limited at this time (the applicant is pursuing follow-up information). However, the patient experienced a thromboembolic event and the outcome of the event was death. OPDRA agreed to provide WHO data on the newly marketed Yasmin. Additionally, DRUDP requested a review of the most recently approved oral contraceptives to determine if any cases of thromboembolic events were reported within the first year of marketing.

Search Date: April 10, 2001	**Search Type(s):** ☒ AERS Literature Other

Search Criteria: Drug Names: Alesse, Cyclessa, Desogen, Estrostep, Micro-Levlen, Mircette, Ortho-Cept, Ortho-Tri-Cyclen
MEDDRA Terms: High Level Group Term: Embolism, Thrombosis and Stenosis

A search of the DSS system identified eight new drug applications, for oral contraceptives, that were approved from 1991 through April 10, 2001. These products were Alesse, Cyclessa, Desogen, Estrostep, Micro-Levlen, Mircette, Ortho-Cept, and Ortho-Tri-Cyclen. The search was expanded to include thromboembolic events that occurred within the first year post approval.

Search Results:

- A search of the World Health Organization's database for all reports associated with the combination product of drospirenone/ethinyl estradiol and the trademarks Yasmin and Petibelle did not identify any adverse event reports.
- The AERS search revealed a total of eight reports associated with: Alesse (4), Estrostep (1), and Mircette (3). The individual reports were not reviewed and may include duplicates. Two of the eight reports occurred within six months of approval (Mircette-4 months and Alesse-5 months). Both patients were diagnosed with deep vein thrombosis.

Discussion / Conclusions:

Drospirenone/ethinyl estradiol has only been on the European market for approximately 6 months, which may account for the lack of adverse event reports in the WHO database. Thromboembolic adverse events have been reported, in the past, within six months of newly marketed oral contraceptives.

Reviewer's Signature / Date: /S/ Denise P. Toyer 4/30/2001	**Team Leader's Signature / Date: /s/ Debra E. Boxwell 4/30/2001**

Acting Division Director Signature / Date: /s/ Kathleen Uhl 4/30/2001

Cc: NDA # 21–098
HFD-580 Best/Hixon/Monroe/Allen
HFD-440 Uhl/Boxwell/Toyer/Dempsey/Drug
Electronic File Name:

APPEARS THIS WAY
ON ORIGINAL

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

12 pages

DRAFT LABELING

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PID#: D010043

DATE: MAR 23 2001

FROM: Carolyn McCloskey, M.D., M.P.H., Medical Officer
Division of Drug Risk Evaluation II, HFD-440
Office of Postmarketing Drug Risk Assessment (OPDRA)

THROUGH: Kathleen Uhl, M.D., Acting Director
Division of Drug Risk Evaluation II, HFD-440 /S/ 3/23/01

TO: Susan Allen, M.D., Director
Division of Reproductive and Urologic Drug Products (DRUDP),
HFD-580

SUBJECT: Consult: Review of Phase 4 Program, Part of NDA Resubmission
Drug(s): Yasmin® 28 (drospirenone/ethinyl estradiol), NDA 21-098
Sponsor: Berlex Laboratories, Inc.

I. EXECUTIVE SUMMARY

This memorandum is provided in reply to a request[1] dated December 5, 2000 from DRUDP to OPDRA for review and comment on the Phase IV Program, part of an NDA resubmission on Yasmin® 28, NDA 21-098, from Berlex Laboratories, Inc. The sponsor's supplement submission of November 6, 2000 was a response to a second "approvable" letter from DRUDP dated July 10, 2000. Yasmin is a combination oral contraceptive containing ethinyl estradiol and drospirenone. Drospirenone is a progestin with anitimineralocorticoid effects. Remaining safety concerns arise from the potential antimineralocorticoid effects, especially hyperkalemia. Another safety concern is for potential birth defects such as esophageal atresia or other branchial pouch congenital anomalies.

In that July 2000 "approvable" letter[3] the following Phase 4 commitments agreed to by the sponsor were listed:

1. Develop an educational outreach program focusing on the contraindications in patients with renal and hepatic impairment and patients predisposed to hyperkalemia.

2. Develop a surveillance program to evaluate the inappropriate prescribing to patients with renal or hepatic dysfunction.
3. Evaluate all patients in a surveillance program who were prescribed Yasmin for adverse outcomes including death, hospitalization, syncope, arrhythmia, hyperkalemia, electrolyte disturbances, dialysis, etc.
4. Analyze all Yasmin-exposed pregnancy outcomes in a surveillance program.

The educational program[4] briefly proposes to educate physicians, nurses and pharmacists to prevent administration of Yasmin to women with diagnoses or histories of hepatic or renal insufficiency. The success of this educational outreach will be monitored through an active surveillance program by evaluating the inappropriate prescribing of Yasmin to women with renal or hepatic insufficiency. They plan to revise the educational program according to the results of the prescribing study.

The active surveillance program[4] is a three-year prospective surveillance cohort study. They propose using [redacted] to evaluate Yasmin users compared with other oral contraceptive (OC) users regarding the three issues listed in the "approvable" letter: inappropriate prescribing, adverse events and pregnancy outcomes. The cohort will enroll all members who were prescribed Yasmin and, for each of these, enroll two members prescribed other OCs who are age- and medical condition-matched controls. Data collection will include demographic data and outcome data for the groups described above. Quarterly reporting will include tabulations of the findings and statistical analyses for estimating relative risks.

The proposed Phase IV Program, as submitted, is acceptable in theory; however, there are many deficiencies and inadequate information. In order for us to evaluate this program fully, the sponsor should address the following concerns before a final decision is made about accepting the proposed program:

- The educational program should also educate patients and more descriptive documentation should be provided for review.
- Continuing nursing and pharmacy education (CNE and CPE) requirements should be met by the educational program, since it is likely that nurse practitioners will be involved.
- The sponsor should provide an intervention plan in case inappropriate prescribing of Yasmin is associated with serious adverse events.
- More subjects may be needed than estimated in the sample size to demonstrate statistical significance for relative risks of various outcomes; an alternative is to require the sponsor demonstrate statistical significance for FDA-specified relative risks
- The sponsor should include in their quarterly reports a review of the quarterly and cumulative data with (1) tabular listing of the outcomes of interest (inappropriate prescribing, all adverse events, all pregnancies and birth defects associated with Yasmin use), (2) statistical analyses and (3) any additional relevant information.
- The sponsor should provide complete documentation of their proposal including training materials, testing plans, patient confidentiality plans, references, algorithms to

identify outcomes in their database, assumptions for calculations and statistical analyses.

II. BACKGROUND

The drospirenone component of Yasmin® 28 (ethinyl estradiol and drospirenone) is a progestin and a new molecular entity. It has antimineralocorticoid effects but has little androgenic, estrogenic, glucocorticoid or antiglucocorticoid activity. Aldosterone antagonists or antimineralocorticoids are known to lower blood pressure (systolic and diastolic) and can cause hyperkalemia, hyperchloremic metabolic acidosis and possible dehydration.

According to a supplemental Medical Officer's Review[5] dated June 16, 2000, the Group Leader Memorandum[6] dated February 23, 2000 and the Office Director Memo[7] dated July 10, 2000, the following are pre-approval clinical findings in women exposed to Yasmin:

- Three mg of drospirenone in a Yasmin tablet is comparable to 25 mg of spironolactone, because the relative antimineralocorticoid potency of drospirenone is about eight times that of spironolactone.
- Serious adverse events (unspecified criteria) in 4.3% of Yasmin-exposed women compared with 2.9% in the Marvelon users, but no cases of dehydration or renal insufficiency and little useful data on serum electrolytes (unreliable measurements due to blood specimen mishandling), in the European trial. The most serious Yasmin-associated adverse events (AE) were three cases requiring a cholecystectomy, one had a pulmonary embolus and others had a variety of AEs such as benign breast tumors, abnormal PAP smear, ovarian cysts, anal fistula, appendectomies, depression and mild elevations of creatinine (maximum 1.4 mg/dl)
- 13% (17/130) of the Yasmin users over 6 cycles discontinued Yasmin for AEs compared with 5% (7/131) who discontinued placebo (safety study 97036)
- In the US trial of 326 subjects: no deaths; no new concerns about serious AEs (unspecified criteria) or discontinuations due to AEs; no significant change in sodium or potassium levels
- Three pregnancies each for Yasmin and an active comparator (Marvelon) out of 900 subjects evenly randomized to Yasmin or Marvelon and followed for 26 cycles in a European study
- One pregnancy out of 333 healthy, Yasmin-exposed women for 13 cycles in a US study
- One esophageal atresia in an infant exposed to Yasmin in-utero out of 14 pregnancies of which 9 were live births; expected rate of esophageal atresia is less than 1 in 1000 live births

DRUDP issued two "approvable" letters[2], the first, sent March 17, 2000, requested results from a study in patients with impairment of renal function, and the second, dated July 10, 2000, requested further clinical studies (reviewed by DRUDP) and Phase IV commitments to assess the risk of hyperkalemia in women using the product.

The July 10, 2000 "approvable" letter[3] to Berlex Laboratories, Inc for Yasmin® 28, outlines the following Phase 4 risk management commitments (quoted in full from the letter):

1. "Develop an educational outreach program for health care providers and patients, focusing on Yasmin's contraindications in patients with renal and hepatic impairment and patients predisposed to hyperkalemia."
2. "Develop a surveillance program to evaluate the inappropriate prescribing of Yasmin to patients with underlying hepatic or renal dysfunction using a database of Yasmin users; the database would provide al list of all Yasmin users, and these patients would then be screened carefully for any past or recent diagnoses of hepatic and/or renal dysfunction; submission of full case report summaries of all such inappropriate prescriptions, including patient outcome, would be required."
3. "Use a database to evaluate all patients prescribed Yasmin for the subsequent outcomes of death, hospitalization, syncope, arrhythmia, hyperkalemia, electrolyte disturbances, dialysis, etc. (other search terms may also be considered appropriate); patients taking Yasmin and experiencing these types of events (or taking Yasmin within one month of such events) would be considered concerning; full case reports summaries, including patient outcome, would be required for these patients."
4. "Analyze more carefully pregnancy outcomes which occur in patients exposed to Yasmin; this could be done in the same cohort of Yasmin users described in the database; in addition, the Organization of Teratogen Information Services (OTIS), or other resources could be used to collect data on all patients reporting a Yasmin exposure; a pregnancy exposure registry is an alternative; outcome on as many patients as possible is desired and may require several years of follow-up; finally, collecting all post-marketing adverse event reports and placing them in a format to help identify signals of developmental toxicity is recommended."

In addition, the "approvable" letter of July 10, 2000 stated that additional clinical studies must be performed to assess the risk of hyperkalemia in women using Yasmin® 28 Tablets. The sponsor's response to that requirement will be reviewed by DRUDP.

DRUDP and OPDRA have conferred on these issues during the initial review cycle for Yasmin. The following sections are a review and evaluation of the Phase 4 Program submitted as part of the NDA resubmission on Yasmin® 28 from Berlex Laboratories, Inc.

III. "Yasmin 28 Tablets Phase IV Program"[4] REVIEW

1. Educational Outreach Program

A. Descriptive Summary

The stated objective is "to educate physicians on the appropriate patient types to whom Yasmin can be prescribed so that use in the at-risk patient is minimized." The "gatekeepers

of contraceptive healthcare" such as physicians, nurses, and pharmacists are the principle audience. To do this they propose using (1) the sales representatives to provide detail aids and information, (2) a nationwide continuing medical education (CME) program, and (3) journal publications.

Reviewer's Comment
There is no mention of an educational program targeted to the patients.

"CD-ROM based" training of the sale representatives is planned and they will be evaluated by "proficiency testing". These sales representatives will provide sales detail aids on DRSP pharmacology with special attention to the antimineralocorticoid property, potassium levels and inappropriate patients. A nationwide CME program is planned consisting of CME conferences and brochures. In addition, publications in peer-reviewed journals are planned.

Reviewer's Comment
No further description was provided for these programs or testing.

To evaluate the success of the education program, communications testing and analysis of prescribing tracking and awareness tracking will be done through market research and commercially available market data. The active surveillance program will be the "measure for changes in prescribing behavior" by monitoring "outcomes" and "detailed patient data" relative to other oral contraceptives. The active surveillance program is described in the following section, 2, "Active Surveillance Study". Quarterly reports will be submitted on statistically significantly higher rates of inappropriate prescribing of Yasmin using 14/100,000 as the cut off for inappropriate prescribing of oral contraceptive to patients with renal impairment. Information regarding the circumstances that potentially lead to inappropriate Yasmin prescribing will be used to revise Berlex's physician education program.

Reviewer's Comment
No further description was provided for the testing, tracking, "outcomes", "patient data", basis for the 14/100,000 rate of prescribing, or means of revising the educational program.

B. OPDRA Comments on the Educational Outreach Program

An educational program aimed at understanding the antimineralocorticoid activity of DRSP and the drug use in patients with hepatic and renal insufficiency is important. Just as important is an effective means of evaluating the success of the program and improving the program.

The educational program is targeted to physicians, nurses and pharmacists but not specifically targeted to patients. No descriptive information was submitted on any of the

educational proposals ("CD-ROM based" training of the sales representatives, CME conferences, or journal publications) nor on the proficiency testing of the sales representatives. There is no reference for the stated rate of 14/100,000 of prescribing of OC to patients with renal impairment. The protocol mentions evaluating patients with renal impairment; however, no mention was made to evaluate prescribing specifically to patients with hepatic impairment and patients predisposed to hyperkalemia. The calculations of power for the statistical analyses of inappropriate prescribing are discussed in the next section on the active surveillance study.

The sponsor should:

- Provide information on how to educate the patients.
- Provide information on evaluating patients with hepatic impairment or hyperkalemia.
- Provide FDA with copies of the training materials for review prior to starting the surveillance study.
- Provide FDA with the sales representatives' "proficiency testing" plans.
- Provide continuing nursing and pharmacy education (CNE and CPE) with accreditation in addition to a "CME program".
- Provide the basis for the stated rate of prescribing OCs to patients with renal impairment as 14/100,000.
- Include in the quarterly reporting the actual counts of patients with renal or hepatic impairment or those predisposed to hyperkalemia who received a prescription or sample of Yasmin.
- Include, in the quarterly reporting, the circumstances surrounding each inappropriate prescribing of Yasmin, even if the numbers are not statistically significant, because this information would be helpful in evaluating and improving the educational program.
- Include a plan for appropriate action if the educational program is not preventing inappropriate prescribing of Yasmin, especially if those patients experience serious adverse events associated with Yasmin.

2. Active Surveillance Study

A. Descriptive Summary

A prospective cohort study is proposed. This study will run for 3 years with quarterly monitoring and reporting of outcomes confirmed by chart review to evaluate:

1. Prescribing of Yasmin compared with prescribing of other OCs to women with hepatic or renal insufficiency
2. Occurrence of death, hospitalization, arrhythmia, dialysis and hyperkalemic adverse events associated with Yasmin compared with other OCs
3. Breakthrough pregnancies associated with Yasmin and any fetal or child malformations

A proposal by the Epidemiology Division of [redacted], referenced by the Berlex Phase IV document, was not submitted for review. The Phase IV document references [redacted], proposal on patient confidentiality plans, institutional review board approval of studies and sample size calculations.

Reviewer's Comment
Although the [redacted] proposal is not available for review, it is commendable that the issues of patient confidentiality plans and institutional review board approval are considered by the sponsor. Sample size calculations are discussed below.

The active surveillance study will be done in the [redacted] which is a large research database integrating information from provider, facility and pharmacy claims. Medical chart abstractions and patient survey mailings with telephone follow-up are available. In 1999 there were 4.5 million people covered by 25 affiliated health plans in 19 states. There is information from a total of 8 million current and past members in this database. Information on the patient and provider is encrypted but a structured unique identifier allows longitudinal follow-up for each patient and their household members. Diagnoses, procedures, drug information (brand name and generic), and administrative information are captured in this database.

There is little to no information on hospital admissions in the [redacted] and Medicare patients are excluded because of their likelihood of care outside the covered plans.

Reviewer's Comments
Whatever hospital admission information on Yasmin users and their controls should be captured and evaluated. Medicare (elderly) patients are not likely to receive prescriptions for contraceptives; however, if they receive Yasmin for other reasons, this would be a limitation.

The study will start at the same time as the marketing launch of Yasmin and data collection will continue for three years. The cohort will include women who are dispensed Yasmin during the study period and who were enrolled 6 months prior to their first dispensed

Yasmin prescription. There will be two controls for each Yasmin user, matched on age and concurrent medical conditions.

Quarterly data collection will capture all members newly prescribed Yasmin. Patient demographic information will be collected including other medical conditions and smoking status. "Standard algorithms" will be used for chronic medical conditions "to translate utilization patterns into presumptive diagnoses". A 3% sample of Yasmin users will be mailed a questionnaire on smoking habits and lifestyle preferences and non-respondents will receive telephone follow-up by interviewers blinded to the patient's health status.

Reviewer's Comment
The "standard algorithms" were not provided in the Phase IV protocol. Even though [redacted] may have excellent, verifiable algorithms, the sponsor should provide the algorithms and their "presumptive diagnoses" to the FDA for review.

Outcomes, including death, hospitalization, arrhythmia, dialysis, unexplained hyperkalemia and electrolyte disturbances, will be identified in the [redacted] physician and facility files using "codes" for the specific outcome or related events. The results will be reviewed for the likelihood of identifying the outcomes of interest by "qualified" nurses or physicians blinded to the type of oral contraceptive dispensed and then rechecked by a physician experienced in claims data analysis.

Reviewer's Comment
In order to find patients with renal or hepatic insufficiency and the serious adverse events of interest, algorithms for using the "codes" to identify those outcomes of interest will probably be developed. FDA should be provided the methodology and algorithms used.

Similarly, pregnancies will be identified using pregnancy-related diagnosis or procedure codes and pharmacy data such as prenatal vitamin prescriptions. For each patient, a conception date (or a range for that date) will be calculated and if it falls during the time of Yasmin or OC use, then both mother and child information will be searched for any fetal or infant malformation information.

A medical chart abstraction will be done for "each possible event detected" using "standardized abstraction forms". Patient and provider confidentiality will be maintained using encrypted identification numbers. A report, including a narrative summary, will be generated containing pertinent information including relevant medical and family history, treatment and outcomes. Additional searches to identify deaths will be done using discharge codes, characteristic patterns of care known to be markers of death and a search of the National Death Index will be requested for those women whose membership was stopped during the study.

Analyses of the data will include tabular presentations of the data by Yasmin and by other OC users stratified by age, year, chronic medical condition and indices of health care utilization. If there is a significant difference in smoking habits between the Yasmin users

and other OC users based on the smoking survey and the baseline patient characteristics, then (1) they will use the Framingham risk equations to model the expected differences in rates of cardiovascular outcomes and (2) they "will combine the survey results in cases with the random sample results to construct a nested case-control study" with the results adjusted for smoking. For those outcomes with 25 or more cases, a multivariate analysis using the Poisson regression will be done.

Sample size calculations come from the [redacted] proposal. They estimated a total [redacted] new Yasmin users over the 3 year study period with an estimated total of 366,653 woman-months and an estimated total of 30,554 woman-years. The assumptions for these calculations were that (1) first Yasmin use is spread evenly throughout the year, (2) the probability of discontinuing Yasmin is 3%, and (3) Yasmin sales to women in [redacted] market. The sample size calculations for Yasmin-exposed pregnancies were based on an estimate of 5 pregnancies per 100 women per year which is based on a rate of 6.9 per 100 women using OCs in the US (Trussel J. Family Planning Perspectives 31(2):64-72,93. Mar/Apr 1999 at www.agi-usa.org/pubs/journals/3106499.html). At the end of 3 years, they estimate 30,554 years of Yasmin use, approximately 1500 pregnancies and an expected 30 malformations based on a prevalence of recognized malformations at birth of 2%.

Reviewer's Comment
Although the 2% rate of birth defects is not referenced, it is an accepted rate within the accepted range 1-3%.

The power for each of the study objectives ((1) risk of dispensing Yasmin to women with contraindications (hepatic and renal insufficiencies), (2) risk of serious AEs including hyperkalemia, and (3) risk of congenital malformations) depends on the estimates of Yasmin use in the cohort, and thus on the sample size calculations and assumptions. Highlights from the power calculations for each of the study objectives are:

- For a risk of 1 inappropriate use in 10,000 women (0.01%), this study is "96.8% certain to identify it by the end of the third year".
- For observing more than 2 outcomes per 1,000 woman-years and detecting a relative risk (RR) of 1.8, the power of this study is 80 percent by the end of 2 years. For a RR of 1.6 at the end of 3 years it will have 90 percent power.
- For pregnancies and possible birth defects, a calculated 1500 pregnancies and an expected 30 malformations will occur in the estimated 30,554 woman-years of Yasmin use (3 years of the study). The power to detect an increased RR of 2.0 for malformations was calculated to be greater than 80% for 800 or more pregnancies in the Yasmin group. A range in the number of pregnancies (400-1500) was used in the power calculations because of the possibility of pregnancy terminations without identifying a malformation and the possibility that the breakthrough pregnancy rate will be lower than the historical rate. For rare malformations with a risk of 0.01% or 0.1%, the power to detect a single case was calculated at 13.9% or 77.7% respectively, at the end of 3 years or 1500 pregnancies.

The reporting of the findings and analyses from the surveillance study will be quarterly and usually include a listing of the Yasmin users with pertinent information and statistical analyses where indicated:

- For those patients with hepatic or renal insufficiency identified as having received Yasmin inappropriately, their health, demographic and prescribing data will be described. "Statistically significantly higher rates of inappropriate prescribing" in the Yasmin users compared to other OC users will be reported quarterly. This information will be used to revise Berlex's physician education program.
- For those patients with hyperkalemia and related events (death, hospitalization, syncope, arrhythmia, hyperkalemia, electrolyte disturbances or dialysis), risk information (events per 1000 users) and incidence rate (events per 1000 woman-months) will be provided along with a narrative summary.
- For those pregnancies exposed to Yasmin, the incidence of pregnancy for Yasmin users and other OC users will be reported in a similar fashion as the other outcomes (tabular and multivariate analysis). For those malformed infants exposed to Yasmin in-utero, the report will include a narrative description of morphology, diagnostic procedures and standard classification of the anomalies. In addition, all breakthrough pregnancies will be followed for an extra 18 months after the end of the study period to allow for pregnancies to come to delivery and for identification and classification of any malformations.

B. OPDRA Comments on the Active Surveillance Study

Positive aspects of the proposed database are:

- [redacted] is a large, geographically diverse database with 800,000 women aged 20-39 in 1999 (about 1 million women aged 15-44 in 1999).
- Medical chart abstractions are available.
- Questionnaire surveys and household member follow-ups are available.
- Important considerations such as patient and provider confidentiality and blinding of interviewers and abstractors are covered.
- The limitation of excluding Medicare (elderly) patients will have little impact on the analyses of Yasmin use in women of reproductive age.

Some excellent ideas proposed by the sponsor for follow-up are:

- to query the National Death Index for possible deaths of women who were lost to follow-up due to lapse in healthcare plan membership,
- to follow any Yasmin-exposed pregnancies for an additional 18 months after the end of the study time period, and,
- to take into account, in calculating sample sizes and power, that there may be terminated pregnancies with no information on birth defects and that the Yasmin breakthrough pregnancy rate may be lower than the historical rate.

Some potential limitations are:

- There is little hospital admission information. Any hospital admission information on Yasmin users and their controls is needed for evaluating underlying hepatic or renal impairment, adverse events and pregnancy outcomes.
- Algorithms for identifying underlying medical conditions and outcomes are not described. These methods are critical to the success of the study and should be reviewed.
- Identification of pregnancies and their outcomes, including infant outcomes, is not described. This can be difficult using claims databases. In addition, pregnancy services received outside the healthcare plan are not usually captured in the claims database and thus this information is lost to the study.
- No references or equations were given for the power calculations in the Berlex proposal. The power calculations for the outcome events is based on a baseline incidence of 2/1,000 which is not a time dependent rate. Events that take time to develop (such as thromboses or organ failure) may not be detected with the same power as those events that develop quickly (such as electrolyte changes).
- The assumptions on which the sample size estimates are based may lead to larger expected sample sizes. Several assumptions used for the sample size calculations are concerning:
  - The months of first Yasmin use are spread out evenly throughout the year may not be true at the launch of Yasmin and also may be influenced by publicity.
  - Using 3% for the number of Yasmin users who will discontinue use may be an underestimate since the medical officer review noted that 17/130 (13%) Yasmin users discontinued Yasmin because of AEs.
  - There was no basis given for the estimate that Yasmin sales in [redacted] of the US market. For women of reproductive age (not Yasmin sales), [redacted] members represent about 1.6% of the US population (about 1 million women aged 15-44 [redacted] and 60 million women aged 15 – 44 in the US (US Census data www.census.gov/population/estimates/nation/). The accuracy of this estimate may be affected by differences in OC prescribing and Yasmin sales such as differences in health insurance status, socioeconomic status, etc. betweer [redacted] members and the general US population.
  - The estimated pregnancy rate for Yasmin users was 5 per 100 women per year; however, the Group Leader Memorandum dated February 23, 2000, noted that there was 1 pregnancy out of 333 healthy, Yasmin-exposed women for 13 cycles in a US study. This is a rate of 0.3%. Using 30,554 woman years over 3 years, gives an estimated 90 pregnancies in the Yasmin users which is much smaller than the 1500 pregnancies estimated in the program. The resulting estimated 1.8 malformations in the Yasmin pregnancies group over the 3 years (2% of 90 pregnancies) is also much smaller than the 30 malformations in 1500 pregnancies (3 years) estimated in the Berlex program.

DRUDP should:

- Consider requiring the sponsor to demonstrate statistically significant findings at a specified RR (such as less than 1.6 or 2.0) for each objective or outcome instead of accepting the sponsor's sample size calculations to determine the length or end of the

study. Demonstrating statistically significant findings for specified RRs may require enrolling more patients than calculated in this proposal.

- Realize that the reporting of data to the database includes a lag time (up to 3-12 months in some databases) so a three year study will have less than three years of Yasmin prescribing and outcome data.

The sponsor should:

- Provide documentation of "standard algorithms" to translate health care utilization patterns into presumptive diagnoses or to translate "codes" into outcomes (hepatic, renal, pregnancy, etc.). FDA reviewers need to understand how inclusive or restrictive the algorithms are for underlying medical conditions or outcomes of interest.
- Provide the proposal from [redacted] that includes the patient and provider confidentiality plan, the institutional review board approval plan and especially the sample size calculations.
- Provide evidence to support their assumptions for the sample size calculations (see list above):
  - The months of first Yasmin use are spread out evenly throughout the year
  - Estimated 3% of Yasmin users will discontinue use
  - Estimate of Yasmin sales in [redacted] of the US market
  - Estimated pregnancy rate for Yasmin users of 5 per 100 women per year; 1500 Yasmin-exposed pregnancies over 3 years; 30 malformations in 1500 pregnancies (3 years)
- Provide equations and references to support their assumptions for the power calculations including those that involve time dependent variables such as renal or hepatic insufficiency.
- Provide information on expected lag times for data to be entered into the database from the provider, facility and pharmacy files.
- Provide documentation of the qualifications of the interviewers and abstractors.
- Provide consistent, standardized quarterly reporting on the results for inappropriate prescribing, adverse events and pregnancies with their outcomes including:
  - listings of Yasmin users and their pertinent findings for the quarter and for the cumulative study period:
    - renal or hepatic insufficiency or a predisposition to hyperkalemia
    - serious adverse events of interest (death, hospitalization, etc.)
    - ALL adverse events
    - ALL pregnancies, pregnancy outcomes (live birth, spontaneous abortion, stillbirth, termination, suspected pregnancies lost to follow-up) and ALL infant outcomes reported over the study time period and the additional 18 month follow-up period.
  - statistical analyses: risk estimates
  - any information on the likelihood of association of the adverse events with Yasmin use that would be helpful in interpreting the other analyses
- Reference the Framingham risk equations if they are used and explain their relevance to the Yasmin and other OC user analyses.

V. CONCLUSIONS

This Phase 4 program outlines a plan to educate gatekeepers of contraceptive healthcare regarding those women with hepatic and renal insufficiency and to conduct a three-year prospective surveillance cohort study to evaluate (1) inappropriate prescribing of Yasmin, (2) adverse events associated with Yasmin, specifically death, hospitalization, arrhythmia, dialysis and hyperkalemic adverse events, and (3) pregnancies associated with Yasmin and any fetal or child malformations.

There is insufficient information to evaluate the educational outreach program. It proposes to evaluate the educational program's effect on prescribing to women with hepatic and renal insufficiency using the active surveillance study. If there is an increased inappropriate prescribing of Yasmin the sponsor plans to revise their educational program accordingly.

The sponsor should provide adequate documentation of the educational program and provide plans for intervention if the rate of prescribing to women with impaired renal or hepatic function does not drop with the progress of the educational program or if those women suffer adverse events to the extent that the risks outweigh the benefits.

The active surveillance study is an acceptable proposal but the sample size calculations may be smaller than needed to obtain statistical significance. The follow-up plans are commendable (checking the National Death Index for deaths and the commitment to an additional 18 months of follow-up for each pregnancy).

The sponsor should provide documentation on the surveillance study for review on the following items:

- "Standard algorithms" to translate health care utilization patterns into presumptive diagnoses, "codes" to translate into outcomes (hepatic, renal, pregnancy, etc.).
- The proposal from [redacted] which includes the confidentiality plan, the institutional review board approval plan and the sample size calculations.
- Evidence to support their assumptions for the sample size and power calculations
- Information on expected lag times for data to be entered into the database
- Documentation of the qualifications of the interviewers and abstractors.
- Reference for the Framingham risk equations and an explanation of their application of the risk of smoking and cardiovascular risks to the Yasmin and other OC user analyses.

The sponsor should provide standardized reporting for each of the study questions: inappropriate prescribing, adverse events and pregnancies and their outcomes. The proposed quarterly reports should include cumulative data for the study period with a tabular listing of cases and their report summaries, statistical analyses to evaluate risk and any additional information that may be helpful.

Overall, this program might be acceptable as long as the sponsor will respond constructively to the deficiencies and omissions listed and discussed.

Comment: It is not clear whether the proposed educational and surveillance programs will really detect and reveal cases of serious hyperkalemia, nor provide evidence that the incidence of hyperkalemia and its complications are reduced by the programs. The sponsor should address issues of how pre-existing, often asymptomatic and unknown, reductions in hepatic and renal function are to be detected so that inappropriate prescribing will not occur. Also, serious effects of hyperkalemia, such as fatal cardiac arrhythmia, may not be attributable to hyperkalemia unless pre-mortum measurements are made.

/S/

Carolyn McCloskey, M.D., M.P.H.
Medical Officer, DDRE2/OPDRA

APPEARS THIS WAY
ON ORIGINAL

References:

1. Request for Consultation; To: OPDRA, HFD-400; From: Jeanine Best, MSN, RN, Project Manager, HFD-580, Division of Reproductive and Urologic Drug Products; dated December 5, 2000; NDA No. 21-098; Type of Document: Phase 4 Program – part of NDA resubmission; Date of Document: November 6, 2000; Name of Drug: Yasmin 28 (drospirenone/ethinyl estradiol) Tablets.
2. Meeting Minutes dated September 25, 2000, NDA 21-098, Yasmin® 28 Tablets (drospirenone and ethinyl estradiol), located in FDA's DFS files.
3. "Approvable" letter dated July 10, 2000 from FDA to Berlex Laboratories, regarding Yasmin® 28, NDA 21-098.
4. "Yasmin® 28 Tablets Phase IV Program", Berlex Laboratories, Inc., November 6, 2000, pages 1-16.
5. Medical Officer's Review of NDA (Supplemental Clinical Information) dated June 16, 2000, NDA 21-098, Yasmin®, Berlex Laboratories, Inc., written by Scott E. Monroe, MD, Medical Officer, DRUDP.
6. Group Leader Memorandum dated February 23, 2000, NDA 21-098, Yasmin®, written by Marianne Mann, MD, Deputy Director of HFD-580.
7. Office Director Memo dated July 10, 2000, NDA 21-098, Yasmin® 28 Tablets (drospirenone/ethinyl estradiol) Berlex Laboratories, Inc., written by Florence Houn, MD, MPH.

Nancy Velez
05/11/01 03:31 PM

Addressing
To: bestj@cder.fda.gov
cc: (bcc: Nancy Velez/MV/USR/SHG)
Subject: Yasmin: Revised PhyPI, Acceptance Phase IV Commitments

Dear Ms. Best,

In follow up to our discussions this morning and this afternoon, attached please find marked and unmarked versions of revised Physician Package Insert for YASMIN reflecting our final changes. This email also serves as documentation that Berlex accepts the Phase 4 commitments as outlined in the telefax and email of May 11, 2001 with the following clarifications:

1. As agreed during the teleconference, the fourth bullet point in Comment 3 will be moved to appear as the fourth bullet point under Comment 1.
2. Also as agreed during the teleconference, the database described in Comment 3 is the database described in our November 6, 2000 submission which contained our Phase IV program.

We await your confirmation that the labeling is acceptable. At that time later today, following receipt of the YASMIN approval letter, a submission containing this same labeling and our acceptance of the Phase IV commitments will be forwarded to you via UPS Overnight Delivery and by telefax.

We anxiously await your feedback and look forward to the approval letter.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5-11-01phypiunmarked.doc

Nancy Velez

APPEARS THIS WAY
ON ORIGINAL

Yasmin®
Phase IV Commitments
May 11, 2001

The Division requests the phase IV commitments to which the sponsor agreed in the submission dated July 7, 2000, with the following modifications:

1. Develop an educational outreach program for health care providers and patients, focusing on Yasmin®'s contraindications in patients with renal or hepatic impairment and in patients predisposed to hyperkalemia.

    - Submit the final protocol to the FDA within 90 days of the approval date, initiate the program within 180 days of the approval date, and submit semi-annual status reports. Submit a final report within 6 months after completion of the program.
    - Include educational outreach for patients, which is not described in the November 6, 2000 proposal.
    - Educate healthcare providers to the importance of reporting all serious adverse events (especially cardiac events) that occur in Yasmin® users.
    - Provide healthcare providers with a mechanism to facilitate the reporting of serious adverse events in Yasmin® users.

2. Develop a surveillance program to a) evaluate the prescribing of Yasmin to contraindicated patients with underlying renal or hepatic impairment using a database of Yasmin users. The database would provide a list of all Yasmin® users, and these patients would then be screened carefully for any past or recent diagnoses of renal and/or hepatic impairment. Submission of full case report summaries of all such contraindicated prescriptions, including patient outcome, would be required, and to b) evaluate compliance of healthcare providers with the serum potassium measurements in the first cycle of Yasmin® use in patients receiving long-term treatment with medications that may increase serum potassium

    - Submit the final protocol to the FDA within 90 days of the approval date, initiate the program within 180 days of the approval date, and submit semi-annual status reports containing line listings, summary tables, and relevant subject narratives. Submit a final report within 6 months after completion of the program.
    - Set acceptable limits approved by FDA for contraindicated prescribing of Yasmin® and describe the corrective actions that will be taken if the limits are exceeded.

3. Use a database to evaluate all patients prescribed Yasmin® for the subsequent outcomes of death, hospitalization, syncope, arrhythmia, hyperkalemia, electrolyte disturbances, dialysis, etc. (other search terms may also be considered appropriate); patients taking Yasmin® and experiencing these types of events (or taking Yasmin® within one month of such events) would be considered concerning; full case reports summaries, including patient outcome, would be required for these patients.

    - Submit the final protocol to the FDA within 90 days of the approval date, initiate the program within 180 days of the approval date, and submit semi-annual status reports containing line listings, summary tables, and relevant subject narratives. Submit a final report within 6 months after completion of the program.

- Ensure that the surveillance program based on the ——— database will identify Yasmin® users who are hospitalized, receive emergency treatment, or who experience other serious adverse events.

4. Analyze more carefully pregnancy outcomes that occur in patients exposed to Yasmin®. This could be done in the same cohort of Yasmin® users described in the database described above. In addition, the Organization of Teratogen Information Services (OTIS), or other resources could be used to collect data on all patients reporting a Yasmin® exposure. A pregnancy exposure registry is an alternative. Outcome on as many patients as possible is desired and may require several years of follow-up. Finally, collecting all post-marketing adverse event reports and placing them in a format to help identify signals of developmental toxicity is recommended. Submit the final protocol to the FDA within 90 days of the approval date, initiate the program within 180 days of the approval date, and submit semi-annual status reports containing line listings, summary tables, and relevant subject narratives.

NDA 21-098
Yasmin® 28 Tablets (drospirenone/ethinyl estradiol)
Berlex Laboratories, Inc.

Sponsor Proposed Phase IV Program, November 6, 2000.

/S/ 1/18/01

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Phase IV Program

Table of Contents

1. Executive Summary

Berlex's proposed Phase IV program consists of two components: (1) an educational outreach program, and (2) an active surveillance program to determine the inappropriate prescribing of Yasmin (i.e. women prescribed Yasmin with hepatic or renal impairment), occurrence of clinical events potentially related to hyperkalemia with use of Yasmin, and the monitoring of breakthrough pregnancies that occur with Yasmin for the occurrence of fetal/child malformations.

The educational outreach program will focus on the medical and pharmacy providers of contraceptive healthcare. The objective is to educate them on appropriate patient types for Yasmin. A basic foundation regarding the pharmacological properties of DRSP, specifically antimineralocorticoid activity is essential to the selection of appropriate patient types, thus minimizing use in at-risk patients. This will be accomplished through various venues including Continuing Medical Education (CME) programs, Sales Representative details, customized brochures as well as peer-reviewed publications. Success of these programs will be measured and programs adjusted as needed.

The surveillance study will identify and follow relevant patient cohorts over three years, utilizing a very large research database such as the . is the nation's second largest health care provider, covering 4.5 million lives, approximately 50% female. The Yasmin cohort would be composed of those members in the study cohort prescribed Yasmin during the study period and the control cohort will be generally comprised of women matched based on age, and concurrent medical conditions selected in a 2:1 ratio with the Yasmin cohort.

Baseline patient characteristics, including age, comorbid conditions and smoking will be collected for comparative analyses. For determination of clinical outcomes associated with Yasmin use, outcomes data will be collected and reported quarterly following initial dispensing. Clinical events will be identified through claims data collection and investigated via a standard medical chart review.

Details regarding the educational outreach program as well as the active surveillance study are described below.

2. Educational Outreach Program

Our primary objective for this program is to educate physicians on the appropriate patient types to whom Yasmin can be prescribed so that use in the at-risk patient is minimized.

Our principle audience are the gatekeepers of contraceptive healthcare, i.e. physicians, nurses, nurse practitioners and pharmacists. To this group, our strategic focus is on the pharmacological properties, primarily the antimineralocorticoid activity of DRSP, which is the basis for understanding the risk for certain patient types.

The best way to provide this information is through our Sales Force. The Berlex Sales Representative will receive CD-ROM based, specialized training and be evaluated by proficiency testing. Sales detail aids will focus on the DRSP pharmacology, specifically the

antimineralocorticoid property and draw attention to potassium levels, as well as the contraindicated patients.

A large nationwide CME program consisting of Lunch and Learn programs, Grand Rounds, Regional Meetings, and professional conference symposia will also be used to deliver this message. Additionally, there will be publications in peer-reviewed journals on the pharmacology and contraindicated patient groups.

For the pharmacy setting, special CME brochures highlighting the pharmacology and at-risk patient, Sales Representative details and publications will be utilized.

An evaluation of the success of these activities will be conducted. Through market research and commercially available market data, we will perform communications testing and analyze prescribing tracking and awareness tracking.

The primary measure for changes in prescribing behavior will be the active surveillance program. This will allow us to monitor outcomes relative to other oral contraceptives and to obtain detailed patient data as needed.

The cut off for inappropriate prescribing of Yasmin would be based off of the already low prescribing of oral contraceptives to renally impaired patients (14/100,000). Statistically significantly higher rates of inappropriate prescribing in the Yasmin cohort, if present, will be reported on a quarterly basis. The results of this analysis will be reviewed to determine the circumstances that appear to lead to inappropriate Yasmin prescribing in these patients. This information will be used to revise and refine Berlex's physician education program described above.

3. Active Surveillance Study

3.1 Introduction

In order to meet the Phase IV requirements set forth by the Food and Drug Administration for the oral contraceptive Yasmin we propose a conducting a prospective cohort study to achieve three goals:

- Assess prescribing of Yasmin and other oral contraceptives to women with hepatic or renal insufficiency;
- Assess the occurrence of clinical events potentially related to hyperkalemia with Yasmin in comparison to other oral contraceptives;
- Monitor breakthrough pregnancies that occur with Yasmin for the occurrence of fetal/child malformations.This study will utilize a large administrative database to identify and follow relevant patient cohorts over a three year time period. Specified outcomes described in this document will be monitored quarterly. Events identified will be confirmed by chart review, with findings for each incident summarized in a full case-report.

3.2 Database Description

We propose using a large research database for achieving the goals of this study. One such database is described below.

The following information for the "Database Description" section has been included exactly as described in a proposal provided by the Epidemiology Division of

The context for this study is a very large research database built from provider, facility, and pharmacy claims at UnitedHealthcare, the nation's second largest health care provider. Among the 4.5 million persons covered by , essentially all health care events are captured for follow-up. maintains a right of review of medical records that underlie claims for payment, and examination of these records permits a full health characterization of patients. The study will use automated health insurance claims data from the

members are brought into the Research Database if they belong to plans in which the costs of pharmaceuticals and health services are reimbursed to providers on an item-by-item basis, so that it is possible to reconstruct all health care utilization. The Research Database currently includes information from 25 affiliated health plans from the following 19 states: Alabama, Arizona, Arkansas, Florida, Georgia, Illinois, Louisiana, Massachusetts, Michigan, Mississippi, Missouri, Nebraska, North Carolina, Ohio, Rhode Island, South Carolina, Tennessee, Texas, and Utah. Beginning with the earliest claims, in 1990, the Research Database has detailed information on approximately 8,000,000 current and past members. The uses these data daily for a wide range of safety, utilization, and economic analyses.

Table 1 shows the age and gender distribution of the 4,500,000 people in the Research Database in 1999.

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Table 1: 1999 UnitedHealthcare Research Database Population

Age	Female	Male	Total
0-9	331,780	349,703	681,483
10-19	337,353	354,549	691,902
20-29	358,816	360,143	718,959
30-39	438,701	447,391	886,092
40-49	424,948	410,365	835,313
50-59	268,869	262,508	531,377
60-64	64,097	67,821	131,918
65+	33,178	37,924	71,102
Total	2,257,742	2,290,404	4,548,146

The database has encrypted patient and physician identifiers that maintain confidentiality yet also allow linkage of records. The raw data represent records of claims transactions, which may be original claims for reimbursement, or transactions involving financial adjustments (debits or credits) to patient accounts.

Member enrollment files record demographic information on all health plan enrollees, including date of birth, gender, place of employment, and benefit package. Legal restrictions preclude health insurers from collecting information on race. A unique identifier is assigned to each member at the time of enrollment. The identifier is structured to allow longitudinal follow-up of the subscribers and their household members.

Detailed transactions data include information on all services, whether they occur in a doctor's office or a medical facility. Each facility service record contains information on up to nine diagnoses, recorded with the International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes, and up to six procedures recorded with ICD-9 procedure codes, Current Procedural Terminology (CPT) or Health Care Financing Agency (HCFA) Common Procedure Coding System (HCPCS) codes. Sites of care include hospital emergency room, hospital outpatient, hospital inpatient, doctor's office, long-term care facility, ambulatory surgical center, and other sites. The facility transactions contain each service category that the facility, e.g., hospital, listed on its claim for reimbursement, such as surgeries, radiologic procedures, laboratory tests, room and board charges, or other billed items. Typically these data do not include any drugs administered in hospital. Total amounts charged by the provider and costs paid by the insurer, the patient, and any other third party are available, thus enabling calculations of costs from both the insurer and patient perspectives.

Claims from individual providers like physicians are recorded in ICD-9 diagnosis codes, and CPT, ICD-9-CM or HCPCS procedure codes. Each doctor service record contains information

on up to four diagnoses, recorded with ICD-9 diagnosis codes, and one procedure code recorded using ICD-9 procedure codes, CPT or HCPCS codes.

Prescription drugs can be identified and selected by National Drug Code (NDC), brand name, generic name, or therapeutic class. Information is available on drug strength, length of prescription (days), total daily dose, route of administration and whether the dispensing was an original prescription or a refill.

The Research Database is constantly receiving new information about enrollment, pharmacy and medical claims. Pharmacy claims are included within about six weeks of their occurrence. Incorporation of medical claims is more variable, with approximately six months required to capture 95% of paid claims.

The data in these databases undergo audits by [redacted] The validity of the [redacted] claims has also been documented through review of medical records.

There is an administrative file separate from the Research Database files that can be used for rapid case ascertainment. The Preadmission Certification File contains information on current and impending hospital admissions. [redacted] staff use this file to record discussions with caregivers concerning the need for, status, duration, and disposition of hospitalized patients, and it is continuously updated in real time.

Medical record abstraction is possible at all sites with health plan permission. No individual written consent is required for research studies. [redacted] has established the right through its member agreements in these 25 plans to review medical records without obtaining individual written consent for each project. In addition to the [redacted] automated data available for research purposes, we are able to use existing resources at [redacted] to conduct patient surveys by mail or telephone.

There are Medicare patients who also are members of [redacted] plans, but these are excluded from our analyses because of the possibility of concurrent care outside the plans. All members in the Research Database have coverage for oral contraceptives, so that essentially all OC dispensing will be captured.

3.3 Methods

3.3.1 Project Timeframe

The initiation of this project will coincide with the launch of Yasmin. Data collection will continue for three years.

3.3.2 Cohort Definition

Inclusion criteria: The study cohort will be comprised of women who have been enrolled with [redacted] for at least six months prior to first dispensing of an oral contraceptive.

Yasmin cohort: The Yasmin cohort will be comprised of those members of the study cohort who are dispensed Yasmin during the study period.

Must ensure that medical providers are prescribing Yasmin

Control cohort: The definition of a Control cohort will vary, based on the outcome in question, but will generally be comprised of women, matched based on age, and concurrent medical conditions selected in a 2:1 ratio with the Yasmin cohort.

3.3.3 Patient Confidentiality and Approvals

The following information for the "Patient Confidentiality and Approvals" section has been included exactly as described in a proposal provided by the I

Patient confidentiality will be maintained throughout the study. Personal identifiers of patients and doctors will be maintained only at the level of source documents. All research documents will be identified by anonymous codes. The keys to these codes will be kept in strict confidence, and will be physically separate from both the original documents and from the statistical analysis.

The protocol will receive the necessary approvals as required by
has established the right through its member agreements in the Research Database to review medical records without obtaining individual written consent for each project; however, permission is required from the medical directors of the health plans and individual health care providers.

Confidentiality and consent provisions of this proposal meet all standards for non-federally funded research in the United States. nd have been monitoring proposed rules concerning the use of medical records in the United States. During the period covered by the study, applicable regulations may change to more extensive review, similar to that required for federally funded experimental research. clinical trials group regularly obtains institutional review board (IRB) approval of all studies, and we can readily extend the same procedures to cover observational studies such as this one.

3.3.4 Data Collection

Every three months, new members to whom Yasmin has been dispensed will be identified. For determination of clinical outcomes associated with Yasmin use, outcomes data will be collected and reported quarterly following this initial dispensing. Such data collection will terminate at the end of the study period, or at the time of member disenrollment from whichever is sooner. Baseline patient characteristics, including age, comorbid conditions and smoking, will be collected for comparative analyses.

A. Baseline Patient Characteristics

Medical utilization and comorbid conditions
The six month period preceding first dispensing of Yasmin and comparison oral contraceptives in each woman will be screened for the presence of chronic medical conditions, and for indices of health care utilization, including number of doctor visits, number of hospitalizations, and total costs of medical care, divided between outpatient services, prescriptions, and inpatient services. For chronic medical

conditions, standard algorithms to translate utilization patterns into presumptive diagnoses will be employed.

Smoking

Smoking status is strongly related to many of the outcomes that we propose to study. For a three percent sample of the cohort (approximately 1,000 Yasmin users and 2,000 users of other oral contraceptives), a survey of smoking habits and lifestyle preferences will be mailed. There will be intensive telephone follow-up of non-respondents. Previous experience with this population suggests that a 70% response rate is feasible. Women with a confirmed outcome (see below) will be approached using the same survey instrument. Interviewers will not be aware of the health status of the women they call.

B. Clinical Events

Claims data collection

Cases of death, hospitalization, arrhythmia, or dialysis, as well as any care attributed to otherwise unexplained hyperkalemia and electrolyte disturbances will be identified by examining all drug dispensing, inpatient services, and outpatient services for the study cohort found in either physician or facility files with an initial database query with very high sensitivity (screening query). Cases may be identified from codes specific for these outcomes (e.g., arrhythmia, hyperkalemia) or those that describe events that may be related to these outcomes (e.g., myocardial infarction, syncope, Holter monitoring, dispensing of antiarrhythmic medications, etc.). Claims records (including diagnostic and procedure codes) for these cases will be compiled, printed and then reviewed by qualified research nurses and/or physicians, who are blinded to the type of oral contraceptive dispensed. Each incident will be categorized as possibly or unlikely to reflect the outcomes of interest. Reviews will be rechecked by a physician with expertise in claims data analysis.

Pregnancies will be identified through review of codes for pregnancy-related services. Patients with at least two codes on different dates for pregnancy-related services, at least one delivery code, one induced abortion code, one spontaneous abortion code, or one prenatal vitamin dispensing between first Yasmin or comparison oral contraceptive use and six months following last Yasmin or comparison oral contraceptive use will be ascertained. A range of possible conception dates is defined as that which is consistent with the dates of service. If the range of possible dates of conception falls during a period of current or recent use of Yasmin or the comparison oral contraceptive, the claims profiles of the mother and child will be reviewed for the presence of any identified malformations of the fetus or infant.

Chart Review and Case Reports

For each possible event detected, a medical record (chart) review will be conducted by trained chart abstracters using standardized abstraction forms created for this study. Encrypted unique patient identification numbers, event dates and location will be forwarded to a centralized chart abstraction group. Chart abstracters will unencrypt the patient and provider numbers and review the relevant medical records. The timing and severity of the outcomes of interest, including the patient's clinical course, management, and final outcome, along with

copies of de-identified physician notes and hospital discharge summaries, will be collected in a chart review report. This report, containing only encrypted patient and provider identifiers, will be returned for analysis. Full case reports for each incidence will be written, and will include a narrative summary for each event based on the administrative database results and chart review reports, including available lab and test results (e.g., potassium values),along with relevant medical and family history, treatment and outcomes data.

Ascertainment of Mortality

Deaths will be identified primarily through inpatient discharge codes indicating death and through characteristic patterns of care that have proven to be reliable markers of demise in previous studies. These include, for example, ambulance services, resuscitation, and codes for cardiac arrest followed by a complete cessation of services afterwards. At the end of the study identifying information on any woman who has terminated membership in UnitedHealthcare will be submitted to the National Death Index. For all deaths the medical record of services leading up to death, in order to classify deaths will be abstracted, where available. The final search of the NDI will be made just before preparation of the final study report.

3.3.5 Study Definitions

A. Current use

The period defined by the dispensing date and the days supplied. This period is reset with every new dispensing.

B. Recent use

The period defined as ≤60 days following the end of the current use date.

C. Past use

The period defined as >60 days following the end of the recent use date.

3.3.6 Outcomes Assessment

A. Baseline Patient Characteristics

Analysis will consist of tabular presentations of the number of Yasmin and comparison oral contraceptive starts and the total number of dispensings stratified by age, by calendar year, and in relation to each chronic medical condition and indices of health care utilization. The results of the survey of smoking habits in Yasmin users and users of comparison oral contraceptives will be presented in a tabular fashion with stratification by age. If potentially significant differences in the smoking habits of these groups are found (after stratification on other subject characteristics that will enter into the multivariate analysis: age, prior oral contraceptive use, region/plan, baseline health characteristics, date of initiation of Yasmin or comparison oral contraceptives), we will model the expected differences in rates of cardiovascular outcomes, using the Framingham risk equations.

B. Oral contraceptive prescribing to women with hepatic or renal insufficiency

Cases of potentially inappropriate prescribing of oral contraceptives will be identified by examining pharmacy claims data for such prescriptions among women with diagnostic codes and services compatible with hepatic or renal dysfunction (Appendix A). The health and demographic characteristics of these women will be described separately, as will the kinds of providers and health services that preceded the dispensing of Yasmin and comparison oral contraceptives. Statistically significantly higher rates of inappropriate prescribing in the Yasmin cohort, if present, will be reported on a quarterly basis. The results of this analysis will be reviewed to determine the circumstances that appear to lead to inappropriate Yasmin prescribing in these patients. This information will be used to revise and refine Berlex's physician education program described above.

Should be no prescribing in contraindicated pop'n

C. Clinical events potentially related to hyperkalemia

The occurrence of each of the outcome events, death, hospitalization, syncope, arrhythmia, hyperkalemia, electrolyte disturbances or dialysis, will be reported in relation to Yasmin or other oral contraceptive use status, providing a risk (events per 1000 users) and the incidence rate (events per 1000 woman-months). Since the Yasmin and comparison groups will be assembled so as to have identical distributions of age, calendar quarter of first use, and health plan, the risk and rate comparison will be balanced with respect to these characteristics, and they will not confound the resulting analysis.

For each tabulated event we will prepare a narrative history based on claims history and the abstracted medical records. The narrative will include a clinical description of the events, results of relevant diagnostic tests, and all available electrolyte values.

If the results of the baseline survey and analysis described above indicate any consequential difference in smoking habits between Yasmin users and users of other oral contraceptives, we will combine the survey results in cases with the random sample results to construct a nested case-control study in which all estimates for the effects of Yasmin will be adjusted for the confounding effect of smoking.

D. The occurrence of fetal/child malformations in breakthrough pregnancies

The incidence of pregnancy among users of Yasmin and comparison oral contraceptives will be reported using the same techniques of tabular and multivariate analysis employed for other outcome events. For identified malformations, a narrative description of morphology and all diagnostic procedures, as well as patient classification according to standard criteria (as determined by a clinical geneticist) will be provided. Because of the necessity of allowing all breakthrough pregnancies to come to term and for any abnormal infant outcomes to be classified, this will follow the end of the cohort observation period by 18 months.

E. Statistical Analysis

Multivariate Analysis

If the number of outcome events among Yasmin users is 25 or larger, we will undertake a multivariate analysis of their incidence, incorporating age, calendar time, health plan, prior oral contraceptive use history, and chronic medical conditions as adjustment variables. The technique for this will be Poisson regression, in which the unit of analysis is the woman-day of observation, the predictor variables change with time and include both current and historical information, and the outcome is associated with the day on which it occurred.

Sample size calculation

The following information for the "Sample Size Calculation" section has been adapted from a proposal provided by the

We have projected the number of Yasmin users in over the three years of study, based on Berlex's projections of Yasmin sales in the United States. The Berlex U.S. projections take the form of the number of new users each year. We have used these data to estimate the number of woman-months of Yasmin use in each of the three years of data collection, and ir Table 2 below is organized according to year of study, which we anticipate will begin with the date of launch. For each year, the table gives the number of new Yasmin users who will accrue during that year, and the estimated number of months of use that will accrue from new users in that year, plus continuing users in previous years.

Table 2: Projected New Users and Woman-Months of Yasmin Use in the United States and in United Healthcare

	United States		UHC		
Year	New Users	Woman-months*	New Users	Woman-months*	Woman-years*
1		1,404,149		28,083	2,340
2		5,702,851		114,057	9,505
3		11,225,664		224,513	18,709
Total		18,332,663		366,653	30,554

*Includes time using Yasmin among women who started in an earlier year.

To make these estimates we have assumed that the months of first use of Yasmin are spread out evenly through the year and that the monthly probability of discontinuing use of Yasmin is 3 percent. We have furthermore assumed that sales to women represented in the will represent about 2 percent of the U.S. market.

Surveillance for Inappropriate Dispensing

The first objective of the study is to conduct an ongoing surveillance for dispensing of Yasmin to women with hepatic or renal impairment. Here, the statistical power of the study relates to the probability of detecting new use of Yasmin in women with hepatic and renal impairment, and the precision of the study corresponds to the precision with which we can estimate the extent of such use. The surveillance hypothesis to be tested in the first case corresponds to no increased use in women with contraindications; the power of the study is the probability of observing at least one case, under different assumptions of the true fraction of Yasmin users who fall into the contraindicated category. The precision of the estimate is the size of the asymptotic 95% confidence interval for the estimate. The following table presents the power and precision of the proposed study through Years 1, 2, and 3 of follow-up, assuming the number of new starts each year in [redacted] as given above, under different assumptions about the true risk of inappropriate prescribing.

Table 3: Power and Precision of Estimates for Inappropriate Prescription

Assumed Risk of Inappropriate Prescription	Power through Year			95% CI , +/-, through Year		
	1	2	3	1	2	3
0.01%	40.5%	84.1%	96.8%	0.027%	0.014%	0.011%
0.05%	92.6%	100.0%	100.0%	0.061%	0.032%	0.024%
0.10%	99.4%	100.0%	100.0%	0.086%	0.046%	0.033%
0.50%	100.0%	100.0%	100.0%	0.192%	0.102%	0.075%

If the risk of inappropriate use is as low as one in ten thousand women (i.e. 0.01%), the proposed study is 96.8% certain to identify such use by the end of the third year. If the prevalence is one in one thousand, the study is 99.4% certain to identify such use in the first year, and to provide sufficiently precise estimates of the frequency to quantify the effects of educational interventions in subsequent years, if required.

Incidence of Sentinel Outcomes during Follow-up

The second objective of this study is to ascertain mortality, hospitalization, and the occurrence of cardiac events that might reflect hyperkalemia in the study cohorts. The outcome events under study are exceedingly rare in women in the age range typical of oral contraceptive users. In a recently completed analysis of [redacted] patients, we have observed one myocardial infarction and one serious ventricular arrhythmia in 8,040 years of experience in women under the age of 40 years. In another recent analysis, we followed a sample of [redacted] patients with a median age of 39 years and of whom 65 percent were female, for 13,300 person years. They experienced the following annual mortality and disease incidence rates:

All cause mortality: 2.3 per 1,000

Cardiovascular mortality: 0.5 per 1,000

Myocardial infarction: 2.0 per 1,000

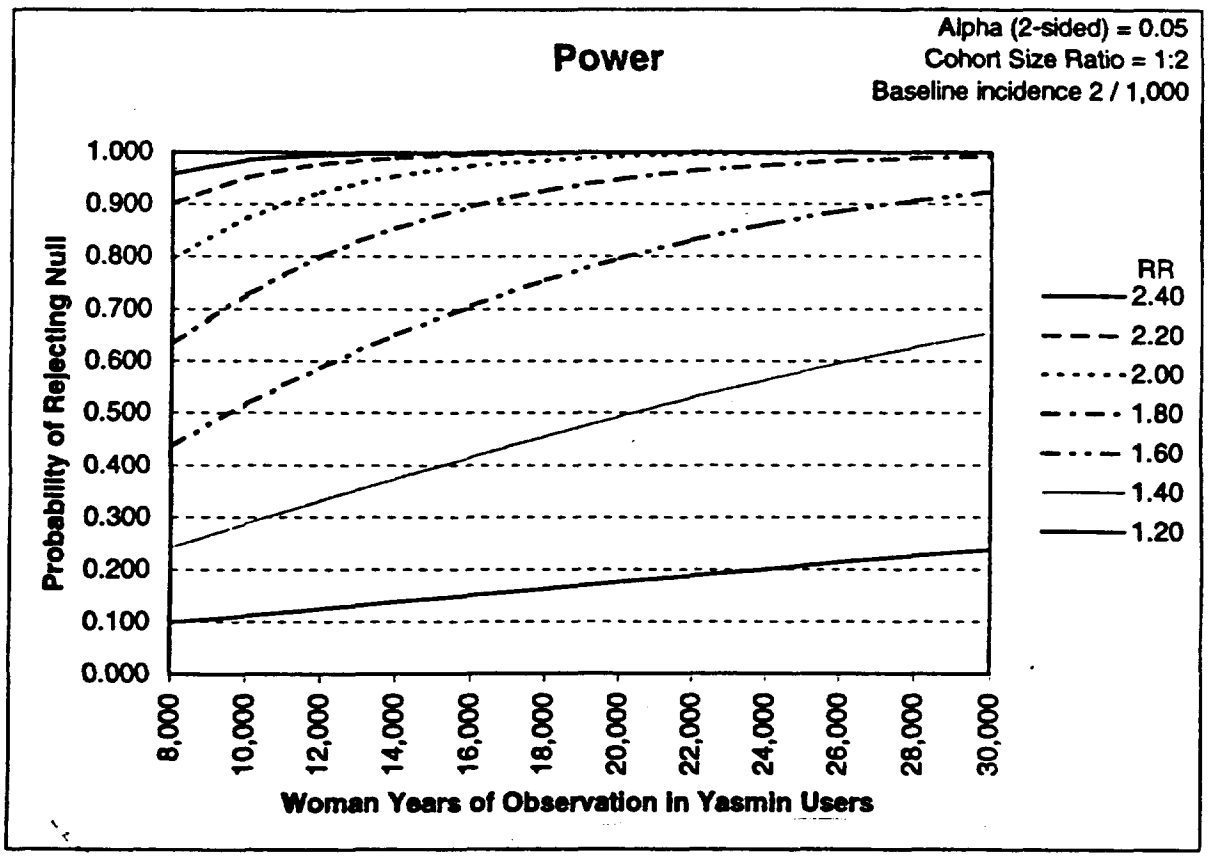
Arrhythmia (narrow definition): 1.8 per 1,000

Arrhythmia (broad definition): 5.6 per 1,000

Since these rates are based on experience in a population somewhat older than the users of oral contraceptives and including one-third males, the figures are higher than we might expect in the present study. For the purposes of calculating power, we have posited a baseline rate of two outcome events per 1,000 woman years of observation.

Figure 1 on the next page gives the power of the proposed study to detect increases in such a risk. By the end of the second year of the study, when there will be approximately 12,000 woman-years of observation in the Yasmin users, it will be possible to identify relative risks as low as 1.8 with greater than 80 percent power. By the end of the third year of the study, relative risks as low as 1.6 will be evident with greater than 90 percent power.

Figure 1: Power to detect increases in the outcome events among Yasmin users, relative to users of other oral contraceptives, in relation to the accumulated duration of follow-up in Yasmin users

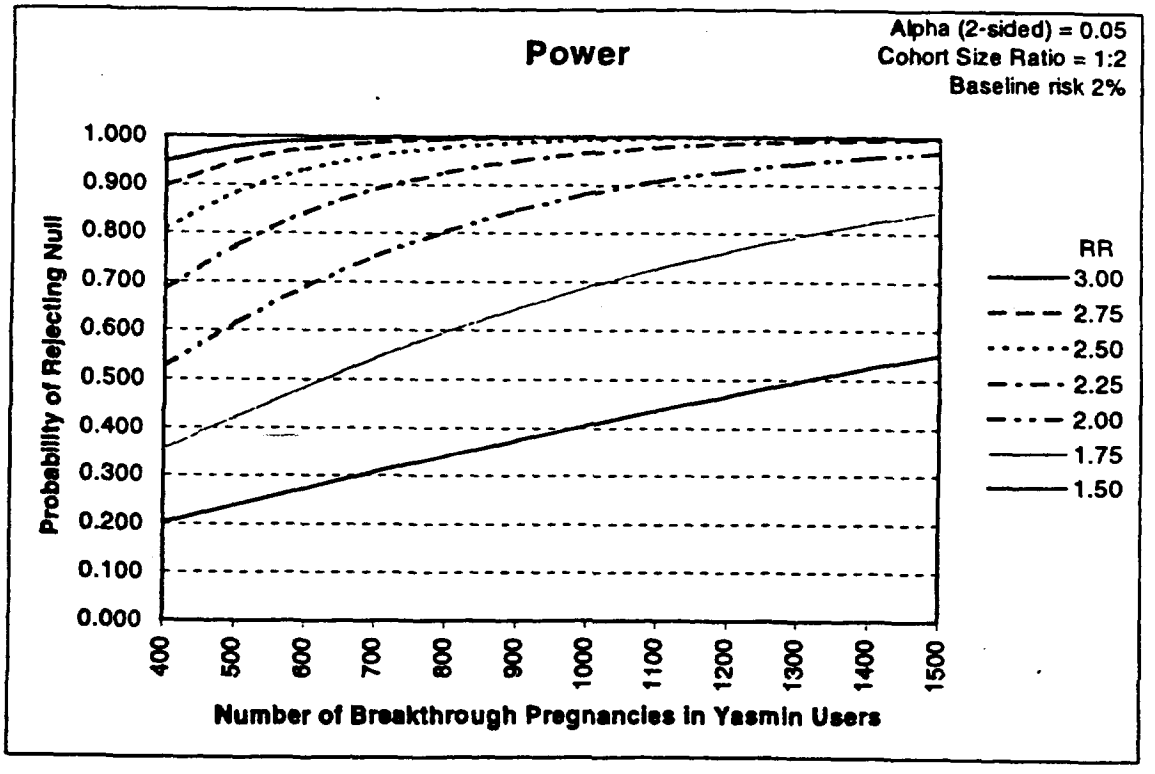


Risks for Congenital Malformations in Breakthrough Pregnancies

The third objective of the study includes surveillance for birth defects in children who were conceived during Yasmin or comparison oral contraceptive use. In 1995, the 12-month failure

rate was 6.9 per 100 women using oral contraceptives in the United States.[1] Anticipating somewhat better than average adherence to oral contraceptives in a health maintenance organization (HMO) population such as that of ——— we have made estimates of pregnancy numbers on an expectation that the pregnancy rate on Yasmin and on comparison oral contraceptives will be 5 per 100 women per year. With 30,554 years of use of Yasmin (see the table at the beginning of this section), we can anticipate approximately 1500 pregnancies in the Yasmin group, and 3000 in the two-fold larger comparison group of users of other oral contraceptives. The prevalence of recognized malformations at birth is approximately two percent, giving an expected count of 30 in the Yasmin breakthrough pregnancies and 60 in the pregnancies arising in the comparison group. The chart below gives the power to detect an overall elevation in the risk of congenital malformations, for numbers of births in the Yasmin group ranging from 400 to 1500. The power in smaller than expected numbers of pregnancies is given to account for the possibility that pregnancies will be terminated without ascertainment of malformations in the fetus, and for the possibility that the breakthrough pregnancy rate will be lower than the historical rate.

Figure 2: Power to Detect Elevations in the Risk of Congenital Malformations



At the anticipated number of pregnancies, the power of the study is excellent (greater than 80%) for relative risks of 1.75 and higher. Even with substantially reduced numbers of pregnancies, the power is excellent for relative risks of 2.00 and higher.

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[1] Trussel J, Vaughan B. Contraceptive failure, method-related discontinuation and resumption of use: Results from the 1995 National Survey of Family Growth. Family Planning Perspectives 31(2): 64-72, 93. Mar./Apr. 1999. (Available: http://www.agi-usa.org/pubs/journals/3106499.html)

For rare individual malformations, the power of a surveillance study corresponds to the probability of detecting a single case. The table below gives the probability of observing a specific malformation in relation to its true prevalence among children conceived during Yasmin use.

Table 4: Probability of Detecting Specific Malformations in a Surveillance Study of Breakthrough Pregnancies in Yasmin Users

	Number of Pregnancies Observed						
Risk	**300**	**500**	**700**	**900**	**1100**	**1300**	**1500**
0.01 %	0.030	0.049	0.068	0.086	0.104	0.122	0.139
0.05 %	0.139	0.221	0.295	0.362	0.423	0.478	0.528
0.1 %	0.259	0.393	0.503	0.593	0.667	0.727	0.777
0.5 %	0.777	0.918	0.970	0.989	0.996	0.998	0.999
1 %	0.950	0.993	0.999	1.000	1.000	1.000	1.000
5 %	1.000	1.000	1.000	1.000	1.000	1.000	1.000

Minimum number to detect = 1

The probability of detecting a malformation becomes excellent at risks between 0.1% and 0.5%. At 0.5% and above, detection is virtually certain, even with substantially fewer pregnancies than anticipated.

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