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APPLICATION NUMBER:

21-676

PHARMACOLOGY REVIEW(S)

Pharmacology/Toxicology Review

Date: 3-15-06

NDA #: 21-676

Date of submission: 6-15-05

Sponsor: Berlex Laboratories, Inc.

Drug Product: YAZ

Indication: Contraception

Subject: P/T prospective about the approval of the NDA

NDA 21-676 originally submitted on 10-17-03 was reviewed on 4-7-04. All pharmacology, ADME, general toxicology, genotoxicity studies, reproductive toxicity studies and carcinogenicity studies reviewed under NDA 21-098 for the approval of Yasmin supported the safety of combination of drospirenone/ethinyl estradiol for the contraception indication. The primary difference between Yasmin and Yasmin 20 (YAZ) is that the reduced amount of ethinyl estradiol in YAZ is complexed with B-cyclodextrin as the EE-B-cyclodextrin clathrate to ensure shelf stability at low concentrations. No new toxicology studies were requested or submitted for NDA 21-676.
Labeling for YAZ is similar to that for approval of NDA 21-098 for Yasmin.

Reviewer: Krishan L. Raheja, D.V.M., Ph.D.

Through P/T Supervisor: Lynnda Reid, Ph.D.

Regulatory action: Based on review and approval of NDA 21-098 for Yasmin, Pharmacology recommends approval of NDA 21-676 for YAZ. The reduction of ethinyl estradiol dose in the YAZ formulation under NDA 21-676 may further improve the safety of the product.

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/s/

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3/15/2006 10:00:53 AM
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PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21-676
Review number: 1
Sequence number/date/type of submission: 000/10-16-03/original submission
Information to sponsor: Yes ( ) No (*)
Sponsor and/or agent: Berlex Laboratories, Inc.
Manufacturer for drug substance: Schering AG Berlin, Germany

Reviewer name: Krishan L. Raheja, D.V.M., Ph.D
Division name: DRUDP
HFD #: 580
Review completion date: 4-18-04

Drug:

Trade name: Yaz
Generic name (list alphabetically): drospirenone 3 mg/ethinyl estradiol 0.02 mg
Code name: ZK 30595 for drospirenone and ZK 4944 for ethinyl estradiol
Chemical name: see review of NDA 21-098
CAS registry number: 67392-87-4 for Drospirenone and 57-63-6 for ethinyl estradiol
Mole file number: -
Molecular formula/molecular weight: $C_{24}H_{30}O_3$/366.5 for drospirenone and $C_{20}H_{24}O_2$/296.4 for ethinyl estradiol
Structure: see attached review of NDA 21-098

Relevant INDs/NDAs/DMFs: IND 51,693; IND 60,738; DMF # — for DRSP and DMF # — for EE; NDA 21-098 for Yasmin (3.0 mg DRSP and 0.03 mg EE tablets) and NDA 21-355 for Angeliq (1.0 or 3.0 mg DRSP and 1.0 mg estradiol tablets)

Drug class: steroid hormones. DRSP a derivative of 17a-spirolactone and EE belongs to the class of estrogens

Indication: contraception

Clinical formulation: Drug product is comprised of drospirenone (DRSP) 3 mg and ethinyl estradiol (EE) 0.020 mg (as the B-cyclodextrin clathrate).

The following is a list of components used in the manufacture of the drug product:

Active tablets (formulation SHT00186D)		Inert tablets (formulation SH T00470PD)		Function
Component	mg/tablet	Component	mg/tablet	
Drospirenone,	3.000	-	-	Active ingredient
Ethinyl estradiol (as EE-B-CDC,	— (=0.020 EE)	-	-	Active ingredient
Lactose monohydrate, NF	—	Lactose monohydrate, N		
Starch NF (maize starch)	—	Starch, NF (maize starch)		
Magnesium stearate, NF	—	Magnesium stearate, NF	—	
-	-	Povidone USP (25,000)	—	
Hypromellose, USP	—	Hypomellose, USP	—	
Talc, USP	—	Talc, USP	—	
Titanium Dioxide, USP	—	Titanium dioxide, USP	—	
Ferric oxide, re, NF	—	-		
Total	83.0000		82.0000	

EE/B-CDC=EE-B-cyclodextrin clathrate

Route of administration: oral

Proposed use: contraception

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

Executive Summary

I. Recommendations

A. Recommendation on Approvability: Pharmacology will recommend approval of NDA 21-676 based on previous finding of safety and prior approval of Yasmin (Berlex NDA 21-098), a contraceptive, which contains 3 mg DRSP and 0.03 mg EE. The present proposed formulation, Yaz has the same indication i.e, contraception and is administered by the same route of administration but contains only 0.02 mg of EE compared to 0.03 mg in Yasmin.

B. Recommendation for Nonclinical Studies: Preclinical safety is supported by reference to studies that were submitted to support approval of NDA 21-098 for Yasmin. In addition this NDA (NDA 21-676) contains eight pharmacology reports (AV65, B273, B283, A04834, AQ61, AF46 and AF45), six ADME reports (B206), AV64, B589, B824, A618 and B320) and eight toxicology reports (AG69, B178, B839, AS78, A09791, A09897, A11703 and A11637), which were not previously submitted in NDA 21-098. These are reviewed and summarized under the appropriate headings in this review.

C. Recommendations on Labeling: Labeling will be similar to that for approved NDA 21-098 for Yasmin.

II. Summary of Nonclinical Findings: see P/T review of attached NDA 21-098

A. Brief Overview of Nonclinical Findings: All pharmacology, ADME, general toxicology, genotoxicity studies, reproductive toxicity studies and carcinogenicity studies reviewed under NDA 21-098 for the approval of Yasmin supported the safety of combination of drospirenone/ethinyl estradiol for the contraception indication. The reduction of ethinyl estradiol dose in the formulation under present NDA 21-676 may further improve the safety.

This submission also contains a summary of nonclinical safety information available in the literature for the inactive excipient, B-cyclodextrin.

The primary difference between Yasmin and Yasmin 20 (YAZ) is that the reduced amount of ethinyl estradiol in Yasmin 20 is complexed with B-cyclodextrin — as the EE-B-cyclodextrin clathrate to ensure shelf stability at low concentrations. The nonclinical safety of B-cyclodextrin is based on review of literature provided by the sponsor and a review of the 27 volume DMF — done by Karen Davis-Bruno, Ph.D.; Supervisory Pharmacologist HFD-510 on 2-11-2003 as consult for ANDA —

B. Pharmacologic Activity: Contraception by inhibition of ovulation and qualitative changes in the cervical mucus.

C. Nonclinical Safety Issues Relevant to Clinical Use: none

APPEARS THIS WAY
ON ORIGINAL

TABLE OF CONTENTS - PHARMACOLOGY/TOXICOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

See attached P/T review of original NDA 21-098 dated 5-14-1999

II. SAFETY PHARMACOLOGY:

See attached P/T reviews of original NDA 21-098 submission dated 5-14-1999

III. PHARMACOKINETICS/TOXICOKINETICS:

See attached P/T review of original NDA submission dated 5-14-1999

The following are concise summaries of the studies, which were not submitted under NDA 21-098 for Yasmin and are included in the present submission for NDA 21-676:

Under study No A618 the sponsor conducted experiments to investigate the stability of DRSP in blood samples from different species and to find suitable inhibitors which could be used to prevent DRSP degradation in ex vivo blood samples.
It was observed that following incubation of 3H-DRSP spiked samples at room temperature, the recovery of DRSP from the plasma of rats, mice and rabbits decreased considerably with increasing incubation time, while the recovery from simian and human plasma samples remained almost unchanged. The ex vivo formation of ZK 15414 was considered to be catalyzed by an estrase.
Sponsor concluded that for reliable determination of DRSP plasma concentration for PK or TK purposes, the esterase reaction can be inhibited by the addition of 4-(2-aminoethyl)-benzenesulfonylfluoride hydrochloride (PEFABLOC SC) to blood from mice and ethyleneglycol-bis (B-aminoethylether)-N-N-tetraacetic acid (EGTA) to samples from rabbits.

Under study No AV64, the tissue distribution and feto-placental transfer of radioactivity after a single intragastric administration of 10 mg/kg ^{14}C-DRSP to rats on day 18 of gestation or to non-pregnant pigmented female was determined.
Results showed that concentration of radioactivity in tissues and organs reached maximum within 1.5h after a single IG administration to rats on 18th day of gestation.
The highest levels were found in the liver, stomach, intestine, adrenal and fat after the administration in pregnant or pigmented rats. The concentration of radioactivity decreased in parallel to radioactivity in plasma but elimination was slower in eyes.
Radioactivity in fetus corresponded to 0.04% of the dose.

PK of DRSP in female rabbits following single IV injection of 1 mg DRSP/kg and single IG administration of 1, 10 and 100 mg DRSP/kg (study No. B206) demonstrated that following IG administration DRSP was rapidly absorbed (Tmax 0.25 to 4.7h) with absolute bioavailabilty of 19-28%. Based on T1/2 of 3.2 - 5.5h it was suggested that drug accumulation is not expected on repeated daily administration. The systemic exposure at the highest dose was about 27 times higher than in women receiving tablets containing 3 g DRSP + 30 ug EE daily.

The LC-MS/MS method enabled the quantitation of DRSP over a concentration range from 100 pg/ml to 30 ng/ml for rabbit and for 100 pg/ml to 20 ng/ml for human plasma (study No.B320).

Under study No B589 it was reported that about 95% of DRSP was bound to proteins in serum of female mice and it was independent of drug concentration up to 5 ug/ml.

It was reported that compared to human plasma, the metabolite pattern of DRSP in mouse serum was quite similar, showing metabolites M9, M11, M14 and M16 as well as highly polar metabolites and DRSP to be present in samples of both species. While the maximum concentrations of PPM, M9, M11, M14 and M16 were estimated to be 8.62, 1.49, 11.54, 7.86 and 1.60 ng-equivalents/ml, respectively, in human plasma after single oral administration of 3.13 mg DRSP/woman, the corresponding concentrations in mouse serum were 86.8, 49.9, 61.6, 182 and 163 ng-equivalents/ml after a single IG administration of 10 mg/kg.

IV. GENERAL TOXICOLOGY:

See attached P/T reviews of NDA 21-098 dated 5-14-1999

V. GENETIC TOXICOLOGY:

See attached P/T original review of NDA 21-098 dated 5-14-1999

Summary results of the few studies which, were not submitted under NDA 21-098 for Yasmin are given below:

In study No. B839 the DNA repair synthesis in hepatocyte primary cultures from rats and humans of both genders exposed to DRSP was determined.

In 4 independent experiments using male and female rats DSRP induced reproducible increases in the net nuclear grains and of the percentage of repairing cells indicative of DNA-repair induction. In contrast, there was no evidence of DNA-repair induction in primary hepatocytes from male and female human donors. DRSP was therefore considered genotoxic in cultured rat hepatocytes of both genders but not in human liver cells under the same experimental conditions.

Using human peripheral blood lymphocytes, the clastogenic potential of DSRP was evaluated in study No. B178. This study was conducted to confirm a previous study (Schering report 8495) in which DSRP did not show any clastogenic potential.
In this study no increase in the frequency of chromosomal aberrations was observed in the assay without metabolic activation at both 20 and 40 hours after a 4-hour treatment and in a assay with S9 mix at the first harvest time. However, in assay with S9 mix at the delayed harvesting time, there was a slight but statistically significant increase in the number of aberrant cells (4.5%) in comparison to solvent control (0%). Since this occurred only in precipitation range and aberration frequency close to the spontaneous rate, this increase was considered of no biological significance.

Under study No. AS78 it was reported that DSRP did not form quantifiable DNA-adducts in rat hepatocytes after incubation with 3H-labeled DSRP.

Study No. A09791 was entitled "Evaluation of a drospirenone (ZK 30595) batch, containing — —as impurity, in a bacterial reverse mutation tests (Ames-test) using Salmonella typhimurium and Escherichia coli." This study was conducted in the absence and presence of an

extrinsic metabolizing system (S9 mix) using ZK 30595 doses ranging from 0.025 to 5.0 mg per plate.
Results: None of 6 tester strains showed increased reversion to prototrophy in both plate incorporation and pre-incubation modification assays, either in the absence or presence of S9 mix. Precipitates in the agar were reported starting from 2.5 mg/plate onwards. It was reported that generally, growth inhibition of the background lawn was not observed. Negative and positive controls produced the expected number of colonies. ZK 30595 was considered not mutagenic in this assay.

Under study No. A09897 sponsor spiked drospirenone (ZK 30595) with the impurity —

at a level of — and tested for chromosomal aberrations in human lymphocytes in vitro with and without extrinsic metabolizing system (S9 mix.).
Results of this study expressed as chromosomal aberrations (% aberrant cells excluding gaps) in cultured human lymphocytes are shown in table below:

Test substance	Concentration (ug/ml)	S9 (4 hours	Cells scored	% aberrant cells (excl.gaps) A	B
DMSO	1% (v/v)	No	200	0.5	1.0
Test item[1]	10 – 60	No	200	0.5 – 1.5	5.0*
Triaziquone	0.017	No	100	12.0*	--
DMSO	1% (v/v)	Yes	200	0.5	0.5
Test item[1]	125 – 225	Yes	200	0.5 – 4.5*	1.0
Cyclophosphamide	2.5	yes	100	13.0*	-

- $p < 0.05$, compared to the concurrent solvent control
- A: first harvesting time
- B: second harvesting time
- [1] Drospirenone batch (ZK 30595) containing — as impurity

Results thus suggested an equivocal clastogenic potential of the DRSP (ZK 30595) containing — as impurity when tested in human peripheral blood lymphocytes in vitro with and without extrinsic metabolizing system. It was stated that in the assay without S9 mix the DRSP batch was tested up to concentration level, which were clearly cytotoxic as indicated by an obvious reduction of the mitotic index. In the assay with S9 mix the test item was also tested up to clearly cytotoxic concentrations at which, additionally, visible precipitates occurred. Sponsor described the increase in aberrant cells of questionable biological relevance.

To confirm the results of the above study, sponsor repeated the study with DRSP batch that contained the impurity — The results are shown in table below:

Chromosomal aberrations (% aberrant cells excluding gaps) in cultured human lymphocytes

Test substance	Concentration (ug/ml)	S9 (4 hours)	Cells scored	% aberrant cells (excl. gaps)
DMSO	1% (v/v)	No	200	1.0
Test item[1]	100 - 230	No	200	1.0 – 8.5*
Truaziquone	0.017	No	100	20*
DMSO	1% (v/v)	No	200	0.5
Test item[1]	160 – 200	No	200	1.0 – 4.5*
Triaziquone	0.017	No	100	16*
DMSO	1% (v/v)	Yes	200	0.5
Test item[1]	100 - 230	Yes	200	0 – 4.0*
Cyclophosphamide	2.5	Yes	100	13*

- $p<0.05$, compared to concurrent solvent control
- [1] drospirenone batch (ZK 30595) containing — as impurity.

The data thus indicated a clastogenic potential of the DRSP batch containing ZK 244395 (an impurity) in vitro with and without an extrinsic metabolizing system. This happened at concentration levels which were cytotoxic (without S9) and resulted in visible precipitates of test item (+/- S9 mix). Based on equivocal clastogenic potential in the first study (report A09897) and positive in the repeat study, although at high and precipitating concentrations, sponsor concluded that test item should be considered as weakly mutagenic. Sponsor however, suggested that as the clastogenic response is very likely associated with the precipitation of test item, it can be assumed that it might be restricted to the in vitro situation and, therefore, only of limited biological relevance. To check the later assumption, sponsor tested the products under in vivo conditions e.g. in the mouse micronucleus test (No. A11637)

In the mouse micronucleus assay, a batch of drospirenone was spiked with in the impurity ' — a level of — Structural chromosomal aberration and aneuploidy were measured by an increase in micronucleated erythrocytes in bone marrow of mice.

Mice were gavaged at dosage of 250, 500 0r 1000 mg/kg body weight. Control animals were given the vehicle at 40 ml/kg in the same manner. CP (30 mg/kg) was gavaged as positive control. 10 females in control, positive control as well as treated groups were killed 24 hours and remaining 10 female of control and high dose group after 48 hours.

A dose of 1000 mg/kg produced slight apathy. After 48 hours there was a significant decrease in the ratio of PCE/NCE in the high dose group, indicating that the test item reached the bone marrow and exerted a cytotoxic effect on the target cells.

Test article treated females in all groups showed neither a biological relevant nor statistically significant increase in micronucleated PCE and NCE as compared to negative control at either 24 or 48 hour sampling time after a single treatment. Positive control gave expected significant increase in micronucleated PCE cell count as compared to negative control after 24 hours.

The test was negative at a high dose of — mg/kg, which corresponds to approx. 500000- fold the expected maximum human intake with regards to the concomitantly tested impurity — assuming a specification limit of — (calculations '

VI. CARCINOGENICITY:

See attached P/T review of NDA 21-098 dated 5-14-1999

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

See attached P/T review of NDA 21-098 dated 5-14-1999

VIII. SPECIAL TOXICOLOGY STUDIES:

None submitted

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Conclusions: Based on previous findings of safety and prior approval of Yasmin (Berlex NDA 21-098) a contraceptive, which contained a higher amount of EE i.e. 0.03 mg compared to 0.02 mg present in the proposed YAZ formulation, Pharmacology considers YAZ may have a better safety profile.

General Toxicology Issues: None

Recommendations: Pharmacology recommends approval of NDA 21-676 for contraception.

Labeling with basis for findings:

X. APPENDIX/ATTACHMENTS:

Addendum to review: P/T review of NDA 21-098 is attached

Other relevant materials (Studies not reviewed, appended consults, etc.): none

Any compliance issues: none

NDA number: NDA 21-098

Note: this review has been previously disclosed and is available in the posted approval package for Yasmin (NDA 21-098)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Krishan L. Raheja
6/23/04 05:44:01 PM
PHARMACOLOGIST

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