CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-098

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE) AND DRUG ADMINISTRATION	**Clinical Pharmacology & Biopharmaceutics (HFD 870)** **Tracking/Action Sheet for Formal/Informal Consults**

From: **Venkateswar Jarugula, Ph.D., HFD-870**

To: DOCUMENT ROOM (LOG-IN and LOG-OUT)
Please log-in this consult and review action for the specified IND/NDA submission

DATE: **06/21/00**	IND No.: Serial No.:	NDA No. **21-098**	DATE OF DOCUMENT **06/15/00**	JUN 22 2000
NAME OF DRUG **Yasmin Tablets**	PRIORITY CONSIDERATION **P**		Date of informal/Formal Consult:	

NAME OF THE SPONSOR: Berlex

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

- ☐ PRE-IND
- ☐ ANIMAL to HUMAN SCALING
- ☐ IN-VITRO METABOLISM
- ☐ PROTOCOL
- ☐ PHASE II PROTOCOL
- ☐ PHASE III PROTOCOL
- ☐ DOSING REGIMEN CONSULT
- ☐ PK/PD- POPPK ISSUES
- ☐ PHASE IV RELATED
- ☐ DISSOLUTION/IN-VITRO RELEASE
- ☒ BIOAVAILABILITY STUDIES
- ☐ IN-VIVO WAIVER REQUEST
- ☐ SUPAC RELATED
- ☐ CMC RELATED
- ☐ PROGRESS REPORT
- ☐ SCIENTIFIC INVESTIGATIONS
- ☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ ANNUAL REPORTS
- ☐ FAX SUBMISSION
- ☒ OTHER *(SPECIFY BELOW)*:
  Comparison of different formulations

REVIEW ACTION

- ☐ NAI (No action indicated)
- ☐ E-mail comments to:
  ☐Medical ☐Chemist ☐Pharm-Tox
  ☐Micro ☐Pharmacometrics ☐Others
  (Check as appropriate and attach e-mail)
- ☐ Oral communication with
  Name: [ ]
- ☐ Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]
- ☐ Formal Review/Memo (attached)
- ☒ See comments below
- ☐ See submission cover letter
- ☐ OTHER *(SPECIFY BELOW)*:
  [ ]

REVIEW COMMENT(S)

☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

COMMENTS/SPECIAL INSTRUCTIONS:
The formulations used in renal impairment study (SH T00470R) and ACE inhibitor drug interaction study (SH T641DA) are different from Yasmin formulation (SH T470 FA final). As per the Agency's request sponsor provided the comparison of formulations used in these studies and Yasmin formulation. According to the information submitted, the composition of these two formulations is similar to that of Yasmin except for the estrogen component (see attached). Manufacturing process of all three formulations is comparable. Hence, the results of these studies have been extrapolated to Yasmin (see review dated 6/15/00).

SIGNATURE OF REVIEWER: /S/ /S/ Date 6/21/00

SIGNATURE OF TEAM LEADER: Date 6/22/00

CC.: HFD # [870]; TL: [Parekh]; DD: [Huang]; PM: [Best]

Yasmin®: Comparison Of Tablets Used In The Renal Impairment Study, ACE Inhibitor Study And The Commercial Formulation

1 Formulations

For an overview of the formulations, please see the following table:

Components	Formulation (mg/tablet)*		
	SH T470 FA (Final)	SH T00470R	SH T 641 DA**
Ethinyl estradiol, USP	0.030	np	np
Estradiol, USP			
Drospirenone, micro 15	3.000	3.000	3.000
Lactose monohydrate, NF			
Corn starch, NF			
Pregelatinized starch, NF			
Povidone 25000, USP			
Magnesium stearate, NF			
Hydroxypropyl methyl cellulose, USP			
Macrogol 6000, NF			
Talc, USP			
Titanium dioxide, USP			
Ferric oxide pigment yellow, NF			
Total tablet weight (mg)			
Report or Protocol No.		Report No. B682[a]	Protocol No. 98106[b]
Study type	Commercial formulation	Renal impairment	ACE Inhibitor

np = Not present

* = Data on file

**=study conducted with HRT formulation, [redacted] submitted September 26, 1997

a) Open-label study to assess the effect of 3 mg drospirenone (DRSP) on serum potassium and to evaluate the pharmacokinetics of DRSP in female volunteers with impaired or normal renal function after repeated oral administration over 14 days (Study no. 303083). This final report was submitted to NDA 21-098 on May 8, 2000.

b) A Double-Blind, Randomized, 2-Parallel Groups Study to Evaluate the Potential for Developing Hyperkalemia when the Hormone Replacement Therapy Combination Drug Product Drospirenone/Estradiol is Coadministered with an ACE Inhibitor in Postmenopausal Women (Protocol No. 98106). The final statistical analysis of serum potassium data from the ACE inhibitor study was submitted to NDA 21-098 on April 20, 2000.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology & Biopharmaceutics (HFD 870)** **Tracking/Action Sheet for Formal/Informal Consults**			
Venkateswar Jarugula, Ph.D., HFD-870			**To: DOCUMENT ROOM (LOG-IN and LOG-OUT)** **Please log-in this consult and review action for the specified IND/NDA submission**	
ATE: 06/15/00	IND No.: Serial No.:	NDA No. 21-098	DATE OF DOCUMENT **05/8/00, 06/12/00**	JUN 15 2000
AME OF DRUG **asmin Tablets**	PRIORITY CONSIDERATION **P**		Date of informal/Formal Consult:	

AME OF THE SPONSOR: Berlex

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

] PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
]ANIMAL to HUMAN SCALING	☒ BIOAVAILABILITY STUDIES	☐ LABELING REVISION
] IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
] PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
] PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
] PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
] DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
] PK/PD- POPPK ISSUES	☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	☐ OTHER *(SPECIFY BELOW)*:
] PHASE IV RELATED		

REVIEW ACTION

...l (No action indicated)	☐ Oral communication with	☒ Formal Review/Memo (attached)
] E-mail comments to:	Name: [ ]	☐ See comments below
]Medical☐Chemist☐Pharm-Tox	☐ Comments communicated in	☐ See submission cover letter
]Micro☐Pharmacometrics☐Others	meeting/Telecon. see meeting minutes	☐ OTHER *(SPECIFY BELOW)*:
Check as appropriate and attach e-mail)	dated: [ ]	[ ]

REVIEW COMMENT(S)

☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

OMMENTS/SPECIAL INSTRUCTIONS:

IGNATURE OF REVIEWER: /S/ /S/ Date 6/15/00

IGNATURE OF TEAM LEADER: Date 6/15/00

C.: HFD # [870]; TL: [Parekh]; DD: [Huang]; PM: [Best]

JUN 15 2000

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA:	21-098
Drug:	Yasmin (Drospirenone and Ethinyl estradiol) tablets
Sponsor:	Berlex
Date of Submission:	05/8/00, 06/12/00
Type of Submission:	Response to approvable letter
Reviewer:	Venkateswar R. Jarugula, Ph.D.

Synopsis

Yasmin is a combination oral contraceptive tablet containing a new synthetic progestin, drospirenone (3 mg) and ethinyl estradiol (35 μg). Drospirenone (DRSP) is a 17α-spirolactone derivative that has shown a combination of progestational and aldosterone-antagonistic properties both preclinically and in humans. The daily dosage is one tablet to be used cyclically, i.e., for 21 days followed by 1 placebo tablet daily for 7 days.

In response to the approvable letter issued by the Agency, sponsor has submitted a complete report for renal impairment study, statistical analysis of serum potassium levels from ACE inhibitor drug interaction study and the revised labeling for Yasmin.

Renal Impairment Study (B682):

The primary objective of the study was to evaluate DRSP's effects on serum potassium to assess the risk of hyperkalemia in female subjects with mild or moderate renal impairment. The secondary objective was to evaluate the effect of renal function on the pharmacokinetics of DRSP. Only DRSP pharmacokinetic results of the study are reviewed here. For a review on serum potassium levels, please refer to the clinical review.

This was an open-label, non-randomized study with one treatment (DRSP 3 mg) in the following three parallel groups:

Group 1: Normal renal function, creatinine clearance > 80 ml/min, N=11
Group 2: Mild renal impairment, creatinine clearance > 50 –80 ml/min, N=10
Group 3: Moderate renal impairment, creatinine clearance 30-50 ml/min, N=7

In total 28 subjects were enrolled. Subjects were classified in various renal function groups based on their creatinine clearance (CrCL) values. For screening, a preliminary classification was carried out using the Cockroft-Gault formula to estimate CrCL value. The final group allocation was based on 24-hour CrCL measured in the pretreatment phase (baseline). In cases where the CrCL estimated at screening differed from the 24-hour clearance at baseline, the value measured at baseline in 24-hour urine was used for group assignment. Each subject was administered one tablet (batch # SH T00470R) containing 3 mg DRSP daily for 14 days (see the attached study synopsis for more details on the design and methods).

The geometric mean (% coefficient of variation) pharmacokinetic parameters of DRSP from the study results are summarized below:

Parameter	Normal renal (N=11)	Mild (N=10)	Moderate (N=7)
C_{max} (ng/ml)	35.8 (44%)	39.6 (31%)	42.4 (43%)
T_{max} # (h)	4.0 (0.5 – 12)	2.0 (1.0 – 12)	2.0 (1.0 – 4.0)
AUC_{0-24h} (ng.h/ml)	549 (31%)	573 (19%)	751 (47%)
$AUC_{0-tlast}$ (ng.h/ml)	1366 (45%)	1340 (34%)	2059 (35%)
$AUC_{0-\infty}$ (ng.h/ml)	1431 (48%)	1394 (39%)	2261 (58%)
$t_{1/2}$ (h)	33.6 (33%)	32.4 (28%)	42.8 (23%)
CL_{ss}/F (ml/min)	91.0 (31%)	87.3 (19%)	66.6 (47%)
Free fraction	4.2% (0.2%)*	5.4% (1.5%)**	3.7% (0.8%)*

Median (range) * N=5 ** N=6

The mean serum concentration profiles of DRSP in subjects with normal renal function and mild renal impairment groups are nearly superimposable (see attached figure). However, subjects with moderate renal impairment showed higher serum DRSP levels compared to those in normal renal function group. Based on AUC_{0-24h} comparison, DRSP exposure was increased on average by 37% when compared to subjects with normal renal function. The terminal half-life was also increased from 33.6 h in normal renal function to 42.8 h in moderate renal impairment.

A linear regression analysis was conducted by the sponsor to estimate the influence of the renal function on the $AUC_{0-24\,h}$ of DRSP and a statistically significant increase of the DRSP exposure with decreasing creatinine clearance was observed ($p = 0.028$, $r = 0.41$). According to this regression analysis, a mean increase of AUC by 3.5% is expected with a decrease in creatinine clearance of 10 ml/min.

The significant increase in exposure (37%) in moderate renal impairment is reported in the labeling, which also includes contraindication of Yasmin in patients with renal insufficiency.

The exposure for DRSP in normal renal function group of this study is found to be lower (approximately 30% lower) than that observed in other multiple dose studies that were

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

1 Page

whereas ANCOVA was done (with baseline serum potassium as covariate) in this study. Since serum potassium is pharmacodynamic marker with a variable baseline, ANCOVA is deemed adequate for statistical analysis.

The formulation and the drug combination used in this study (DRSP/E2) are different from that of Yasmin. However, the serum trough concentrations of DRSP at steady state from this study were approximately 25 ng/ml and are comparable to the levels reported in the original NDA for Yasmin. Therefore, the results (DRSP effects on serum potassium) from this study have been extrapolated to Yasmin.

The clinical pharmacology and biopharmaceutics comments regarding labeling have been conveyed to the clinical division in the labeling meeting dated 06/02/00.

Recommendation

The results of the renal impairment study and bioequivalence analysis of potassium levels from ACE inhibitor drug interaction study have been reviewed and found to be acceptable from pharmacokinetic perspective. No comments need to be conveyed to the sponsor.

/S/

Venkateswar Jarugula, Ph.D., Reviewer, HFD-870

/S/

Ameeta Parekh, Ph.D., Team Leader, HFD-870

6/15/00

cc: NDA 21-098, HFD-580 (Monroe, Best), HFD-870 (Huang, Parekh), B.Murphy (Drugs)

APPEARS THIS WAY
ON ORIGINAL

2. Synopsis

Name of finished product:	--	
Name of active ingredient:	Drospirenone (DRSP)	
Title of study:	Open-label study to assess the effect of 3 mg drospirenone (DRSP) on serum potassium and to evaluate the pharmacokinetics of DRSP in female volunteers with impaired or normal renal function after repeated oral administration over 14 days	
Investigator(s):	Prof. Dr. B. Rouveix, Dr. med. C. Kreutz, Dr. med. P. Pinta	
Study center(s):	One center in France	
Publication :	None	
Study period (years)	**date of first enrollment:** Oct 1999 **date of last completion:** Mar 2000	**Clinical phase:** 1
Objectives:	The study was conducted to: - evaluate DRSP's effects on serum potassium to assess the risk of hyperkalemia in female subjects with mild or moderate renal insufficiency - evaluate the effect of renal function on the pharmacokinetics of DRSP	
Methodology:	Primary variable: Serum potassium concentrations. Comparison of the mean potassium serum concentrations measured on the last 3 days of steady-state treatment with the corresponding pretreatment concentrations. Secondary variable: Serum DRSP levels. Determination of DRSP serum levels by a specific radioimmunoassay (RIA) for 168 hours after last dose. Determination of the pharmacokinetic parameters C_{max}, t_{max}, $t_{1/2}$, $AUC_{(0\text{-}24h)}$, AUC.	
Total number of subjects (planned and analyzed):	Planned: 30 subjects; 10 per group Analyzed: 28 subjects (Group 1: 11; Group 2: 10; Group 3: 7) Valid cases: 28 subjects (Group 1: 11; Group 2: 10; Group 3: 7)	
Diagnosis and main criteria for inclusion:	Non-hospitalized women, age 18 - 75; classified by creatinine clearance (CC): Group 1 (normal renal function) evidenced by CC > 80 ml/min Group 2 (mild renal impairment) evidenced by CC > 50 – 80 ml/min Group 3 (moderate renal impairment) evidenced by CC 30 – 50 ml/min Groups 1, 2, 3 matched for age if possible	
Test product: **dose:** **administration mode:** **batch number:**	SH T00470R, daily oral administration 1 tablet containing 3 mg drospirenone (DRSP) oral AC009	
Duration of treatment:	14 days	
Reference therapy:	None	
Evaluation criteria: **Efficacy:** **Safety:** **Pharmacokinetics:** **Pharmacodynamics:**	 Not applicable Adverse events (AEs) observed, mentioned upon general questioning or spontaneously reported were recorded, physical and laboratory examinations Determination of DRSP serum levels by a specific radioimmunoassay (RIA) for 168 hours after last dose. Determination of the pharmacokinetic parameters Cmax, tmax, t1/2, AUC(0-24h), AUC Comparison of the mean potassium serum concentrations measured on the last 3 days of treatment with the corresponding pre-treatment concentrations, evaluation of treatment effect on serum creatinine and sodium levels, blood gas analysis parameters	
Statistical methods:	Descriptive statistics, multiple regression. No interim analysis	

Synopsis (cont'd)

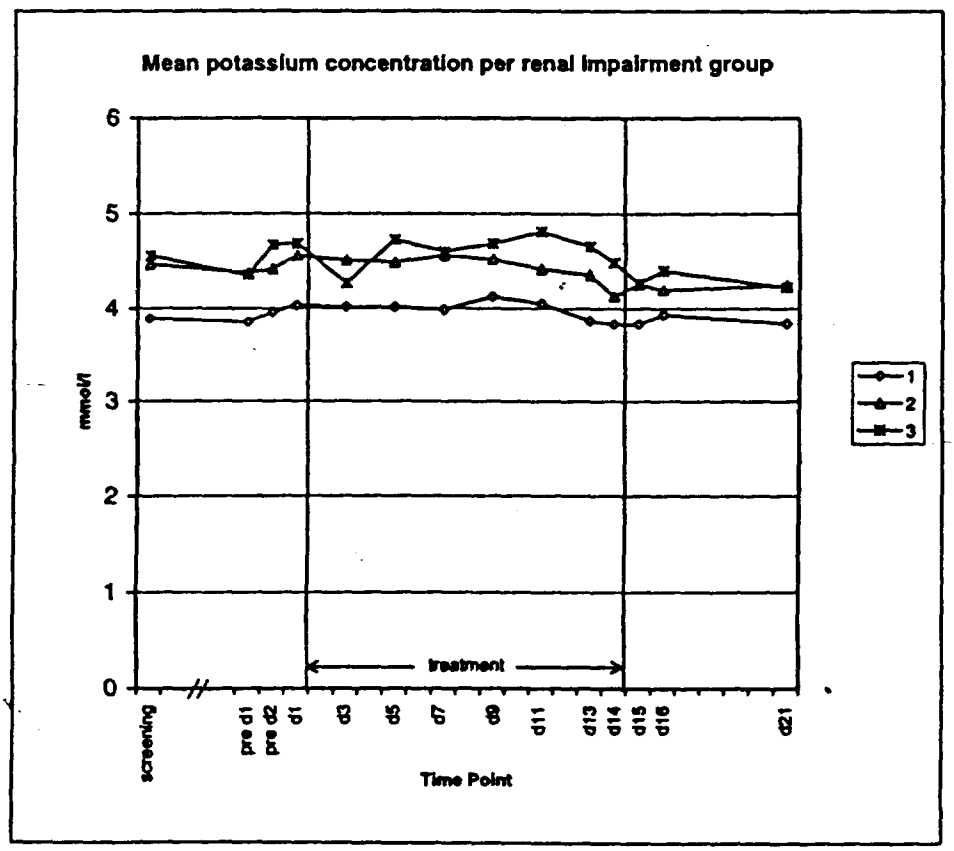
Summary/conclusions:

The aim of the study was to evaluate DRSP's effects on serum potassium to assess the risk of hyperkalemia in female subjects with mild or moderate renal insufficiency compared to subjects with normal renal function. Also the effect of renal function on the pharmacokinetics of DRSP were evaluated.

Pharmacodynamic results:

Overall, the mean potassium serum concentration did not show a clinically significant change during steady-state treatment with DRSP in any of the renal function groups. The mean differences in the steady-state minus pretreatment mean values were negligible in all three renal function groups (Group 1 – normal renal function (N=11): -0.10 mmol/l; Group 2 – mild renal impairment (N=10): -0.20 mmol/l; and Group 3 - moderate renal impairment (N=7): -0.10 mmol/l). A difference in the pharmacodynamic effects of DRSP on the serum potassium concentration in subjects with mild or moderate renal insufficiency compared to subjects with normal renal function was not found.

TF 1: Mean potassium concentration for all three renal function groups (1-3) during entire study



Also, all steady-state treatment potassium concentration values measured for the target variable were under 5.5 mmol/l for all study participants in all three renal function groups. One subject (Group 3: NR 22) had one borderline hyperkalemia value (5.5 mmol/l) in the safety analysis on Treatment Day 9. The value normalized to 5.2 mmol/l on Treatment Day 11 and remained under this value for the rest of the study. All other potassium concentrations measured after treatment begin were 5.3 mmol/l or less.

After 14 days of treatment all three renal groups had slight changes in their acid-base household parameters. On the average, both renally impaired groups developed slightly more acidic venous blood gas values, but all three groups were able to adequately compensate these changes. The mean serum creatinine values for all three renal function groups did not change during treatment with DRSP. A slight decrease in the mean serum sodium values, which was somewhat more pronounced in the renally impaired groups, reflected the mild antimineralocorticoid effect of DRSP treatment.

Pharmacokinetic results:

The mean pharmacokinetic parameters are summarized in TT 1.

The geometric mean and the geometric coefficient of variation (in parenthesis) are listed for the pharmacokinetic parameters Cmax, t1/2, CLss/F and different AUC values. For tmax, the median and the range (in parenthesis) is described. The arithmetic mean and standard deviation is given for the free fraction of DRSP in serum.

TT 1: Pharmacokinetic parameters for DRSP by renal function group

Parameter	Descriptive statistic	Group 1 (N = 11)	Group 2 (N = 10)	Group 3 (N = 7)
Cmax	geo mean (geo CV)	35.8 ng/ml (44%)	39.6 ng/ml (31%)	42.4 ng/ml (43%)
tmax	median (range)	4.0 h (0.5-12 h)	2.0 h (1.0-12 h)	2.0 h (1.0-4.0 h)
$t_{1/2}$	geo mean (geo CV)	33.6 h (33%)	32.4 h (28%)	42.8 h (23%)
$t_{1/2}$	range	20.9 – 165 h	22.4 – 165 h	20.0 – 168 h
AUC(0-tlast)	geo mean (geo CV)	1366 ng·h/ml (45%)	1340 ng·h/ml (34%)	2261 ng·h/ml (58%)
AUC	geo mean (geo CV)	1431 ng·h/ml (48%)	1394 ng·h/ml (39%)	2059 ng·h/ml (35%)
AUC(0-24h)	geo mean (geo CV)	549 ng·h/ml (31%)	573 ng·h/ml (19%)	751 ng·h/ml (47%)
CLss/F	geo mean (geo CV)	91.0 ml/min (31%)	87.3 ml/min (19%)	66.6 ml/min (47%)
Free fraction	mean (SD)	4.2% (0.2%)*	5.4% (1.5%)**	3.7% (0.8%)*

*: N = 5 **: N = 6
C_{max}: maximum concentration of drug in serum after drug administration
t_{max}: time to reach maximum concentration following drug administration
$t_{1/2}$: half-life of the last perceivable disposition phase
AUC(0-tlast): area under the concentration versus time curve from dosing time up to the last quantifiable concentration before the lower limit of quantification was reached for the first time
AUC: area under the concentration versus time curve from dosing time extrapolated to infinity
AUC(0-24h): area under the concentration versus time curve from dosing time to 24 hours
CLss/F: oral clearance at steady-state
geo mean: geometrical mean
geo CV: geometrical coefficient of variation
mean: arithmetic mean
SD: arithmetic standard deviation

Statistical results:

A model, based on pretreatment potassium values and concomitant medication intake, was developed to predict serum potassium concentration changes during treatment with DRSP. Although not observed in the study, a potential for an increased hyperkalemia risk exists in the renally impaired if potassium sparing drugs are concomitantly taken during DRSP treatment. If pre-treatment potassium concentration values are greater than 4.8 mmol/l, the upper limit of the one-sided 99% prediction interval (confidence interval of the individual prediction) of treatment potassium concentrations surpasses the critical limit for hyperkalemia (5.5 mmol/l) in subjects who concomitantly take these medications.

Safety results:

A total of 10 AEs were reported in 7 (25%) of the 28 subjects during the treatment phase of the study. Only 4 of the 10 AEs, reported in 3 subjects, were assessed as possibly related to the study drug. All of the AEs were mild or moderate and all were transient. The test preparation was well tolerated by all of the subjects. No serious nor unexpected AEs were reported. None of the subjects withdrew from the study prematurely due to AEs. No clinically relevant changes in the general safety laboratory parameters were observed.

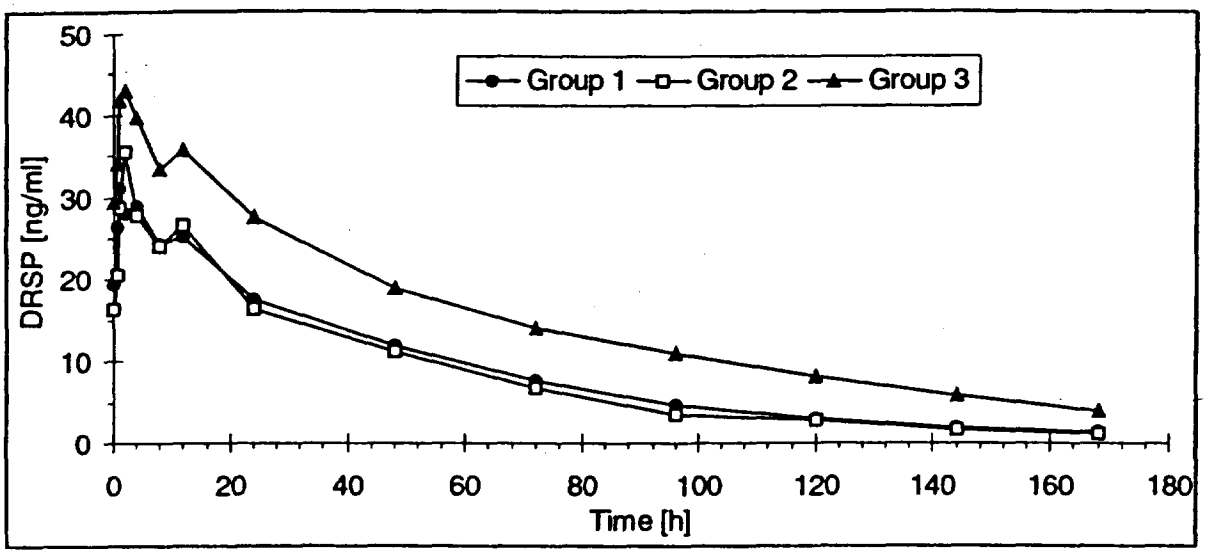
Conclusions:

Overall, the mean potassium serum concentration did not show a clinically significant change during steady-state treatment with DRSP in all renal function groups. A difference in the pharmacodynamic effects of DRSP on the serum potassium concentration in subjects with mild or moderate renal insufficiency compared to subjects with normal renal function was not found. Also, all treatment potassium concentration values measured were 5.5 mmol/l or under for all study participants in all three renal function groups.

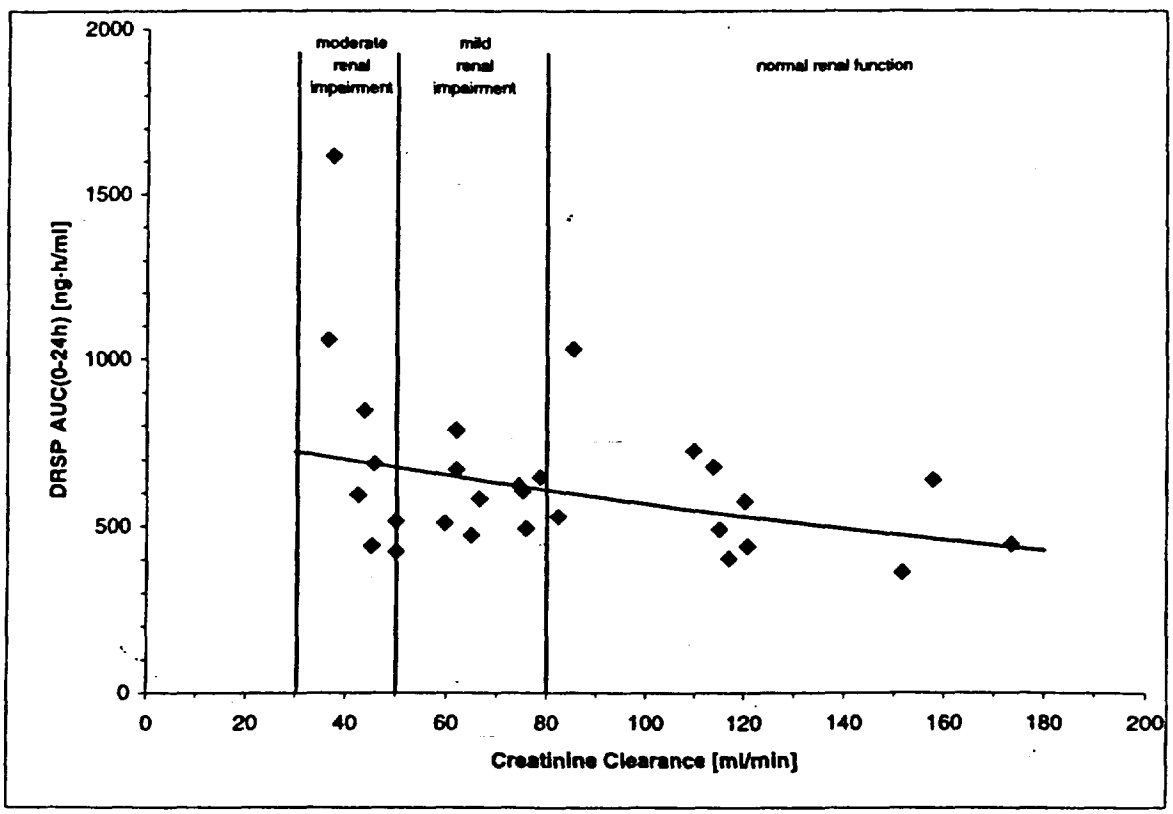
The pharmacokinetic data indicate that the DRSP concentrations in serum increased moderately with decreasing creatinine clearance. This change is not expected to be of clinical relevance due the excellent tolerability of DRSP.

Based on a statistical model, the concomitant intake of potassium sparing drugs (ACE inhibitors and beta receptor inhibitors) could elevate the potassium concentration in the renally impaired during DRSP intake if their pretreatment potassium concentrations are at least in the upper normal range.

TF 15: **Mean DRSP concentration versus time curves after 14 daily administrations of 3 mg DRSP to women with normal renal function (Group 1) and mild (Group 2) and moderate (Group 3) renal impairment**



TF 16: **Plot of DRSP AUC(0-24h) values at steady-state (day 14) versus creatinine clearance in 24-hour urine at baseline**



FEB 24 2000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-098

Generic name, dose and formulation:	Drospirenone 3 mg/ethinyl estradiol 30 µg tablets
Trade name:	YASMIN™ 21/28 TABLETS
Sponsor:	Berlex Laboratories, Inc.
Type of submission:	Original NDA/NME, Category 1S
Date of submission:	05/14/1999, 11/18/99, 01/18/00, 02/10/00, 02/17/00 and 02/18/00
Reviewers:	Monique Wakelkamp-Barnes, M.D., Ph.D. Venkateswar R. Jarugula, Ph.D.

I SYNOPSIS

The NDA 21-098 for Yasmin (drospirenone 3 mg/ethinyl estradiol 30 µg) was submitted by Berlex Laboratories, Inc. on 05/14/1999 for the proposed indication of oral contraception. Each cycle of Yasmin 21 consists of 21 active film-coated tablets, each containing drospirenone (DRSP) 3 mg and ethinyl estradiol (EE) 30 µg. Yasmin 28 contains an additional seven inert film-coated tablets. DRSP is a 17-α spirolactone derivative with progestational, anti-androgenic and anti-mineralocorticoid activity. DRSP is a new chemical entity.

In the Human Pharmacokinetics and Bioavailability section of the NDA, a total of 17 studies were submitted, of which 12 were *in vivo* studies and 5 were *in vitro* studies. The *in vivo* studies addressed mass-balance, absolute and relative bioavailability, single- and multiple-dose pharmacokinetics of DRSP alone and in combination with EE, bioequivalence, influence of food intake, excretion of DRSP into breast milk and pharmacodynamic effects of the DRSP/EE combination. The *in vitro* studies presented data on DRSP metabolism, DRSP cytochrome P_{450} inhibition and the effect of DRSP on EE metabolism. As an amendment to the NDA, an *in vivo* interaction study of DRSP and omeprazole was submitted as well. All studies were conducted by the parent company of Berlex Laboratories, which is Schering AG, Berlin, Germany, at the Institute of Clinical Pharmacology, Schering AG, Müllerstrasse 178, 13342 Berlin, Germany. A question-based approach has been followed for the review of this NDA.

The results submitted in the NDA showed that:

Drospirenone (DRSP) and ethinyl estradiol were rapidly absorbed from the tablet formulation with maximum plasma concentrations occurring between 1 and 3 hours after oral administration. The absolute bioavailability of DRSP (from DRSP alone tablets) was 76 ± 13%. Following single dose administration of Yasmin, the relative bioavailability of DRSP and EE was 107% and 117%, respectively, compared to a suspension.

The pharmacokinetics of DRSP was dose proportional in the range of 1 – 10 mg, following oral administration. Steady-state was reached after 10 days of daily administration with accumulation ratios of 2 to 3 based on AUC comparison. The systemic clearance of DRSP was low (1.5 ml/min/kg) and the apparent volume of distribution at steady-state (V_{ss}) following I.V. administration was about 4 L/kg, indicating tissue distribution. Plasma concentrations of DRSP declined in a biphasic manner with a terminal half-life of about 30 hrs.

In the presence of high-fat food, the rate of absorption of DRSP and EE was slower with C_{max} of both drugs reduced by about 40%. The extent of DRSP absorption remained unchanged, while that of EE was reduced by about 20%. However, since clinical trials were conducted uncontrolled with respect to food in take, no specific dosing instructions regarding food intake were recommended in the labeling.

DRSP is 97% bound to plasma proteins and protein binding was found to be constant at trough levels following multiple-dose administration of a 2-4 mg dose range. DRSP does not bind to sex hormone binding globulin (SHBG) or corticosteroid binding globulin (CBG). Although it has not unequivocally been shown that DRSP does not interfere with SHBG and CBG inducing effects of EE, this is not an issue in the current NDA since neither DRSP nor EE binds to SHBG or CBG.

A mass-balance study has shown that approximately 38.5% of total radioactivity was excreted in urine and 44.3% in feces within 10 days following oral administration of 3.13.mg of ^{14}C-DRSP. This indicates that both renal excretion and biliary secretion are important mechanisms of elimination, because DRSP is highly absorbed. Two major metabolites that could be identified, M11 (the acid form of DRSP formed by opening of the 21,17 carbolactone ring) and M14 (4,5 dihydro-DRSP-3-sulfate) and another highly polar fraction were detected in the plasma. These two metabolites are reported not to be pharmacologically active and are formed independently of the cytochrome P450 sytem. DRSP was extensively metabolized and only trace amounts (1-2%) were excreted unchanged in urine and feces. About 20 metabolites were detected in urine and feces, each of the peaks accounting for less than 5% of the dose. About 29-34% of radioactivity that was excreted in urine, was excreted as glucuronide conjugates and about 9-12% as sulfate conjugates. About 5% of radioactivity that was excreted in feces, was excreted as glucuronides and 12-15% as sulfates.

In vitro studies have shown that DRSP was metabolized only to a minor extent (4-7%) by cytochrome P_{450} enzymes, mainly by CYP 3A4. *In vitro*, DRSP exhibited no or minimum inhibition of CYP2D6 and 1A2, moderate inhibition of 2C9 (IC50=36.5 μM) and 3A4 (IC50=31.2 μM) and more potent inhibition of 2C19 (IC50=3.39 to 10.7 μM) and 1A1 (IC50=14.5 μM). The concentrations needed to inhibit 50% of CYP450 enzyme activity was about 14 (CYP2C19), 152 (CYP2C9) and 130 (CYP3A4) fold higher, respectively, than the steady-state C_{max} of total DRSP (0.24 μM) following administration of Yasmin. *In vitro* results suggest that DRSP at 3 mg doses might have potential to interact, in vivo, with drugs metabolized by CYP 2C19. *In vivo*, DRSP at steady-state did not inhibit the pharmacokinetics of omeprazole, a classic 2C19 substrate, indicating that DRSP is not likely to interact with drugs metabolized by 2C19. DRSP also did not inhibit the formation of the omeprazole sulfone metabolite, a minor metabolic pathway, mediated by 3A4.

Reviewer Comments

1. As of date, the sponsor has not submitted the study investigating DRSP pharmacokinetics and safety in renally impaired patients to the NDA. Since DRSP is a spironolactone analogue and a new molecular entity with potassium sparing effects, the pharmacodynamic findings of this study are important for the safe and efficacious use of Yasmin in patients with renal impairment. Depending on the results of this study, the labeling of this product may recommend appropriate caution (as evaluated by the clinical review team) regarding the use of Yasmin in this group of patients. It should be noted that the clinical division is recommending the NDA to be approvable (as per sponsor's request) pending the submission of the data on the safety of Yasmin in patients with renal impairment.

2. There is no information on the pharmacokinetics of DRSP in patients with hepatic impairment. Since DRSP is extensively metabolized, sponsor was recommended to consider a study in hepatic impairment patients. However, sponsor reported that they were planning to contra-indicate Yasmin in patients with hepatic disease and did so in the labeling.

3. Based on information submitted on 02/10/00 (Report B283), the two major metabolites observed in plasma, the open-ring acid form of DRSP and 4,5-dihydrodrospirenone-3-sulfate, are not pharmacologically active. These two metabolites are formed independently of the CYP enzyme system.

4. Based upon the dissolution data for the clinical trial batches, the *in vitro* dissolution specifications for the proposed dissolution method (using the USP II Paddle method, water as medium, speed of 50 rpm) should be revised to [redacted]. This recommendation has been discussed with and agreed upon by the sponsor.

II RECOMMENDATION

The Human Pharmacokinetics and Bioavailability section of NDA 21-098 is acceptable to support the BA and BE regulation covered by 21 CFR part 320.

APPEARS THIS WAY
ON ORIGINAL

Reviewer	Date	Reviewer	Date
/S/		/S/	2/24/00

Monique Wakelkamp-Barnes, M.D., Ph.D. Venkateswar R. Jarugula, Ph.D.

Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

Final version signed by Ameeta Parekh, Ph.D., teamleader /S/ 2/24/00

cc NDA 20-713:

HFD-870: Shiew-Mei Huang
Ameeta Parekh
Monique Wakelkamp-Barnes
Venkat Jarugula

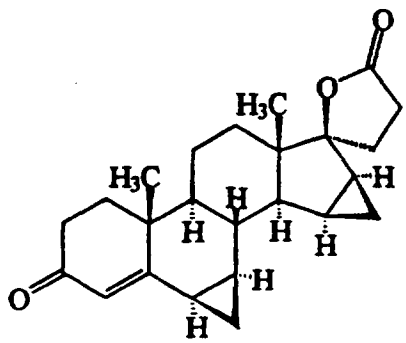
HFD-580: Jeanine Best
Dena Hixon

CDR: Barbara Murphy

APPEARS THIS WAY
ON ORIGINAL

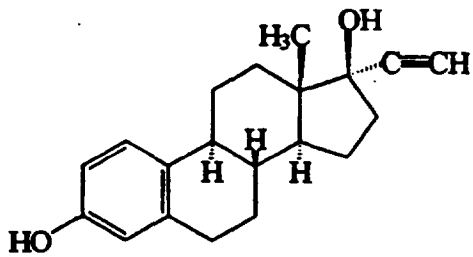
III BACKGROUND

Q.	*What is drospirenone? What are its pharmacological characteristics?*



Drospirenone

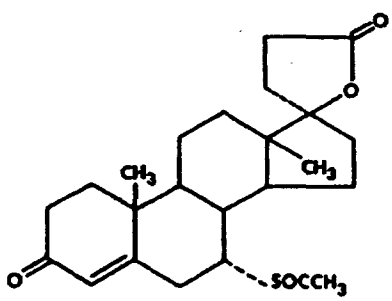
Fig. 1a



Ethinyl estradiol

Fig. 1b

Drospirenone (DRSP) (Fig. 1a) is a steroid compound and a 17-α-spirolactone derivative, in resemblance to the aldosterone antagonist drug spironolactone (Fig. 2). DRSP has mainly progestogenic, anti-mineralocorticoid and anti-androgenic activity and exerts no significant androgenic, estrogenic or glucocorticoid action. Yasmin is a combination preparation of 3 mg DRSP and 30 μg ethinyl estradiol (EE) (Fig. 1b), proposed for the indication of oral contraception.

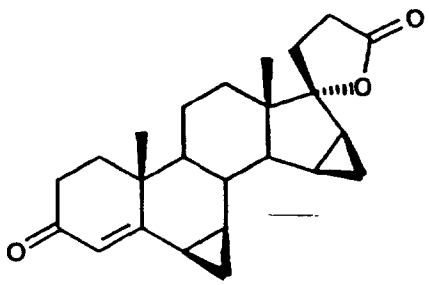


Spironolactone

Fig. 2

In nonclinical pharmacological studies comparing the anti-mineralocorticoid activity of various steroids, it has been reported that with a spironolactone potency defined as 1, the relative potency of DRSP was about 8. The anti-mineralocorticoid activity of DRSP at the level of the renal tubule may cause a decrease in sodium reabsorption and may lead to an increased secretion of aldosterone by the adrenal cortex.

DRSP undergoes rearrangement into its stereo-isomer in 0.1 N hydrochloric acid. The isomer is reported to be not pharmacologically active.



Isomer of DRSP

Fig. 3

The potential isomerization and, subsequently, inactivation of DRSP in an acid environment initially raised concerns with regard to vulnerability of the drug to gastric acid in the stomach. This is the reason why a number of early pharmacokinetic studies incorporated an enteric-coated formulation of DRSP (studies 8235, 6737 and 8256). No significant differences were found in a number of pharmacokinetic parameters between normal and enteric-coated tablets in these studies. Also, chromatographic analysis (study A166) demonstrated that only small amounts of the isomer were present in plasma, corresponding to 1-5% of DRSP.

IV ASSAY METHODOLOGY AND VALIDATION

Q.	***What are the assay methods for the determination of DRSP and EE concentrations? How sensitive and specific are the assays?***

Concentrations and amounts of DRSP in *serum* (studies A166, A951, A733, A470, 9776, 9274, A198, A199 and B277), *plasma* (studies 8235, 8256 and 6737), *breast milk* (study A199) *urine* (studies A166 and 8235) and *feces* (study A166) were analyzed by radioimmunoassay (RIA).

A separate assay validation report for DRSP was not supplied. However, assay validation parameters were supplied for individual studies and generally indicated acceptable accuracy and precision of the method. The lower limit of quantitation was set at in most studies.

According to a specificity study (Report 6632), cross-reacting metabolites were found to contribute to a maximum of about 11%, with lower values for early sampling times. Thus, the

specificity of the antibody appears to be acceptable for the pharmacokinetic analysis of DRSP. The lactone isomer of DRSP showed a cross-reactivity of only 0.24%.

V FORMULATION

Q.	***What are the changes between the clinical trials formulation and the to-be-marketed formulation?***

[redacted]

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

21 pages

Number of Pages Redacted 31

❖❖❖

Draft Labeling
(not releasable

JUN 2 9 1999

MEMORANDUM

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

DATE: July 14, 1999

FROM: Venkateswar R. Jarugula, Ph.D. (HFD-870) /S/ /S/

THROUGH: Ameeta Parekh, Ph.D., Team Leader (HFD-870)

7/25/99

TO: HFD-580

RE: Filing Meeting for NDA 21-098 (Yasmin™ 21/28 tablets)

SUMMARY

NDA 21-098 for Yasmin tablets was submitted by Berlex on 05/14/99. Each cycle of Yasmin 21consists of 21 active film coated tablets each containing drospirinone (DRSP) 3 mg and ethinyl estradiol (EE) 0.030 mg. Yasmin 28 consists of an additional seven inert film coated tablets. The proposed indication is oral contraception. Drospirinone (DRSP) is derivative of 17α-spirolactone and is a new molecular entity.

The Human Pharmacokinetics and Bioavailability section of the NDA includes a total of 17 studies performed using DRSP alone or in combination with EE. Out of these, twelve in vivo studies provide data on bioavailability, metabolism and mass balance, single and multiple dose pharmacokinetics, food effect, the effect of EE on pharmacokinetics of DRSP, distribution of DRSP into breast milk, and pharmacodynamic effects of the combination. Five *in vitro* studies present data on DRSP metabolism, DRSP cytochrome450 inhibition, and the effect of DRSP on EE metabolism. A list of studies is included in the attachment. In addition, sponsor stated that they are planning a study in renally impaired patients. Sponsor also plans to conduct a drug interaction study to test the interaction between DRSP and a CYP2C19 substrate omeprazole.

The formulation of Yasmin tablets was changed twice during the clinical development program. In most of the phase II studies the preliminary formulation SH T 470 F was used. While phase II studies were in progress, the formulation SH T 470 F was modified in the composition of the coating. The resulting formulation SH T470 FA was shown to be bioequivalent to SH T 470 F (Report A951). Formulation SH T 470 FA was used in the pivotal European clinical trial (A 151). This formulation was again modified as given below:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

Since this is considered a narrow therapeutic drug under SUPAC IR guidance, the above changes may be considered under Level 2 equipment changes and Level 3 compositional changes that require a bioequivalence study. However, bioequivalence study can be waived because of the following reasons:

- The to be marketed formulation was used in one pivotal clinical trial (98180) and the earlier formulation was used in another pivotal trail (A151). Although this is considered a narrow therapeutic drug, the safety and efficacy information on the to be marketed formulation is available.
-
-

- The *in vitro* dissolution of the clinical and to be marketed formulation shows rapid and similar dissolution in water at 50 rpm with USP II paddle method. In vivo pharmacokinetic studies of the clinical trials formulation showed rapid absorption with Tmax of about 1 to 2 hours for both DRSP and EE.
- The bioavailability of DRSP and EE from tablet formulation (SH T 470FA:earlier formulation) relative to the suspension was 107% and 117%, respectively and the rate of absorption was similar between tablet and suspension.
- This drug product is considered rapidly dissolving and the drug substances (at the given dose) are soluble in 250ml water and are considered highly permeable based on their partition coefficients (log P_{ow} is 3.08 for DRSP, 4.20 for EE).

Concentrations of DRSP in serum, breast milk and urine and concentrations of EE in serum were measured by radioimmunoassay. The assay validation for DRSP was not included in the submission. For the assay of EE, literature article was included. However, only mean data on quality control samples for both DRSP and EE were provided with each study report.

In vitro dissolution method and dissolution profiles of batches used in clinical pharmacology and clinical studies are included in the submission.

Comments:

1. To support the changes in composition and equipment in the to be marketed formulation, sponsor should provide comparative *in vitro* dissolution profiles of clinical trial formulation (SH T 470FA) and to be marketed formulation (SH T 470FA final) in multiple media (Case C profiles as per SUPAC IR guidance).
2. It is not clear from the application which formulation was used in the supportive trial AJ06. Sponsor should be requested to provide this information.

3. A complete report on analytical method validation for DRSP assay including cross-reactivity information should be submitted to the PK section. The individual data supporting the mean quality control parameters and calibration curves for the assay of DRSP and EE should be submitted to each study report for PK studies.

4. To facilitate review of section 6 of NDA, the sponsor should be requested to provide summary of Human PK and bioavailability, individual study synopses, raw data analyzed in PK studies and labeling in electronic format.

RECOMMENDATION

NDA 21-098 is fileable from pharmacokinetics and biopharmaceutics perspective. The above mentioned comments should be conveyed to the sponsor as appropriate.

Number of Pages Redacted 8

❖❖❖

Confidential,
Commercial Information

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

Abuse potential for this drug product is NA.

/S/

4/18/01

APPEARS THIS WAY
ON ORIGINAL

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

A Microbiology (Efficacy) Review is NA for this application.

/S/

4/18/07

APPEARS THIS WAY
ON ORIGINAL

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

There were no DSI inspections requested this review cycle.

/S/

4/18/01

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: January 24, 2000

TO: J. Best, Regulatory Project Manager
D. Hixon, M.D. Clinical Reviewer
Division of Reproductive and Urologic Drug Products, HFD-580

THROUGH: David A. Lepay, M.D., Ph.D
Division Director, HFD-45
Division of Scientific Investigations

FROM: Roy Blay, Ph.D.,
Senior Regulatory Review Officer
Good Clinical Practices Branch 1, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-098

APPLICANT: Berlex Laboratories

DRUG: Yasmin

THERAPEUTIC CLASSIFICATION: 3(S)

INDICATION: Contraception

REVIEW DIVISION GOAL DATE: February 1, 2000
ACTION GOAL DATE (PDUFA Date): March 17, 2000

I. BACKGROUND:

The goal of inspection included validation of submitted data and compliance of study activities with Federal regulations and good clinical practices. Among the study elements reviewed for compliance were subject record accuracy, appropriate informed consent, appropriate use of inclusion/exclusion criteria, adherence to protocol, randomization procedures, and documentation of serious adverse events. The indication for this NDA submission is contraception.

Site #3
Jeffrey M. Adelglass, M.D.
Research Across America
RHD Professional Plaza 4
5 Medical Parkway, Suite 202
Dallas, TX 75234
Acceptable

a. It appears that the field investigator inspected the study-related records for all 28 subjects that completed the protocol of the 50 subjects enrolled at Dr. Adelglass' site. The data appear acceptable for use in support of drug claims.

b. There were no limitations on the inspection.

c. The inspection of this site was unremarkable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Overall, the violations observed at two sites were minor in scope and would not affect the reliability or integrity of the data submitted in support of this NDA.

Follow-up action: None needed

/S/ 00
Roy Blay, Ph.D., Clinical Reviewer
DSI/GCPBI

CONCURRENCE:

/S/
David Lepay, M.D., Ph.D.
Division Director
Division of Scientific Investigations

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

/S/

580

Food and Drug Administration
Rockville MD 20857

JAN 18 1999

Steven C. Bowman, M.D.
Tampa Bay Medical Research Inc.
3253 Mcmullen Booth Road
Clearwater, FL 34621

Dear Dr.Bowman:

The purpose of this letter is to inform you of our conclusions concerning your conduct of the clinical study (protocol #96049B) of Yasmin Tablets that you conducted for Berlex laboratories.

From October 13 to October 15, 1999, Ms. Karen G. Hirshfield, representing the Food and Drug Administration (FDA), inspected the study identified above. This inspection is part of the FDA's Bioresearch Monitoring Program. This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected.

At the close of the inspection, Ms. Hirshfield presented her inspectional observations (i.e., Form FDA 483) and discussed these observations with you. From our evaluation of: (a) the inspection report; (b) copies of study records obtained during the inspection; and (c) your oral responses during the inspection to the inspectional observations, we conclude that you did not adhere to all pertinent Federal regulations and/or good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects. In particular we note that you failed to promptly report all problems involving study subjects to the IRB and the sponsor and that all reported adverse events could not be documented.

We note your response to the observations and your assurance that corrective actions will be taken to prevent similar problems in your current and future studies.

We appreciate the cooperation shown Ms. Hirshfield during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

David A. Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Suite 103
Rockville, MD 20855

DEPARTMENT OF HEALTH & HUMAN SERVICES

/S/ 580

Food and Drug Administration
Rockville MD 20857

JAN 18 1999

Jeffrey M. Adelglass, M.D.
Research Across America
RHD Professional Plaza 4
5 Medical Parkway, Suite 202
Dallas, TX 75234

Dear Dr. Adelglass:

The purpose of this letter is to inform you of our conclusions concerning your conduct of the clinical study (protocol # 96049B) of Yasmin (drospirenone & ethinyl estradiol) that you conducted for Berlex Laboratories.

Between September 21 and September 24, 1999, Ms. Kelly J. Pegg, representing the Food and Drug Administration (Agency), inspected the study identified above. We reviewed the inspection report prepared by the Agency's inspector and copies of study records obtained during the inspection. Based on our review, we conclude that you conducted your study in compliance with the Federal regulations that apply to clinical studies of investigational new drugs and with an acceptable standard of good clinical practices.

This inspection is part of the Agency's Bioresearch Monitoring Program. This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected.

We appreciate the cooperation shown Ms. Pegg during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

David A. Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Suite 103
Rockville, MD 20855

21098

Food and Drug Administration
Rockville MD 20857

Dan C. Henry, M.D.
Foothill Family Clinic
2295 Foothill Drive
Salt Lake City, UT 84109

NOV 23 1999

Dear Dr. Henry:

The purpose of this letter is to inform you of our conclusions concerning your conduct of the clinical study (Protocol Number 96049) of the investigational drug Yasmin that you conducted for Berlex Laboratories, Inc.

From October 5, 1999 to October 8, 1999, Ms. Margaret M. Annes, representing the Food and Drug Administration (FDA), inspected the study identified above. This inspection is part of the Agency's Bioresearch Monitoring Program. This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected.

At the close of the inspection, Ms. Annes provided you with her inspectional observations (Form FDA 483) and discussed these observations with you. We have reviewed (a) the inspection report, (b) the documents copied during the inspection, and (c) your oral responses to the inspectional observations during the inspection. Based on our review, we find that you adhered to most of the Federal regulations and good clinical practices governing your conduct of clinical studies of investigational new drugs and the protection of human subjects. Essentially, we find that you failed to conduct your study in accordance with the approved protocol in that the 3-month post study visits were not done in your office. Your intention to correct the deficiencies is noted.

We appreciate the cooperation shown Ms. Annes during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

Bette L. Barton, Ph.D., M.D.
Chief
Good Clinical Practices Branch I, (HFD-46)
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Suite 125
Rockville, MD 20855

cc:
HFA-224
HFD-580 Doc. Rm. NDA 21-098
HFD-580 Review Div.Dir. Rarick
HFD-580 MOHixon
HFD-580 PM/CSO Mercier
HFD- 45 Reading File
HFD- 46 Chron File
HFD- 46 CIB File #6022
HFD- 46 Turner
HFR-SW-250 DIB Singleton
HFR-SW-250 BIMO MONITOR Sherer
HFR-Sw-250 FIELD INVESTIGATORAnnes

CFN: #1722878/FEI 1000517431

Field Classification:VAI
Headquarters Classification:
_____1)NAI
X 2)VAI no response required
_____3)VAI-R response requested
_____4)VAI-RR adequate response received prior to issuance of VAI-R letter
_____5)OAI-W warning letter
_____6)OAI NIDPOE letter

If the Field and Headquarters classifications are different, explain why:

Deficiencies noted:
_____ inadequate consent form
_____ inadequate drug accountability
__X_ deviations from protocol
__X_ inadequate and/or inaccurate records
_____ failure to report ADRs
_____ other (specify)

drafted/GDT:11/2/99
reviewed/BLB/(date)
revised/(initials of GCPB1 reviewer)/(date)

Note to Review Division and DSI Recommendation:
The field investigator inspected the records for 27 of the 64 subjects enrolled in protocol #96049 at the Henry site. The data appear acceptable for use in support of drug claims. The major problem found involved the failure to conduct the 3 month post study visit in the Investigator's office.