and the known biochemical pathways of steroids (see reference provided in Attachment 3: *Biochemical Pathways (1999), G Michal (ed), Spektrum Akademischer Verlag, Heidelberg, Berlin, p 93-98*[3]). The formation of the acid derivative (ZK 151414) of DRSP is most probably catalyzed by a nonspecific esterase by cleavage of the ester linkage in the 17,21 carbolactone ring. The 4,5-dihydro-DRSP-3-sulphate (ZK 202313) is most probably formed via the two intermediate products designated 2 and 3 in Figure 1. The intermediate 2 is generated by reduction of the 4,5 double bond, a reaction which is known to be catalyzed by the enzyme 5α-reductase (see again *Biochemical Pathways* reference, Attachment 3). This metabolite is further reduced at position C3 via a reaction known to be catalyzed by the 3-OH-steroid dehydrogenase resulting in the 3-hydroxylated metabolite. The latter compound is a substrate for the 3-OH-steroid-sulfotransferase, which catalyzes the conjugation reaction leading to the observed metabolite ZK 202313.

Although the complete biotransformation pathways of DRSP are not known at present, the involvement of the cytochrome P450 (CYP) enzymes can be assessed based on in vitro experiments with liver microsomes (Report AY74, NDA Vol. 51, page 6 04521) and with genetically engineered cell lines expressing different single CYP isoenzymes (see again Report B186, Attachment 1). As shown in Report AY74, DRSP is considered to be only a minor substrate for the CYP enzymes. The few metabolites detected in vitro were mostly formed by CYP3A4. On the other hand, DRSP was not metabolized by CYP1A2, 2A6, 2C9, 2C19, 2D6 and 2E1 (see again Report B186).

QUESTION 2

On February 15th, Ms. Best asked the undersigned if all of the pharmacokinetic assays of DRSP for the studies included in the NDA were done with stereo specific assays. She said if they were not, the reviewer would like to know which ones were done with stereo specific assays and which were not. She explained that because many of the studies were done back in the 1980s, the processes may have been different. Our response is provided below.

Stereo Specificity of the DRSP Radioimmunoassay

The determination of DRSP concentrations in biological matrices was generally performed using the same radioimmunological method and a certain antiserum preparation (except for the study reported in B206[4], where a LC-MS/MS method was used). This antiserum was tested with regard to cross-reactivity against DRSP's 17β stereo-isomer ZK 35 096 (see Figure 2, Attachment 4) according to GEJ Abraham (1969), Clin Endocrinol Metab 28: 866. As shown in Figure 3 (see Attachment 4), ZK 35 096 shows a negligible cross reactivity of only 0.2 %, thus indicating the ability of the antiserum to distinguish between the stereo isomers at position 17.

In all studies, DRSP was administered as a pure compound, thus no other stereoisomers would be expected in biological samples except for those formed due to metabolic reactions. The

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[3] This reference is currently only available in German. However, the most important information being referenced is contained in the schematics which appear in English. The reference is being translated and will be available upon request.

[4] This report was submitted to the NDA on February 15, 2000 in response to Pharmacology/Toxicology review questions. It was not available at the time of the initial NDA submission.

specificity of the DRSP radioimmunoassay was determined in several species in the presence of metabolites by [redacted]. The results of these investigations were reported (Reports **6632** [human, NDA Vol. 35, page 5 12558], **8590** [monkeys, NDA Vol. 35, page 5 12545], **8889** [rats, NDA Vol. 35, page 5 12533], **AO72** [rats, NDA Vol. 35, page 5 12569], **AV03** [mice, NDA Vol. 35, page 5 12502]) and showed a cross reactivity of about 12 % at most.

Thus, all DRSP determinations in clinical and nonclinical biological samples were done with the same assay which is stereo-specific with regard to position 17 of the DRSP molecule.

QUESTION 3

On February 15th, Ms. Best asked the undersigned if the subjects in study Report 8235[5] fasted prior to treatment. She requested a more detailed protocol for the study, especially with regard to food intake and dosing instructions.

The study described in Report 8235 was conducted by Schering AG. Schering AG has confirmed that, according to the protocol, the subjects fasted for ten hours prior to arriving at the study site at 7:30 a.m. Drug was administered at 8:00 a.m. and a standard breakfast was served one hour later. A copy of the protocol for the study, Protocol 87163, was available only in German at the time of this request but has been translated and is provided in Attachment 5 for your review.

We trust that the information provided in this submission addresses all of your concerns. Should you require any additional information or have any questions regarding this submission, please feel free to call me at (973) 276-2305. My fax number is (973) 276-2016.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpoc044

Desk copy (cover letter): Ms. Jeanine Best

APPEARS THIS WAY
ON ORIGINAL

[5] "Absolute and Relative Bioavailability of ZK 30 595 (Drospirenone) After Oral Administration of SH T 470 C and SH T 470 D, Respectively, to 8 Young Women"

ORIGINAL

BERLEX

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February 15, 2000

ORIG AMENDMENT
BP

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Office of Drug Evaluation II
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5600 Fishers Lane
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Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: Response to Pharmacology/Toxicology Review Questions

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 mg Tablets], an oral contraceptive (OC) product.

Reference is also made to a voice mail communication from Ms. Jeanine Best of the Division to the undersigned on February 9th, 2000 in which she communicated review questions from the Pharmacology/Toxicology Team Leader. This submission provides responses to those questions. The Pharmacology/Toxicology Team Leader's questions are provided first in bold, followed by our responses.

1. **What is the AUC of drospirenone (DRSP) in women taking the contraceptive dose on Day 21 after several cycles? Is the average of 4 studies 917 ng x h/mL? If so, why is the AUC for humans reported to be 1600 - 1800 in the Pharm/Tox section?**

The average AUC (0-24 hours) on Day 21 in women taking the contraceptive dose after several cycles is 917 ng x h/mL. This value was obtained by considering all available pharmacokinetic data obtained after repeated daily administration of the anticipated oral contraceptive dose (3 mg drospirenone + 0.03 mg ethinyl estradiol) over at least three treatment cycles and therefore is the average of the results of 4 mean AUC (0-24h) values from 2 studies reported in Report AW45. Please refer to Report AW45 *(NDA 21-098, Vol. 10, Page 5 01868)*, for a more

detailed explanation and for further justification for using this value as the basis of comparison of animal and human exposures under steady state conditions.

The AUC for humans reported in the toxicology reports of the Pharmacology/Toxicology section (1600 to 1800 ng x h/mL) represents the total AUC, not the AUC (0-24 hours). Both values were used in the past for calculation of relative exposures until the data base became more complete and the exposures were recalculated as summarized in Report AW45 *(NDA 21-098, Vol. 10, Page 5 01868)*. An AUC of 1600 ng x h/mL corresponds to the mean AUC obtained at steady-state at the end of cycles 1 and 3 after daily oral administration of 3 mg DRSP + 30 µg EE to 26-28 young women (Report A470, *NDA 21-098, Volume 44, Page 6 01749*). The AUC value of about 1800 ng x h/mL for the DRSP/EE 3/30 dose is obtained by interpolation from the values reported for the 2/30 and the 4/30 doses in the clinical study Report 9274 (*NDA 21-098, Volume 45, Page 6 02311*).

2. **For Report 9918 (Segment II study in rats, dose levels of 5 to 45 mg/kg), Report 9998 (Segment II study in rabbits, dose levels of 10 to 100 mg/kg) and Report A740 (Segment II study in monkeys, dose levels of 1 to 10 mg/kg):**

   What is the best estimate of AUC of DRSP and best estimate of the multiple of the exposure in animals to the exposure in humans?

Estimated systemic and relative exposures			
Study Report No.	Dose levels (mg/kg/day)		
Report 9918	**5**	**15**	**45**
Systemic exposure	5362	15965	47894
Relative exposure	5.8	17.4	52.2
Report 9998	**1**	**10**	**100**
Systemic exposure	1670	5010	24423
Relative exposure	1.8	5.5	27
Report A740	**1**	**3**	**10**
Systemic exposure	2535	7606	28517
Relative exposure	2.8	8.3	31.1

Drug level measurements made in the studies reported in Reports 9918, 9998 and A740 were restricted to very few time points. This limited sampling protocol was intended to estimate Cmax, and to serve as a compliance control, while at the same time, minimizing the risk of spontaneous abortion due to multiple blood withdrawals. The limited drug concentration data obtained from these studies were used as compliance control but were not considered to be sufficient for a reliable estimation of the relative systemic exposures achieved. Because the Segment II studies reported in Reports 9918 and 9998 were conducted before it was learned that DRSP was not stable in rat and rabbit blood ex vivo, the exposure estimates reported in these two studies are biased (i.e., too low) and real exposures are assumed to be higher. However, a rough estimation of systemic exposures achieved in all three Segment II studies has been made, and the estimated exposures have been compared with the average AUC (0-24 hours) on Day 21 in women taking the contraceptive dose after several cycles (917 ng x h/mL).

Report 9918

Doses of 5, 15 and 45 mg DRSP/kg per day were administered intragastrically to pregnant rats from Day 6 to Day 15 of gestation. Drospirenone Cmax values measured on the first and the last day of treatment were 431 and 554 ng/mL after 5 mg/kg/day, 1690 and 2270 ng/mL after 15 mg/kg/day, and 1650 and 2800 ng/mL after 45 mg/kg/day of DRSP. As stated above, these values were most probably underdetermined due to the ex vivo degradation of DRSP that occurred during handling of samples.

Compared to the DRSP concentrations determined in another multiple dose study in rats where the ex vivo degradation was inhibited (Report AG75) (*NDA 21-098, Vol. 26, Page 5 08846*), a DRSP Cmax of about 805 ng/mL would have been expected for the dose of 5 mg/kg/day (extrapolated from a dose of 3 mg/kg/day administered in AG75). Considering the ex vivo degradation, this value is in good agreement with those actually determined. Taking the reliable DRSP data reported in Report AG75 as a basis to estimate the systemic and relative exposures probably achieved in Report 9918, the administration of 5, 15, and 45 mg DRSP/kg/day would have led to estimated systemic exposures of 5362, 15965 and 47894 ng x h/mL and estimated relative exposures of 5.8, 17.4, and 52.2 times the human exposure (for calculation also see Report AW45, Table 5) *(NDA 21-098, Vol. 10, Page 5 01868)*. However, this is only a rough estimate based on linear extrapolation, which bears some uncertainty especially in the highest dose group, since pharmacokinetics of DRSP in rats are not dose linear (Report AF68) *(NDA 21-098, Vol. 36, Page 5 12734)*.

Report 9998

In this rabbit study, doses of 10, 30 and 100 mg DRSP/kg/day were administered intragastrically to pregnant animals from Day 6 to Day 18 of gestation. DRSP AUC (0-24h) values were calculated based on the DRSP concentrations determined without inhibition of the ex vivo degradation. Meanwhile, a pharmacokinetic study was performed in rabbits (see attached Report B206[1]) after intragastric administration of 1, 10 and 100 mg DRSP/kg, where DRSP levels were measured in the presence of an appropriate inhibitor. The systemic exposures probably achieved in Study Report 9998 were estimated to be 1670, 5010 and 24423 ng x h/mL. Based on the data obtained in that study and the human exposure reported in Report AW45 *(NDA 21-098, Vol. 10, Page 5 01868)*, the relative exposures achieved in Study Report 9998 were estimated to be 1.8, 5.5 and 27 times the human exposure after intragastric administration of 10, 30 and 100 mg DRSP/kg/day to rabbits (please see again attached Report B206, page 21).

Report A740

DRSP doses of 1, 3, and 10 mg/kg/day were administered intragastrically to pregnant cynomolgus monkeys in combination with ethinyl estradiol at a ratio of 100:1 from Day 20 to Day 90 of gestation. The DRSP concentrations were determined 1 and 2 hours after drug administration on Days 20, 34, 48, 62, 76 and 90 post coitum and were summarized in Report A460 *(NDA 21-098, Vol. 30, Page 5 10607)*. As demonstrated in attached Report A618[2], the determination of DRSP in monkey samples is not biased by ex vivo degradation. The DRSP

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[1] This study was conducted by our parent company, Schering AG, in Berlin, Germany, was received after submission of our NDA, and was therefore not included.

[2] This study was conducted by our parent company, Schering AG, in Berlin, Germany, was received after submission of our NDA, and was therefore not included.

concentrations measured at these time points were in good agreement with those measured in a 1-year systemic toxicity study with DRSP in female cynomolgus monkeys at comparable dose levels (Report A456) *(NDA 21-098, Vol. 15, Page 5 04118)*. Considering this similarity, the relative exposures can be estimated in analogy to those summarized in Report AW45 *(NDA 21-098, Vol. 10, Page 5 01868)* for data from Report A456. The estimated systemic exposures for pregnant cynomolgus monkeys given 1, 3 or 10 mg/kg/day (in combination with ethinyl estradiol) were 2535, 7606 and 28517 ng x h/mL, and the estimated relative exposures achieved in Study Report A740 were calculated to approximately 2.8, 8.3, and 31.1 times the human exposure.

Should you require any additional information or have any questions regarding this submission, please feel free to call me at (973) 276-2305. My fax number is (973) 276-2016.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpoc042

Desk copy (cover letter): Ms. Jeanine Best

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

CSO ACTION
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

ORIG AMENDMENT

BB

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February 10, 2000

ORIGINAL

Susan Allen, M.D, MPH, Acting Director
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Office of Drug Evaluation II
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: Response to Biopharmaceutical Request Regarding Metabolites

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 mg Tablets], an oral contraceptive (OC) product.

Reference is also made to a telephone conversation between Ms. Jeanine Best of the Division and the undersigned on February 9, 2000. Ms. Best informed the undersigned that the Biopharmaceutical Reviewer was reviewing the Metabolism section of the Package Insert [(PI), submitted January 14th] and referred to the following sentence, "The two main metabolites of DRSP found in human plasma were identified to be the acid form of DRSP generated by opening of the lactone ring and the 4,5-dihydrodrospirenone-3-sulfate". She said it is unknown if the metabolites are pharmacologically active.

In response to the Biopharmaceutical Reviewer's question, the pharmacological activity of the main DRSP metabolites have been assessed in a nonclinical model. The results are provided in attached **Report B283**, entitled, "Steroid Hormone Receptor Binding Profile Of The Drospirenone Metabolites ZK 151414 And ZK 225135 (ZK 202313) And Detection Of Steroid Receptor Binding Components In Urine Of Drospirenone Treated Or Untreated Postmenopausal Women".

In summary, the report concludes that the major human plasma metabolites of DRSP, ZK 225135 (ZK 202313) and ZK 151414, do not or only marginally bind to the steroid hormone receptors (estrogen, progestogen, glucocorticoid, androgen and mineralocorticoid receptors). The compounds are, therefore, not expected to exhibit direct steroid hormone receptor related pharmacological effects in vivo.

This study was conducted by our parent company, Schering AG, in Berlin, Germany, was received after submission of our NDA and was therefore not included. An archival and review copy of the report are provided.

Should you require any additional information or have any questions regarding this submission, please feel free to call me at (973) 276-2305. My fax number is (973) 276-2016.

Sincerely,

BERLEX LABORATORIES

Nancy R. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpoc036

Desk copy (cover letter): Ms. Jeanine Best

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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BIB

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February 7, 2000

Susan Allen, M.D, MPH, Acting Director
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Office of Drug Evaluation II
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5600 Fishers Lane
Rockville, Maryland 20857-1706

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: SAS Printout for Report B277 (Drug Interaction Study)

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 mg Tablets], an oral contraceptive (OC) product.

Reference is also made to our submission of January 18, 2000 of the final study report for our drug interaction study, Report B277, entitled, "Open-Label, Crossover Study To Assess The Potential Of Drospirenone (DRSP) To Inhibit CYP2C19 By Evaluating The Metabolic Interaction Between DRSP And Omeprazole As Model Substrate In Healthy Postmenopausal Volunteers Genotyped For Polymorphism Of CYP2C19" (Protocol ME98231). On February 3rd, Ms. Jeanine Best of the Division informed the undersigned that the Biopharmaceutical Reviewer was reviewing the report and would like a SAS printout similar to that provided in another report in the NDA, Report A951. The Reviewer referenced Appendix 9 from Report A951, "Documentation of Statistical Methods".

Per your request, attached please find for Report B277 (Study 98231), a SAS printout that documents the statistical methods used in the study.

REVIEWS COMPLETED	
ACTION:	
☐ LETTER ☐ N.A.I. ☐ MEMO	
INITIALS	DATE

Should you require any additional information or have any questions regarding this submission, please feel free to call me at (973) 276-2305. My fax number is (973) 276-2016.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpoc032

Desk copy (cover letter): Ms. Jeanine Best

APPEARS THIS WAY
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February 4, 2000

ORIG AMENDMENT

BP

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Rockville, Maryland 20857-1706

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: Animal Pharmacology/Toxicology Section for Package Insert

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 mg Tablets], an oral contraceptive (OC) product.

Reference is also made to our submission of December 3, 1999 of our DRAFT Package Insert (PI). Preliminary Chemistry, Biopharmaceutical and Clinical comments on this PI were received from the Division on December 9th. Additional reference is made to our revised PI which was submitted on January 14, 2000, incorporating all comments received up to that time. On January 18th, Ms. Jeanine Best of the Division told the undersigned that the PI had been received. She informed the undersigned that because YASMIN is a new molecular entity, not a known progestin, and not just a combined OC, a full Pharmacology/Toxicology section would be required in the PI. On January 20th, the undersigned left a voice mail message for Ms. Best asking whether the request for the Pharmacology/Toxicology section had come from the Clinical or Nonclinical Pharmacologist.

On January 24th, Ms. Sharon Brown of Berlex spoke with Ms. Best who informed Ms. Brown that the request had come from the Nonclinical Pharmacologist, Dr. Krishan Raheja. In response to Ms. Brown's questions, Ms. Best informed her that she wasn't sure if Dr. Raheja had completed his review but that there weren't any comments from him to date. With regard to the Pharmacology/Toxicology section in the package insert, Ms. Brown mentioned that the regulations state if the information can be described in other parts of the labeling, such as,

"carcinogenicity, mutagenicity, and impairment of fertility", then a separate section is not required. Ms. Best replied again that because YASMIN is a new chemical entity, Dr. Raheja requested a full Pharmacology/Toxicology section. In response to Ms. Brown's question whether Dr. Raheja had any specific wording or suggestions as to what he would like see in this section, she replied that he has not suggested any wording.

In response to the Division's request, Berlex has prepared an Animal Pharmacology and/or Toxicology section for the PI. Electronic and hard copies of this section are attached to this cover letter. This section contains a summary of information typically found in other sections of the PI, such as the results of the carcinogenicity, mutagenicity, impairment of fertility and teratogenicity studies. This section will appear in the DRAFT PI provided to the Division in our submission of January 14, 2000 after the "HOW SUPPLIED" section and before "REFERENCES FURNISHED UPON REQUEST".

The electronic copy is provided on one 3.5 inch diskette labeled "DRSP 3 mg/EE 0.03 mg Tablets Animal Pharm/Tox Section of PI" dated February 4, 2000 in Microsoft® Word 97 SR-1 format. Berlex Laboratories certifies that the diskette was scanned for viruses and is virus free using Network Associates VirusScanNT 4.0.3a created January 26, 2000.

In accordance with previous procedure, this electronic copy was also sent to Ms. Best via the Internet today.

We trust that the information provided in this submission addresses all of your concerns and will enable you to complete the review of the NDA. Should you require any additional information or have any questions regarding this submission, please feel free to call me at (973) 276-2305. My fax number is (973) 276-2016.

Sincerely,
BERLEX LABORATORIES

Nancy F. Velez

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpoc028

Desk copy (cover letter): Ms. Jeanine Best

REVIEWS COMPLETED

SO ACTION:
LETTER N.A.I MEMO

INITIALS DATE

YASMIN® 21/28 TABLETS

Animal Pharmacology and/or Toxicology

Drospirenone, a spironolactone analogue, is a novel progestin with antimineralocorticoid and antiandrogenic activity. [Reports 3906, 3435, 5995/II, 9995, A085, 9800, A076, 9629, 4559, A427, A276, 9964] Drospirenone is devoid of significant androgenic, estrogenic, glucocorticoid and antiglucocorticoid activity. [Reports 9527, 9528, A982, 9691]

Drospirenone was not a gene mutagen in a standard battery of bacterial and mammalian cell mutagenicity assays conducted in the presence and absence of metabolic activation. [Reports 8467, 8494, 9211, 9313, 8495, 8724] Although interactions between drospirenone and DNA of liver cells (compound-specific adducts and/or unscheduled DNA synthesis) were found in vitro and after repeated oral administration of 10 mg/kg/day to rats and mice in vivo, no such findings were observed in human liver cells incubated in vitro with concentrations of drospirenone which were up to 333 times the average maximum serum level in humans (0.0627 ug/mL). [Reports AW44, AG18, AN95, A934, AG49, B839]

Drospirenone was not carcinogenic when administered to female mice and rats for 2 years at doses up to 10 mg/kg/day, alone or in combination with ethinyl estradiol (100:1). [Reports AZ86, AG63] Based on AUC, this dose level represents relative exposures of 2.3 to 2.9 times (mice) and 9.6 to 11.6 times (rats) the exposure in women given the contraceptive dose of 3 mg/day. [Reports AW44, AW45]

Estrogens and progestins should not be used during pregnancy. Like other combination estrogen and progestin contraceptives, oral administration of drospirenone combined with ethinyl estradiol (100:1) to female rats prior to mating inhibited normal estrus (at dose levels of 5.0 mg/kg/day and higher) and delayed the return of fertility (at dose levels of 15.0 mg/kg/day and higher).

Oral administration of drospirenone to pregnant rats or rabbits did not cause any teratogenic effects at dose levels up to 45 (rats) or 100 mg/kg/day (rabbits). [Reports 9918, 9998, A807] In addition, no teratogenic effects were observed in cynomolgus monkeys orally administered drospirenone combined with ethinyl estradiol (100:1) at doses up to 3.0 mg/kg/day. [Report A740]

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February 3, 2000

ORIGINAL

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REPORT

SU

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: Safety Update Report

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 mg Tablets], an oral contraceptive (OC) product.

Reference is also made to a conversation between Ms. Jeanine Best of the Division and the undersigned on January 3, 2000. Ms. Best informed the undersigned that the Division anticipates an approvable action on our application by the 10-month PDUFA goal date (March 17, 2000) if outstanding information is received, with the exception of the final renal study data. The Division would commit to a 2-month review clock for the final renal impairment study data and the renal impairment labeling if all other section and labeling reviews are complete. Ms. Best stated that as an outstanding item, a Safety Update statement was needed as soon as possible. She explained that a brief statement would be sufficient, especially if everything has been completed. She added that, of course, if there was any new information, it would have to be included.

In accordance with 21 CFR 314.50(d)(5)(vi)(b), attached please find the first Safety Update Report submitted for NDA 21-098. This update is being submitted approximately 9 months after the initial NDA submission rather than at the 4-month timepoint referenced in the regulations based on past experience and a recommendation by Ms. Jennifer Mercier of the Division during a conversation with the undersigned on August 13, 1999. Ms. Mercier had stated that the first update should not be older than 3 – 4 months at the time of action on the application or the

Division would be obligated to ask for another update to determine if there was any additional new information.

The reporting interval for this Safety Update is August 1, 1998 – January 15, 2000. These dates correspond to the cut-off date for inclusion of data into the NDA[1] and the cut-off date established for inclusion of data into this update, respectively.

As described in the Guideline for the Format and Content of the Clinical and Statistical Sections of an Application (July 1988), this Safety Update refers only to new data obtained during the interval. These additional data are relatively few, therefore, only serious or potentially serious adverse events (AE), an unusually high frequency of a less serious event, subjects who died and subjects who failed to complete a clinical study due to an AE are described. Commercial marketing experience, foreign regulatory actions and the results of literature searches are also provided for your information.

It was concluded that there is no new safety information learned about DRSP 3 mg and EE 0.030 mg Tablets that may reasonably affect the statement of contraindications, warnings, precautions and adverse reactions in the draft labeling.

1.1 Serious Or Potentially Serious AEs (SAEs)

There were no serious or potentially serious AEs in any of the studies that were ongoing during the reporting interval.

1.2 Unusually High Frequency Of A Less Serious Event

There was not an unusually high frequency of a less serious event in any of the studies that were ongoing during the reporting interval.

1.3 Subjects Who Died Or Discontinued A Clinical Study Due To An AE

1.3.1 Deaths

No subjects died in the studies that were ongoing during the reporting interval.

1.3.2 Discontinuations Due to AEs

Protocol 97036 entitled, "A Multicenter, Double-Blind, Randomized, Placebo Controlled, Parallel-Group Study to Evaluate the Efficacy of a Monophasic Oral Contraceptive Preparation, Containing Drospirenone 3 mg and Ethinyl Estradiol 30 µg, in the Treatment or Premenstrual Syndrome (PMS)" was being conducted under our ——— (premenstrual syndrome indication being reviewed by the Division of Neuropharmacological Drug Products) during the reporting period. The study was completed and is currently undergoing analysis. Available preliminary data revealed two cases of palpitations in women of reproductive age in the DRSP/EE treated group that were felt to be possibly related to drug and led to discontinuation.

[1] Cut-off dates for Nonclinical and Clinical data in the NDA were 7/31/98 and 11/1/98, respectively.

Subject 12070 experienced palpitations after being on drug for 21 days. The event was coded as moderate in severity and the study drug was discontinued. Subject 19014 experienced palpitations after being on drug for 14 days. The event was coded as moderate in severity and the study drug was discontinued. Palpitations are not specifically included in OC labeling.

There were no other discontinuations due to AEs occurring in any of the other studies ongoing during the reporting period.

1.4 Commercial Marketing Experience And Foreign Regulatory Actions

1.4.1 List Of Countries In Which The Drug Has Been Approved

DRSP 3 mg and EE 0.030 mg Tablets have not been marketed in any country to date.

1.4.2 List Of Countries In Which The Drug Has Been Submitted For Approval And The Applications Are Pending

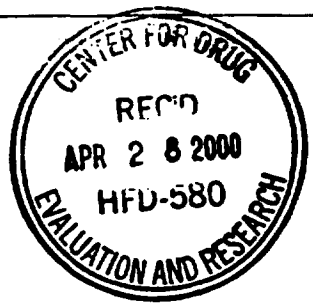
During the reporting interval, applications were submitted for approval in the following countries:

Country	Submission Date
	March 2, 1999
	March 2, 1999
	May 7, 1999
	May 10, 1999
	May 14, 1999
	June 23, 1999
	July 14, 1999
	September 1, 1999
	October 13, 1999
	December 3, 1999
	December 10, 1999

UPS OVERNIGHT

ORIGINAL

BERLEX



Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
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Telephone: (973) 276-2000

April 27, 2000

ORIG AMENDMENT

BM

Susan Allen, M.D., MPH, Acting Director
DIVISION OF REPRODUCTIVE AND UROLOGIC
DRUG PRODUCTS, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
AMENDMENT TO PENDING APPLICATION:
DRAFT REPORT – RENALLY IMPAIRED STUDY

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 mg Tablets], an oral contraceptive (OC) product.

References are also made to our teleconference on December 15, 1999 and the submission dated January 6, 2000. In the January 6th submission, Berlex provided a timeline as to the status of three studies outstanding at the time. The final report for the *Omeprazole Drug Interaction Study* was submitted on January 18, 2000. A "Summary of Serum Potassium Results" from the *ACE Inhibitor Study* was submitted on February 28, 2000. The DRAFT statistical analysis of serum potassium data from the ACE inhibitor study was submitted on March 16, 2000.

The FINAL abbreviated report entitled, "Final Statistical Analysis of Serum Potassium Data" for the ACE Inhibitor study entitled, "A Double-Blind, Randomized, Two-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 98106) was submitted on April 20.

REVIEWS COMPLETED

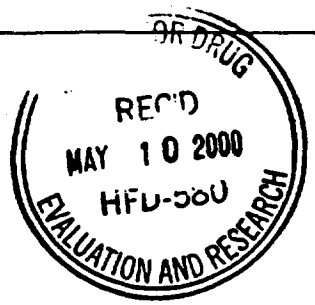
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

TELEFAX
UPS OVERNIGHT

ORIGINAL

BERLEX



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May 9, 2000

Susan Allen, M.D., MPH, Acting Director
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DRUG PRODUCTS, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706

ORIG AMENDMENT

BL

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 Tablets)
AMENDMENT TO PENDING APPLICATION: Revised Physician Package Insert

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 Tablets], an oral contraceptive (OC) product.

Additional reference is made to our submission dated February 29, 2000 which included revised electronic labeling [Physician Package Insert (PI), Brief Summary Patient PI and Detailed Patient PI] and container mock-ups (blister, day label, pouch and carton).

Reference is also made to the approvable letter dated March 17, 2000 and our response dated March 29, 2000. A copy of the approvable letter is attached for your convenience.

The approvable letter stated that Berlex needed to submit the final study results of the effects of YASMIN® in renally-impaired patients. The final report for this study was submitted on May 8, 2000.

The letter also requested revised labeling that included appropriate information from the renal impairment study. This submission includes the revised physician PI incorporating the results of the renal impairment study as well as the ACE inhibitor study.

Electronic Labeling

This submission amends NDA 21-098 to provide for a revised electronic Physician PI reflecting all of the Division's comments to date.

These electronic copies of the labeling are provided in Microsoft® Word 97 SR-1 format on one 3.5 inch diskette labeled "YASMIN® 21/28 TABLETS Labeling" dated May 9, 2000 (see Attachment 1).

In accordance with previous procedure, a clean copy as well as a strike out version of the Physician PI are provided, identified as "unmarked" and "marked", respectively. Please note that electronic copies of the Division's comments provided via the Internet by Ms. Best to the undersigned on February 23rd and 28th were used to generate the strike out version.

Berlex Laboratories certifies that the diskette provided herewith was scanned for viruses and is virus free using Network Associates VirusScanNT 4.0.3a created April 12, 2000.

Berlex attempted to transmit the electronic Physician PI through the internet and learned today from Ms. Best that the firewall is in effect and no external e-mails are being accepted.

Please note the following when reviewing the strike out version of the labeling:

In addition to the editorial changes Berlex has proposed, Berlex is providing justification for changes with a scientific basis:

PRECAUTIONS: CARCINOGENESIS and PREGNANCY

10. Carcinogenesis:

Berlex disputes the following statement and proposes that it be removed:

"...a significant dose related increase in pituitary adenomas in mice receiving the combination"

The increased incidence of pituitary adenomas observed in mice given all doses of the combination of drospirenone and ethinyl estradiol is attributed to the ethinyl estradiol component of the combination. In general, the incidence of pituitary adenomas observed in mice given the combination of drospirenone and ethinyl estradiol is less than that observed in the groups of mice given ethinyl estradiol alone (See table which follows). This, coupled with a very low incidence of pituitary adenomas in animals given drospirenone alone indicates that this is an estrogenic effect. This is also consistent with information in the literature (Heywood R, Wadsworth PF. The experimental toxicology of estrogens. In: Chaudhury RR (ed). *Pharmacology of Estrogens.* New York, New York:Pergamon Press, 1981;63-80.)

Incidence of Pituitary adenoma									
Control	Combination			E2 alone			DRSP alone		
4/110	11/55	13/54	23/55	7/55	27/55	41/55	1/54	0/55	0/55

Berlex disputes the following statement and proposes that it be removed:

"...an increase in carcinomas of the harderian gland (a retro-orbital gland not present in humans) in the group that received the high dose of drospirenone alone, but not the combination"

Reference is made to the Safety Update submitted on May 4, 2000. The Carcinogenesis section of the package insert has been updated to include a histopathological re-examination of the neoplastic Harderian gland findings. The report concludes that the incidences of adenomas and adenocarcinomas of the Harderian glands were not influenced by the treatment with DRSP, EE or the combination of DRSP and EE. The resulting report entitled, "ZK 4.944 and ZK 30.595 Histopathological Re-examination to: Oncogenicity Study by Oral Gavage Administration to Female CD-1 Mice for 104 Weeks was included in Attachement 3 of the Safety Update.

Berlex disputes the following statement and proposes that it be removed:

"...a significant, positive dose response in hepatocellular adenomas of the liver..."

The incidence of hepatocellular adenoma in groups of animals given drospirenone alone was low and not significantly different than controls [0/55 (0%), 0/55 (0%) and 1/55 (2%) in the animals given the low-, mid- and high-doses, respectively, versus 1/110 (1%) in the controls].

11. Pregnancy

Berlex disputes the following statement and proposes that it be removed:

The historical normal range for this finding in Han:Wistar rats at Schering AG is 0.7% to 34.1% of fetuses/group. Although the incidence for this finding in this study was significantly greater than controls, the incidence (6.1%) is within the historical range at the testing laboratory and therefore not noteworthy. Historical range data is available upon request.

ADVERSE REACTIONS

With regard to the following statement in this section, "The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related", the Division states that the adverse reactions that follow the statement are not listed in order of frequency. In response, Berlex has not changed this section as this information is class labeling, is not available to Berlex, and appears in this order in all other marketed OCs. Berlex agrees to revise this section if the Division provides the pertinent information.

In the archival copy of this submission, Berlex is submitted a hard copy version of the unmarked version in Attachment 2 and Attachment 3 contains the marked version.

With the submission of the revised package insert, Berlex has provided a complete response to the March 17, 2000 approvable letter. As stated previously, Berlex will call to begin the dialogue that leads to approval. Berlex hopes to launch the product by early July and will be available to discuss any issues that need resolution.

Should you require any additional information or have any questions regarding this submission, please feel free to call me at (973) 276-2305. My fax number is (973) 276-2016.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpoc109

Desk copy: Ms. Jeanine Best – cover letter

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

INITIALS DATE

TELEFAX
UPS OVERNIGHT

BERLEX

May 8, 2000

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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Susan Allen, M.D., MPH, Acting Director
DIVISION OF REPRODUCTIVE AND UROLOGIC
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5600 Fishers Lane
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ORIGINAL

ORIG AMENDMENT

b2

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
AMENDMENT TO PENDING APPLICATION:
FINAL REPORT – RENAL IMPAIRMENT STUDY

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 mg Tablets], an oral contraceptive (OC) product.

References are also made to our teleconference on December 15, 1999 and the submission dated January 6, 2000. In the January 6th submission, Berlex provided a timeline as to the status of three studies outstanding at the time. Please note:

1. The final report for the *Omeprazole Drug Interaction Study* was submitted on January 18, 2000.
2. A "Summary of Serum Potassium Results" from the *ACE Inhibitor Study* was submitted on February 28, 2000. The DRAFT statistical analysis of serum potassium data from the *ACE Inhibitor Study*[1] was submitted on March 16, 2000 and the FINAL statistical analysis[2] on April 20, 2000.
3. On April 4, 2000 a "Summary of Potassium Results" from the *Renal Impairment Study* was submitted. The DRAFT report of this study was submitted on April 27th.

[1] Abbreviated Report
[2] Abbreviated Report

Today's submission fulfills our commitments in the January 6 letter and provides for the two volume FINAL report of the renal impairment study, Report B682 (Study No. 303063) entitled, "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 repated oral administration over 14 days". This FINAL report confirms the results of the DRAFT report. There are no substantial changes between the DRAFT and FINAL report.

As stated in the April 27th submission, this study was an open-labeled, non-randomized study with one treatment. Because subjects with varying degrees of renal function were included, each individual was classified to a renal function group by her creatinine clearance. The study has four phases: screening took place up to four weeks before treatment, pretreatment took place two days prior to treatment, treatment occurred for 14 days and post-treatment occurred 14 days after treatment.

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 and to evaluate the effect of renal function on the pharmacokinetics of DRSP.

The conclusion of the study revealed that the mean potassium serum concentration did not show a clinically significantly 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 steady-state treatment potassium concentration values measured were 5.5 mmol/l or under for all study participants in all three renal groups.

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. 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 to the excellent tolerability of DRSP.

As noted in a telephone conversation between Ms. Best and the undersigned on April 12, 2000, it is understood that the review clock will begin upon receipt of this submission.

Berlex is currently finalizing the revised labeling that includes appropriate information from this FINAL renal impairment study and will submit this within the next day or two.

Berlex will call tomorrow to confirm receipt of this FINAL report for the renal impairment study and to discuss the next steps to arrange a teleconference to prepare for a labeling day (previously referred to as NDA day). It is hoped that we will address any outstanding issues, discuss and finalize the labeling at that time.

Should you require any additional information or have any questions regarding this submission, please feel free to call me at (973) 276-2305. My fax number is (973) 276-2016.

Sincerely,
BERLEX LABORATORIES

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpoc106

Desk copy (cover letter): Ms. Jeanine Best

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

CSO ACTION
☐ LETTER ☐ N.A.I. ☐ MEMO

INITIALS DATE

BERLEX

UPS OVERNIGHT

May 8, 2000

ORIGINAL

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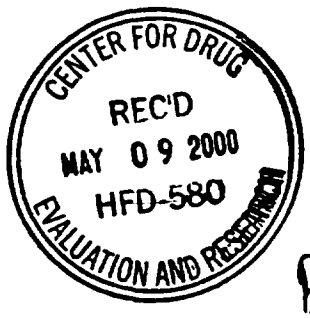

BM

Dear Dr. Allen:

ORIG AMENDMENT

Re: NDA 21-098 – YASMIN® 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
AMENDMENT TO PENDING APPLICATION:
CORRECTION TO: Final Statistical Analysis of Serum Potassium Data from ACE Inhibitor Study

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 mg Tablets], an oral contraceptive (OC) product.

Reference is made to the April 20, 2000 submission of the final statistical analysis of serum potassium data from the abbreviated report entitled, "Final Statistical Analysis of Serum Potassium Data" for the ACE Inhibitor study entitled, "A Double-Blind, Randomized, Two-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 98106).

As described in the submissions of February 28th and March 16th, in this study, drospirenone (DRSP) 3 mg/estradiol (E2) 1 mg or placebo tablet was orally administered daily for fourteen days to mild hypertensive postmenopausal females maintained on 10 mg bid enalapril maleate therapy. Twenty-four (24) volunteers entered and completed this double-blind, randomized, two parallel groups study. Serum potassium concentrations were determined over a 24-hour period on pretreatment Day 1 (prior to the first DRSP/E2 dose) and on treatment Day 14 (after last treatment dose). In addition, a pre-morning dose single serum potassium determination was performed on pretreatment day 2 and treatment days 2, 4, 6, 8, 10, and 12 to continuously monitor serum potassium concentrations.

The FINAL statistical analysis confirms and expands on the results provided in the DRAFT statistical analysis. Results of the statistical analysis of serum potassium log-transformed Cmax and AUC show that there were no statistically significant differences between placebo and DRSP/E2 treatment groups in terms of both serum potassium Cmax and AUC. The obtained narrow 90% confidence intervals on both Cmax and AUC further demonstrate the precision of the observed parameter ratio measurements. The data supports the conclusion that there are no clinically or statistically significant differences in serum potassium concentrations in mildly hypertensive postmenopausal women maintained on enalapril therapy who are administered DRSP/E2 or placebo for 14 days.

This report has been amended. The change does not affect the final results of the study. The change is that the **90% confidence limits for both Cmax and AUC (Table 6, Section 7.2) were amended due to an inaccuracy in the reported values. The title page of the report reflects the amendment date of May 5, 2000. Page 19 of 47 of the report has been changed to reflect the change. Both the title page and page 19 of 47 are attached.**

Should you require any additional information or have any questions regarding this submission, please feel free to call me at (973) 276-2305. My fax number is (973) 276-2016.

Sincerely,
BERLEX LABORATORIES

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpo107

Desk copy (cover letter): Ms. Jeanine Best

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

BERLEX

UPS OVERNIGHT

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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May 4, 2000

ORIGINAL

Susan Allen, M.D, MPH, Acting Director
DIVISION OF REPRODUCTIVE AND UROLOGIC
DRUG PRODUCTS, HFD-580
Office of Drug Evaluation II
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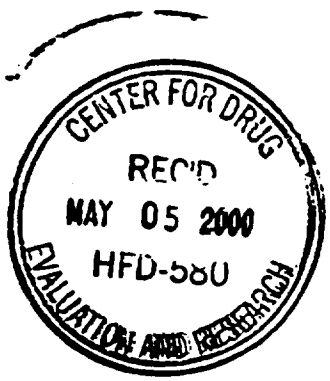

SU

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: Safety Update Report

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 mg Tablets], an oral contraceptive (OC) product.

Reference is also made to the approvable letter dated March 17, 2000 (attached immediately following this cover letter for your reference), voice mail communications on March 22nd and 23rd between Ms. Jeanine Best of the Division and the undersigned and our response to the approvable letter dated March 29th.

In accordance with 21 CFR § 314.50 (d) (5) (vi) (b), a Safety Update Report was requested in the approvable letter by submitting all of the information we now have regarding YASMIN®. On March 22nd and 23rd, Ms. Best confirmed for the undersigned that Berlex could update the NDA with any new information that was obtained since the last period submitted in the previous Safety Update Report. The undersigned stated that Berlex would use the same format as was used in the previous report. In our response to the approvable letter, Berlex stated that the requested Safety Update Report would be submitted in April 2000.

Attached please find the second Safety Update Report submitted for NDA 21-098. The reporting period for this Safety Update is January 16 – March 17, 2000. These dates correspond to the cut-off date for inclusion of data into the previous Safety Update Report (submitted on February 3, 2000) and the date of the approvable letter.
As with the previous Safety Update report, this report refers only to new data obtained during the reporting period. These additional data are relatively few, therefore, only serious or

potentially serious adverse events (AE), an unusually high frequency of a less serious event, subjects who died, subjects who failed to complete a clinical study due to an AE and the results of one nonclinical study are described. Commercial marketing experience, foreign regulatory actions and the results of literature searches are also provided for your information.

It was concluded that there is no new safety information learned about DRSP 3 mg and EE 0.030 mg Tablets that may reasonably affect the statement of Contraindications, Warnings and Adverse Reactions in the DRAFT labeling[1]. The nonclinical report completed during the reporting period contains safety information about DRSP 3 mg and EE 0.030 mg Tablets that affects Item 10, Carcinogenesis, of the Precautions section in the DRAFT labeling (see section 1.6 below).

1.1 Serious Or Potentially Serious AEs (SAEs)

As stated in our first Safety Update of February 3, 2000, Protocol 97036 entitled, "A Multicenter, Double-Blind, Randomized, Placebo Controlled, Parallel-Group Study to Evaluate the Efficacy of a Monophasic Oral Contraceptive Preparation, Containing Drospirenone 3 mg and Ethinyl Estradiol 30 µg, in the Treatment or Premenstrual Syndrome (PMS)" had been conducted under our [redacted] (premenstrual syndrome indication being reviewed by the Division of Neuropharmacological Drug Products) and was undergoing analysis. Preliminary data were reviewed for the previous Safety Update.

Final data for Protocol 97036 are now available. Two hundred and sixty one (261) subjects were randomized in the study. One hundred and five (105) subjects completed the six cycle study. One hundred and thirty (130) subjects were treated with the DRSP/EE product and one hundred and thirty one (131) with placebo.

Five subjects experienced seven serious AEs during the study. Two of these subjects were treated with placebo and three with the DRSP 3 mg/EE 30 µg product. Narratives for the three subjects (three AEs) treated with DRSP/EE (Subjects 03001, 07038 and 24014) are provided below. It was concluded that these serious AEs do not affect the DRAFT labeling.

> Subject 03001 was randomized to DRSP 3 mg/ EE 30 µg in Study 97036. She was admitted to the hospital on June 6, 1998 with complaints of coughing blood for two days. She was examined by pulmonary and infectious disease physicians and diagnosed by bronchoscopy with tuberculosis. The subject was started on a 4-drug Tuberculosis treatment plan. The drug relationship was classified as not related.
>
> Subject 07038 was randomized to DRSP 3 mg/ EE 30 µg in Study 97036. She was diagnosed with migraine headaches on March 19, 1999 and given the diagnosis of recurrent Bell's Palsy in April 1999. She was treated with Neurontin® and Vicodin®. The first episode of Bell's Palsy occurred in 1995, prior to enrollment in the study. The drug relationship was classified as not related.

[1] Submitted to the Division on February 29, 2000

Subject 24014 was randomized to DRSP 3 mg/ EE 30 µg in Study 97036. She was diagnosed with basal cell carcinoma of the nose on 11/13/98 following a biopsy of the lesion. The lesion was surgically removed on 12/23/98. The drug relationship was classified as not related.

There were no other serious or potentially serious AEs in any of the studies that were ongoing during the reporting interval.

1.2 Unusually High Frequency Of A Less Serious Event

There was not an unusually high frequency of a less serious event in any of the studies that were ongoing during the reporting interval.

1.3 Subjects Who Died Or Discontinued A Clinical Study Due To An AE

1.3.1 Deaths

No subjects died in the studies that were ongoing during the reporting interval.

1.3.2 Discontinuations Due to AEs

Final data from Protocol 97036 reveal that there were 27 subjects that discontinued the study due to AEs. Twenty subjects were treated with the DRSP 3 mg/EE 30 µg product and seven with placebo. These subjects and the AEs they experienced are identified in a table in Attachment 1. It was concluded that these discontinuations due to AEs do not affect the DRAFT labeling.

There were no other discontinuations due to AEs occurring in any of the other studies ongoing during the reporting period.

1.4 Commercial Marketing Experience And Foreign Regulatory Actions

1.4.1 List Of Countries In Which The Drug Has Been Approved

DRSP 3 mg and EE 0.030 mg Tablets have not been marketed in any country to date.

1.4.2 List Of Countries In Which The Drug Has Been Submitted For Approval And The Applications Are Pending

During the reporting interval, DRSP 3 mg and EE 0.030 mg Tablets were approved for marketing in the Netherlands. The application was submitted on November 18, 1998 and was approved on March 7, 2000. No additional applications were approved or submitted for approval during the reporting period. The approvable letter states English translations of any approved foreign labeling should be submitted in the Safety Update. The approved Dutch labeling, as well as an English translation, are provided in Attachment 2.

1.4.3 Reports from Foreign Regulatory Authorities, Foreign Affiliates, Licensors or Licensees of the Applicant

Because the product has not been marketed to date, there are no reports of, or analyses of, AEs, warning letters sent to physicians, and major changes in marketing status or labeling information resulting from marketing or other experience with DRSP 3 mg and EE 0.030 mg Tablets from foreign regulatory authorities, foreign affiliates, licensors or licensees of the applicant.

1.4.4 Epidemiological Studies

There are no reports of epidemiological studies or studies underway with DRSP 3 mg and EE 0.030 mg Tablets.

1.4.5 Spontaneous Reports From Foreign Marketing Experience

Because the product is not marketed, there were no spontaneous reports from foreign marketing experience.

1.5 Reports From Literature

Nonclinical and clinical literature searches for DRSP 3 mg and EE 0.030 mg Tablets were performed for the reporting interval. The searches revealed that there is no new safety information in the literature that may reasonably affect the statement of contraindications, warnings, precautions and adverse reactions in the DRAFT labeling.

1.6 Nonclinical Reports

A histopathological re-examination of the neoplastic Harderian gland findings reported in the mouse carcinogenicity study (Report AZ86, "ZK 4944 and ZK 30595 Oncogenicity Study by Oral Gavage Administration to Female CD-1 Mice for 104 Weeks", NDA Vol. 15, page 5 04195) was conducted during the reporting period. The resulting report entitled, "ZK 4.944 and ZK 30.595 Histopathological Re-examination to: Oncogenicity Study by Oral Gavage Administration to Female CD-1 Mice for 104 Weeks", is provided in Attachment 3. The report concludes that the incidences of adenomas and adenocarcinomas of the Harderian glands were not influenced by treatment with DRSP, EE or the combination of DRSP and EE. No statistically significant results for any pairwise comparisons were observed. The DRAFT labeling submitted to the Division on February 29, 2000 for Item 10, Carcinogenesis, of the Precautions section is provided in Attachment 4. It contains the following statement:

"In a 24-month oral carcinogenicity study in mice dosed with 1+0.01, 3+0.03 and 10+0.1 mg/kg/day of drospirenone and ethinyl estradiol, 0.1 to 2 times the exposure (AUC of drospirenone) of women taking a contraceptive dose, there was an increase in carcinomas of the harderian gland (a retro-orbital gland not present in humans) in the group that received the high dose of drospirenone alone, but not the combination."

Berlex proposes that, based on the histopathological re-evaluation of the neoplastic Harderian gland findings, the statement be modified to read:

"In a 24-month oral carcinogenicity study in mice dosed with 1+0.01, 3+0.03 and 10+0.1 mg/kg/day of drospirenone and ethinyl estradiol, 0.1 to 2 times the exposure (AUC of drospirenone) of women taking a contraceptive dose, no drospirenone-related carcinogenic findings were observed."

The new labeling for Item 10, Carcinogenesis, of the Precautions section, incorporating this change, is provided in Attachment 5. Both a strike-out version and clean copy are included for ease of review.

Berlex acknowledges that this submission does not constitute a complete response to all of the deficiencies identified in the approvable letter of March 17th. The remaining outstanding items, the final report of the renal impairment study and the revised labeling that includes appropriate information from that study, will be submitted in the next few days. In the meantime, we would like the Division to have today's submission immediately available.

Should you require any additional information or have any questions regarding this submission, please feel free to call me at (973) 276-2305. My fax number is (973) 276-2016.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpoc093

Desk copy (cover letter): Ms. Jeanine Best

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

BERLEX

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Drug Development & Technology
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ORIGINAL

January 14, 2000

Lisa Rarick, M.D., Director
DIVISION OF REPRODUCTIVE AND UROLOGIC
DRUG PRODUCTS, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706

ORIG AMENDMENT

BL

Dear Dr. Rarick:

Re: NDA 21-098 – YASMIN® 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 Tablets)
OTHER: Revised Electronic Package Insert

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 Tablets], an oral contraceptive (OC) product.

On December 3, 1999, per the Division's request, Berlex Laboratories submitted electronic copies of the YASMIN labeling in Word format and PDF format, including both annotated and unannotated versions. On December 9th, Ms. Jeanine Best of the Division forwarded to the undersigned via the Internet preliminary Clinical, Clinical Pharmacology and Chemistry comments on the package insert (PI). These comments were discussed briefly in a teleconference between the Division and Berlex on December 15th. Division minutes of this teleconference were received in a letter dated December 16th. Ms. Best and the undersigned reviewed the December 9th comments line by line on December 21st to clarify inconsistencies between preliminary comments. In all of these communications, the Division asked that a revised PI be submitted to the Division around January 1, 2000.

On January 3rd and 4th, telephone conversations were held between Ms. Best and the undersigned and Ms. Best, Dr. Marianne Mann and the undersigned, respectively, during which the undersigned was informed that the Division anticipates an approvable action on our application by the 10 month PDUFA goal date of March 17, 2000 if outstanding information is received, and section and labeling reviews are completed, all in a timely manner. Dr. Mann stated that the conditions of this approvable action would be that the Division would complete their review of the application, with the exception of the final renal impairment study data and the renal impairment labeling. The final renal impairment study report should be submitted as soon as it is completed and the Division would commit to a two month review of the renal

impairment data and renal impairment labeling. Dr. Mann asked that we submit a revised PI addressing the December 9th comments from the Division now and that Berlex and the Division could work together later to resolve the labeling with regard to renal impairment, safety and spironolactone. Minutes of the January 4th conversation were summarized in a telefax from the Division dated January 11, 2000.

In response to the Division's request for a revised PI, attached please find one 3.5 inch diskette labeled "DRSP 3 mg/EE 0.03 mg Tablets Labeling" dated January 14, 2000 (see Attachment 1). The diskette contains the Physician PI in Microsoft® Word 97 SR-1 format. Per Ms. Best's request on January 4th, a clean copy of the revised labeling as well as a strike out version are provided. The files are identified as "unmarked.doc" and "marked.doc", respectively. Please note that Berlex understands that the three sets of comments (Chemistry, Biopharmaceutical and Clinical) provided on December 9th were preliminary. Because they do conflict in a few sections, as a general rule, the Clinical comments were used as the master comments. They were also used to generate the strike out version.

Berlex Laboratories certifies that the diskette was scanned for viruses and is virus free using Network Associates VirusScanNT 4.0.3a created November 24, 1999.

Please note the following when reviewing the strike out version of the labeling:

- In accordance with the Biopharmaceutical comments and in some cases initiated by Berlex for additional clarity, some of the information appearing in the CLINICAL PHARMACOLOGY and PHARMACOKINETICS sections was moved to different subsections and was summarized more concisely. This information will appear as "struck out" in the original subsection and "new" in the revised section. The most obvious example of this is the original Dose Proportionality/Multiple Dosing subsection that was moved under the Absorption subsection. It should be noted that in these cases the information is not new.

- The Class Labeling wording for Drug Interactions in the PRECAUTIONS section has been modified considering that YASMIN does not contain norethindrone. The proposed wording includes all points from the Class Labeling in a manner as specific as possible to the components of YASMIN (DRSP and EE). With regard to drug interaction between EE and ascorbic acid (AA), we are providing an explanation (see Attachment 2) to delete the interaction between EE and AA from the Class Labeling.

- In order to maintain consistency with our other marketed products, Levlen®, Tri-Levlen® and Levlite®, the following Adverse Reactions have been added under the section entitled, "The following adverse reactions have been reported in users of oral contraceptives and the association has been neither confirmed nor refuted":.

    - Congenital anomalies
    - Optic neuritis
    - Sickle-Cell Disease
    - Cerebral-vascular disease with mitral valve prolapse
    - Lupus-like Syndromes

Please also note that our proposed trade name, YASMIN®, appears throughout the labeling. Dr. Moo-Jhong Rhee of the Division informed the undersigned in a telephone conversation on November 30, 1999 that the responsibility of approving our trade name was transferred from the Labeling and Nomenclature Committee to the Office of Post Marketing Drug Risk Assessment (OPDRA). He assured the undersigned that our name "YASMIN" was transferred by the Division to OPDRA and the Division would inform Berlex when it is approved. To date, we have not received any information regarding the status of the name.

In accordance with previous procedure, this revised version of the Physician PI was also sent to Ms. Best via the Internet today.

Should you require any additional information or have any questions regarding this submission, please feel free to call me at (973) 276-2305. My fax number is (973) 276-2016.

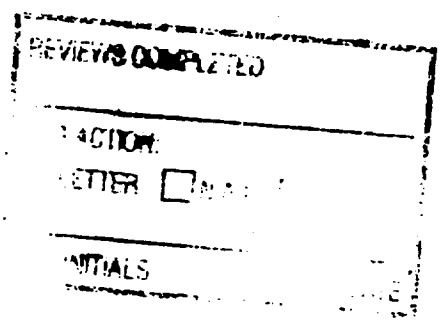
Sincerely,

BERLEX LABORATORIES

Nancy E. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpoc006

Desk copy: Ms. Jeanine Best



APPEARS THIS WAY
ON ORIGINAL

BERLEX

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January 7, 2000

ORIGINAL

Lisa Rarick, M.D., Director
DIVISION OF REPRODUCTIVE AND UROLOGIC
DRUG PRODUCTS, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706

ORIG AMENDMENT

13 c

Dear Dr. Rarick:

Re: NDA 21-098 – YASMIN® 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 Tablets)
AMENDMENT TO PENDING APPLICATION

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 Tablets], an oral contraceptive (OC) product.

Reference is also made to the Phase 3 meeting of February 12, 1997 between Berlex Laboratories and the Division during which the development program for DRSP/EE was discussed.

Additional reference is also made to a teleconference held on December 15, 1999 between representatives of the Division and Berlex Laboratories during which Dr. Rhee of the Division asked for the status of additional stability data (12 month) which Berlex previously committed to submit during the NDA review. Berlex stated that the amendment was being prepared and would be submitted within two weeks.

Please also refer to the Chemistry Information Request Letter from the Division dated December 16, 1999 wherein Berlex is asked to provide the additional stability data, a proposed shelf-life for YASMIN tablets and a post-approval stability protocol.

As agreed during the Phase 3 meeting of February 12, 1997 between Berlex and the Division, Berlex submitted 6-month drug product stability data in the NDA with the understanding that 12-month stability data would be amended to the NDA with during the review process. This

submission amends Item 4 of NDA 21-098 to provide for 12-month controlled room temperature stability data on the 3 full scale production batches described in the NDA. These batches were manufactured in the full-scale production facility of Schering GmbH and Co. Productions KG, Weimar, Germany. The following reports are provided in Attachment 1:

QE2-025.3/98: Stability Report on SH T 470 FA (with pouch)

QE2-025.3/98: Annex to Stability Report on SH T 470 FA (with pouch)

As committed in Section 4.1.2.8.1 of the NDA (Volume 4, page 4 – 528), formal stability commitment statements for both active and inert DRSP/EE tablets are provided in Attachment 2.

As committed in Section 4.1.2.8.2 (page 4 – 528), Berlex proposes, based on the results of the 12-month stability determinations, that YASMIN® Tablets be given 2-year expiration dating.

A new NDA page 4 – 528, incorporating the stability commitment information and proposed expiration dating is provided in Attachment 3.

This submission also amends NDA 21-098 to provide for the following additional alternate packaging subcontractors for secondary packaging:

- Berlex Laboratories, Inc., Wayne, NJ;
- [redacted]

[redacted] facility supports this application. Please refer to this DMF for facility information. Type 1 [redacted] describe the GPS and PCI facilities, respectively. New NDA pages 4 - 52 and 4 - 52 - 1, incorporating these alternate secondary packagers, as well as copies of the letters of authorization for [redacted] (page 4 - 54 - 3 are provided in Attachment 4.

Reference is also made to telephone communications between Dr. Moo-Jhong Rhee of the Division and the undersigned on November 30 and December 1 and 2, 1999. Dr. Rhee had questioned whether the drug substance name "drospirenone" was an established name approved by the United States Adopted Names (USAN) Council. Dr. Rhee commented that the name appeared in the 1998 USAN (USP Dictionary of USAN and International Drug Names) but was not bold faced nor was a year of approval cited.

The undersigned informed Dr. Rhee that our parent company, Schering AG, Berlin, Germany, submitted a request to USAN on November 13, 1996 asking that it adopt (publish) the name "drospirenone" for the compound ZK 30595. Schering AG received a letter from USAN on February 26, 1997 stating that it had adopted the name and planned on publishing it in the journal of Clinical Pharmacology and Therapeutics unless a delay was requested by Schering AG (see Attachment 5). Schering AG was asked to initial the "Statement of Adoption" and return it. Schering AG returned the signed statement in June of 1998. The undersigned explained that this is why the name did not appear in the 1998 USAN, although it had been adopted at the beginning of 1997. The undersigned informed Dr. Rhee that the name drospirenone appears as an adopted USAN name in the January 1999 issue of Clinical

Pharmacology and Therapeutics on page 79 (see Attachment 6). Dr. Rhee asked that all of this information communicated to him regarding the name be amended to the NDA, including the letter from USAN stating that the name was adopted.

Should you require any additional information or have any questions regarding this submission, please feel free to call me at (973) 276-2305. My fax number is (973) 276-2016.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpoc003

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

CSO ACTION
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

ORIG AMEN...

BERLEX

TELEFAX
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BZ ORIGINAL

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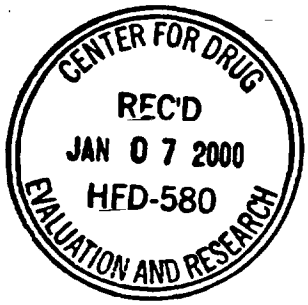
January 6, 2000



Lisa Rarick, M.D., Director
DIVISION OF REPRODUCTIVE AND UROLOGIC
DRUG PRODUCTS, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706

Dear Dr. Rarick:

Re: NDA 21-098 – YASMIN® 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 Tablets)
OTHER: Status of Ongoing Studies, Copy of
Renal Impairment Protocol

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 Tablets], an oral contraceptive (OC) product.

Reference is also made to a teleconference held on December 15, 1999 between representatives of the Division and Berlex Laboratories to discuss Clinical, Clinical Pharmacology and Chemistry issues that will impact the approval and labeling of our drug product. During the teleconference, Dr. Marianne Mann of the Division asked for the status of two studies which she noted were discussed during our Pre-NDA meeting held on January 28, 1999 and were described in the initial NDA under review: 1) study being conducted in renally impaired patients and 2) drug interaction study. Dr. Mann also asked for an update on the ACE inhibitor study which Berlex explained is being conducted under ———, our IND for a ———. Berlex provided dates during the teleconference when draft and final data from these three studies would be available for submission. Berlex committed to submit these timelines to the Division.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

The table below provides the timelines for submission of data to the Division for the three ongoing studies:

Study Type	Some Results Available	Draft Report Available	Final Report Available
Renally Impaired Patients	End of March 2000	End of April 2000	End of May 2000
Drug Interaction Study	Not Applicable	Beginning of January 2000	End of January 2000
ACE Inhibitor Study	End of February 2000 (Potassium Data Only)	Mid March 2000[1]	End of March 2000[1]

Please note that these are optimistic dates, however, every effort is being made to meet them.

The titles of each of the three studies and some additional details are provided below:

1. Study in Renally Impaired Patients: "Open-Label Study To Assess The Effects 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" (Protocol 303063)

   As requested by Dr. Marianne Mann in a telephone conversation with the undersigned on January 4, 2000, a copy of Protocol 303063 is attached for the Division's review. This study investigated both pharmacodynamics (effect on serum potassium) and pharmacokinetics of DRSP under multiple dose, steady-state conditions (14 days of daily DRSP dosing) in three groups of female subjects with three levels of renal impairment (as determined by creatinine clearance, CC).

   Serum potassium levels (primary variable: pharmacodynamics) and serum DRSP levels (secondary variable: pharmacokinetics) were investigated in three groups (Group 1: CC >80 mL/min, Group 2: CC, 50-80 mL/min and Group 3: CC, 30-50 mL/min; 10 subjects per group) of female volunteers (age 18-75). The test drug, 3 mg DRSP, was administered once a day for 14 days. The pretreatment serum potassium levels were determined on three consecutive days, just prior to 14-days of DRSP regimen. The serum potassium levels at DRSP steady state condition were determined on the last three days of the DRSP regimen. Blood samples for pharmacokinetics determinations were obtained on just before (baseline) and on the last day of DRSP regimen and for 7-days thereafter.

   This study is being conducted by our parent company, Schering AG, in Berlin, Germany and began in October 1999.

2. Drug Interaction Study: "Open-Label, Crossover Study To Assess The Potential Of Drospirenone (DRSP) To Inhibit CYP2C19 By Evaluating The Metabolic Interaction Between DRSP And Omeprazole As Model Substrate In Healthy Postmenopausal Volunteers Genotyped For Polymorphism Of CYP2C19" (Protocol ME98231)

   This study was conducted by our parent company, Schering AG, in Berlin, Germany and

[1] Abbreviated report

completed in November 1999. A draft of the protocol for the study was submitted to [redacted] on April 16, 1999 (Serial No. 031) in follow up to our Pre-NDA meeting where the Division suggested that Berlex consider conducting such a study.

As briefly communicated in the teleconference on December 15th, preliminary results indicate that no significant influence from the co-administration of DRSP on the bioavailability (AUC) of the CYP2C19 enzyme substrate (Omeprazole) and the CYP2C19 enzyme product (5-hydroxy-Omeprazole) was found. Similar results were found for the CYP3A4 enzyme product (Omeprazole sulfone). Therefore, the results of this clinical study did not demonstrate an inhibition of the cytochrome P450 enzymes 2C19 and 3A4 by DRSP in humans. Drug-drug interactions between DRSP and drugs whose metabolic pathways are catalyzed by CYP2C19 and CYP3A4 appear highly unlikely.

3. ACE Inhibitor Study: "A Double-Blind, Randomized, Two-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 98106)

   In this study, drospirenone (DRSP) 3mg/estradiol (E2) 1 mg or placebo tablet is orally administered daily for fourteen days to volunteers maintained on 10 mg bid enalapril maleate therapy in order to evaluate the potential for hyperkalemia when the HRT combination product is given with the ACE inhibitor. Serum potassium concentrations (primary variable) measured over a 24-hour period on pretreatment Day 1 (prior to first DRSP/E2 dose) and on treatment Day 14 (after last treatment dose) will be evaluated. An assessment of twenty four-hour systolic and diastolic blood pressure (secondary variable) will be obtained on pretreatment Day 1 and Treatment Day 14. Twenty-four (24) postmenopausal women will be enrolled in this double-blind, randomized, two-parallel groups [twelve (12) HRT and twelve (12) placebo] study.

   As stated during the teleconference on December 15th, this study is being conducted under [redacted] For your reference, the protocol was submitted on November 16, 1999 (Serial No. 032). The study began in December of 1999.

Revised Package Insert (PI)
Please note that a revised PI incorporating the Chemistry, Biopharmaceutical and Clinical comments received on December 9th and discussed during the December 15th teleconference will be submitted for your review early next week.

Should you require any additional information or have any questions regarding this submission, please feel free to call me at (973) 276-2305. My fax number is (973) 276-2016.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpoc001

BERLEX

TELEFAX
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ORIGINAL

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December 3, 1999

ORIG AMENDMENT

BL

Lisa Rarick, M.D., Director
DIVISION OF REPRODUCTIVE AND UROLOGIC
DRUG PRODUCTS, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
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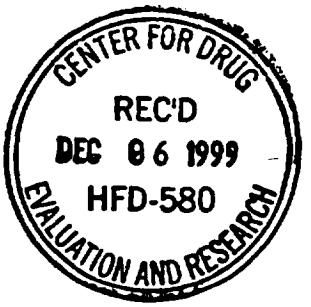

Dear Dr. Rarick:

Re: NDA 21-098 – YASMIN™ 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 Tablets)
OTHER: Electronic Copies of Labeling

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN™ 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 Tablets], an oral contraceptive (OC) product.

Reference is also made to telephone communications between the undersigned and Ms. Jeanine Best of the Division on October 18th and November 22, 1999. Ms. Best asked that Berlex provide electronic copies of the drospirenone 3 mg and ethinyl estradiol 0.030 tablets labeling in Word format and, if possible, also in PDF format. In response to the undersigned's question regarding annotations, Ms. Best replied that annotated copies be provided for the review copies[1] and unannotated copies for the final printed labeling. She stated that one copy of the diskette would suffice.

In response to Ms. Best's request, attached please find one 3.5 inch diskette labeled "DRSP 3 mg/EE 0.03 mg Tablets Labeling" dated December 3, 1999. The diskette contains copies of the labeling, as identified below, for both 21 and 28 tablets:

Blister
Brief Summary Patient Package Insert
Carton
Day Label
Detailed Patient Labeling
Physician Package Insert (both unannotated and annotated[2])
Pouch

[1] An unannotated copy was also requested for the Medical Reviewer
[2] Files identified as "ocpl" and "ocpiann", respectively

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

These electronic files represent the current version of the labeling, as submitted in the original NDA, with the following exceptions:

- **Brief Summary Patient Package Insert:** The trade name "YASMIN" erroneously appeared in the original NDA copy as "YASMINE". This typographical error has been corrected.

- **Carton:** Labeling for three unit cartons only was previously submitted in the original NDA. Labeling for single units has been added. In addition, the labeling for the 3 unit cartons has been revised (consistent with the new 1 unit labeling) with regard to storage conditions in order to be consistent with the new USP definition of controlled room temperature (25°C with excursions permitted between 15-30°C). Also, wording on the carton describing the package and information for the patient has been revised for additional clarity.

- **Physician Package Insert:** As described above, the storage conditions have been changed.

Each of the files is provided in Microsoft® Word 97 SR-1 format, as well as Adobe Acrobat (Exchange™ 3.0) format. Please note that graphics in the PDF files do not translate exactly as they appear in the Word files.

Berlex Laboratories certifies that the diskette was scanned for viruses and is virus free using Network Associates VirusScanNT 4.0.3a created November 24, 1999.

Please note that our proposed trade name, YASMIN™, appears throughout the labeling. Dr. Moo-Jhong Rhee of the Division informed the undersigned in a telephone conversation on November 30, 1999 that the responsibility of approving our trade name was recently transferred from the Labeling and Nomenclature Committee to the Office of Post Marketing Drug Risk Assessment (OPDRA). He assured the undersigned that our name "YASMIN" was transferred by the Division to OPDRA and the Division would inform Berlex when it is approved.

Should you require any additional information or have any questions regarding this submission, please feel free to call me at (973) 276-2305. My fax number is (973) 276-2016.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpoc148

Desk copy: Ms. Jeanine Best

ORIGINAL
ORIG AMENDMENT
BP

BERLEX

UPS OVERNIGHT

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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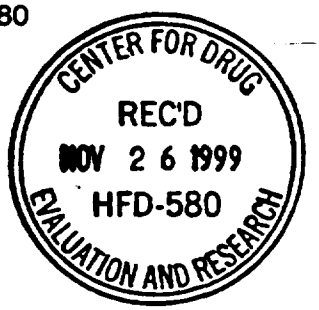
November 24, 1999

Lisa Rarick, M.D., Director
Division of Urologic & Reproductive Drug Products, HFD-580
Office of Drug Evaluation II
U.S. Food and Drug Administration
Parklawn Building, Room 17-B-45
5600 Fishers Lane
Rockville, Maryland 20857



Dear Dr. Rarick:

Re: NDA 21-098 – YASMIN™ 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 Tablets)
AMENDMENT TO PENDING APPLICATION:
Carcinogenicity Data

Reference is made to our pending NDA 21-098 submitted on May 14, 1999 for YASMIN™ 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 Tablets], an oral contraceptive (OC) product.

Reference is also made to [redacted] [Serial No. 024] where carcinogenicity information was submitted on November 5, 1998. Additional reference is made to conversations between the FDA pharmacologists and Berlex Laboratories that took place on January 28, 1999, July 13 & 15, 1999.

As a result of these conversations, Berlex has prepared an amendment which contains: information on plasma protein binding; metabolite patterns; important biotransformation differences between drospirenone and spironolactone; relative exposure based on AUC; results of the mouse and rat dose range-finding studies; results of the mouse and rat carcinogenicity studies; assessment of the dose selection for the mouse and rat carcinogenicity and the conclusions.

A total of three new study reports are provided in Appendix F to support of this amendment

Finally, reference is made to a telephone conversation on November 23 between your representative, Dr. Raheja and the undersigned. During this conversation, Dr. Raheja asked about a GLP statement for the rat study, organ weight information for the rat, histopathology tables; metabolite identification and what studies included an esterase inhibitor. Berlex believes that the attached amendment along with the responses provided by the undersigned has adequately addressed Dr. Raheja's comments.

In the event that the data included in this submission are forwarded to the Carcinogenicity Assessment Committee (CAC) for review, please provide Berlex with the Committee's final report as soon as it becomes available. Should any issues surface during a CAC review, Berlex is ready to meet with the committee to resolve those issues in a timely manner.

This amendment consists of 1 volume. A table of contents immediately follows this cover letter. Page numbers in the table of contents and the amendment refer to the page number in the lower right hand corner.

Should you have any questions regarding this submission, please contact the undersigned at (973) 276-2305.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez
Manager
Drug Regulatory Affairs

Two desk copies: Ms. Jeanine Best, Project Manager

NFV/letter/drspoc147

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

TELEFAX
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ORIGINAL

ORIG AMENDMENT
BB

Drug Development & Technology
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November 19, 1999

Lisa Rarick, M.D., Director
DIVISION OF REPRODUCTIVE AND UROLOGIC
DRUG PRODUCTS, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation & Research
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5600 Fishers Lane
Rockville, Maryland 20857-1706

Dear Dr. Rarick:

Re: NDA 21-098 – YASMIN™ 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 Tablets)
OTHER: Additional Copies of Item 6 and 8 Replacement Pages

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN™ 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 Tablets], an oral contraceptive (OC) product.

Reference is also made to our letter dated November 18, 1999 which was a response to your letter of July 20, 1999. The July 20th letter contained comments and information requests which resulted during the preliminary review of the Clinical Pharmacology and Biopharmaceutics section of our NDA. Additional reference is made to a teleconference held on August 18, 1999 between Dr. Venkat Jarugula and Ms. Jennifer Mercier of the Division and Berlex representatives to discuss these comments in more detail.

In preparing the responses to the July 20th letter, it was necessary to issue replacement pages for Items 6 (Human Pharmacokinetics and Bioavailability) and 8 (Clinical Data) because the NDA contained incorrect information. These replacement pages were included in our November 18th letter for Dr. Jarugula. During the teleconference on August 18th, Dr. Jarugala and Ms. Mercier asked that any replacement pages be provided not only for the Human PK and BA reviewer, but that extra copies be forwarded for the Chemistry and Medical Reviewers.

In accordance with that request and as committed in the November 18th letter, this submission contains two additional copies of the replacement pages for Items 6 and 8 to be forwarded to the Chemistry and Medical Reviewers.

Please note that the original NDA page number appears in the bottom right corner of each page. A dash and the letter "R" have been added to indicate that these are replacement pages.

The **Item 6** replacement pages are as follows:

6 00039-R	6 00099-R
6 00040-R	6 00100-R
6 00045-R	6 00101-R
6 00046-R	6 00103-R
6 00079-R	6 00104-R
6 00080-R	6 00105-R
6 00089-R	6 00111-R

For **Item 8**, individual pages were affected that discussed Reports A951, A733, AI98 and AI99 (Pages 8 00083-R – 86-R, 8 00091-R – 93-R). Because text flow was affected as a result of the added changes on these pages, making it different from what appeared in the NDA, the entire span of pages from 8 00083-R – 8 00098-R, are provided to avoid confusion.

Should you require any additional information or have any questions regarding this submission, please feel free to call me at (973) 276-2305. My fax number is (973) 276-2016.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpoc145

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

AMENDMENT

BB

TELEFAX
UPS OVERNIGHT

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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November 18, 1999

Lisa Rarick, M.D., Director
DIVISION OF REPRODUCTIVE AND UROLOGIC
DRUG PRODUCTS, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706

Dear Dr. Rarick:

Re: NDA 21-098 – YASMIN™ 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 Tablets)
AMENDMENT TO PENDING APPLICATION

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN™ 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 Tablets], an oral contraceptive (OC) product.

Reference is also made to your letter of July 20, 1999 which contained comments and information requests which resulted during the preliminary review of the Clinical Pharmacology and Biopharmaceutics section of our NDA. Additional reference is made to a teleconference held on August 18, 1999 between Dr. Venkat Jarugula and Ms. Jennifer Mercier of the Division and Dr. Monika Wolff and the undersigned of Berlex to discuss these comments in more detail.

This submission amends NDA 21-098 to provide responses to your comments in the letter of July 20th. (A copy of the July 20th letter immediately follows this cover letter for your reference.) The Division's comments are provided first in bold, followed by our responses.

1. **To support the changes in composition and equipment in the to-be-marketed formulation, please provide comparative in vitro dissolution profiles of the clinical trial formulation (SH T 470FA) and the to-be-marketed formulation (SH T 470FA final) in multiple media (Case C profiles as per SUPAC IR guidance).**

DISSOLUTION TESTING

During the teleconference on August 18th, Berlex explained to Dr. Jarugula and Ms. Mercier that in researching the responses to the comments in the July 20th letter, Berlex realized that the NDA contained incorrect information. Dr. Jarugula was informed that the formulation **SH T 470 FA** was never used in clinical trials. The NDA had incorrectly indicated that it was used in the bioequivalence (BE) study (Report A951), and the pivotal European study (Report AI51), as well as some other studies.

Dr. Jarugula was very concerned, primarily because his requests were based on this incorrect information. Berlex told Dr. Jarugula that it is now known that all of the clinical trials in the NDA used the **SH T 470 FA Final** formulation. The BE study compared the clinical service formulation (SH T 470 F) to the final formulation (SH T 470 FA Final, not FA) used in the pivotal European and US clinical trials.

Berlex stated that based on this new information and realizing the intent of Dr. Jarugula's original request in Comment 1 for comparative dissolution profiles to support the changes in composition and equipment in the to-be-marketed formulation, Berlex prepared the "Proposal for Comparative Dissolution Profiles" that was telefaxed to Ms. Mercier on August 16th in preparation for the teleconference (see Attachment 1). Because Dr. Jarugula had not received the telefax prior to the teleconference, Berlex explained that the proposed dissolution testing would be a comparison of two FA Final formulations, one being a pilot scale lot used in the pivotal US study and produced in the [redacted], and the other a production scale lot produced in the [redacted]. After Dr. Jarugula understood what formulations were actually used in the studies included in the NDA, he accepted the Berlex proposal. He said as long as what Berlex told him about the formulations was true and that the dissolution comparison constituted just a site and scale up change, it looked fine[1].

Our parent company, Schering AG, has performed the dissolution testing as agreed during the teleconference on August 18th. The results can be found in Attachment 2 in "Yasmin 30/SH T00470FA/Working Report No. AE2 088.1/99" dated October 23, 1999. Please note that in the Working Report, "SH T00470FA" refers to the SH T 470 FA Final formulation. The distinction between the SH T 470 FA and SH T 470 FA Final formulations is now clarified solely for ease of review where applicable in the summary documents of the NDA. Schering AG will continue to refer to the final formulation as "SH T 470 FA".

CORRECTED PAGES

Dr. Jarugula asked that the incorrect information in Item 6 regarding the formulations used be corrected and the affected pages be sent to him as soon as possible. Both he and Ms. Mercier asked that the CMC (Item 4) and Clinical (Item 8) sections be reviewed to determine if incorrect information with regard to formulation also appeared there and that corrected pages be

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[1] 1. As part of the proposal, Berlex asked to eliminate testing at the pH = 1 (0.1 N HCl) buffer because significant isomerization had been shown to occur rapidly at this pH in vitro. Dr. Jarugala questioned whether isomerization was seen in vivo. Berlex telefaxed a response to this question to Dr. Jarugala on August 20th. On August 31st, Berlex was informed by Ms. Mercier that Dr. Jarugala was satisfied and the testing at pH = 1 did not have to be done.
2. Because water will be Berlex's official method, it was agreed to perform new dissolution testing on 12 tablets/lot rather than rely on the results for 6 tablets/lot previously provided in the NDA.
3. Dr. Jarugala agreed that the sampling times in the proposal were fine with the following clarification: the testing should be continued until both 90% of the drug is dissolved and an asymptote is reached; however, if both were not obtained by 120 minutes, the testing could be stopped.

provided for those reviewers. In any case, they felt that the corrected pages in Item 6 should be forwarded to the Chemistry and Medical Reviewers. Berlex agreed to send any corrected pages from Items 4 and 8 and to send extra copies of the Item 6 pages for the CMC and Medical reviewers.

Corrected pages for each of the three NDA items are discussed below. Again, please note that the distinction between the FA and FA Final formulations is now clarified solely for ease of review where applicable in the summary documents, e.g., the individual study summaries (Items 6 and 8), drug formulation development summaries and tables and comparative dissolution summary (Item 6). Replacement pages for final marketed product production documentation and clinical study reports generated by our parent company, Schering AG, Berlin Germany, will not be issued. Our parent company will continue to refer to the final marketed product as "SH T 470 FA".

ITEM 4 PAGES

Item 4 (CMC) provides drug product information only for the marketed product, SH T 470 FA. In this item, the name "SH T 470 FA" refers to the final formulation of the product which, in other NDA items was referred to as "SH T 470 FA Final". The vast majority of Item 4 (master formulae, master batch records, executed batch records, specifications, methods, certificates of analysis, and stability data) uses the term "SH T 470 FA" when referring to the final market formulation "SH T 470 FA Final". It is not feasible to provide replacement pages for the finalized documents in this Item. In addition, Schering AG will continue to refer to the final marketed product as "SH T 470 FA".

ITEM 6 PAGES

"Final" has been added after the formulation number SH T 470 FA where necessary to distinguish between the formulation SH T 470 FA, which was never used in clinical trials, and SH T 470 FA Final, which is now known to have been used in all of the clinical trials in the NDA.

Pages were corrected in Section 6.4.3.2, DRSP/EE In-Vivo Pharmacokinetic Studies, which contained the individual study summaries for Reports A951, A733, AI98 and AI99. In addition, in Section 6.5, Drug Formulation Development, and Section 6.7.3, Comparative Dissolution, pages were revised.

Attachment 3 contains the NDA pages identified below that were corrected in Item 6. Please note that the original NDA page number appears in the bottom right corner. A dash and the letter "R" have been added to indicate that this is a replacement page:

6 00039-R	6 00099-R
6 00040-R	6 00100-R
6 00045-R	6 00101-R
6 00046-R	6 00103-R
6 00079-R	6 00104-R
6 00080-R	6 00105-R
6 00089-R	6 00111-R

ITEM 8 PAGES

Again, "Final" was added after the formulation number SH T 470 FA where necessary to distinguish it from the SH T 470 FA formulation. Pages were corrected in Section 8.4.5, DRSP/EE Individual Study Summaries of In-Vivo Pharmacokinetic Studies, for Reports A951,

A733, AI98 and AI99 (Pages 8 00083 – 86, 8 00091 – 93). None of the other study summaries in that section were changed but because of the added changes, the text flow was different from that in the original NDA. Therefore, the entire span of pages from 8 00083 – 8 00098, which also includes sections 8.4.6 and 8.4.7, are being provided in Attachment 4 to avoid confusion. As in Item 6, a dash and the letter "R" have been added after the original NDA page numbers to indicate that these are replacement pages.

To accommodate Dr. Jarugula's request that copies of the corrected pages be provided for the Chemistry and Clinical Reviewers, two additional copies of the pages are being sent tomorrow to the Project Manager, Jeanine Best, under separate cover.

2. Please clarify which formulation was used in the supportive trial AJ06.

The formulation SH T 470 FA Final was used in the supportive trial AJ06. The composition of this formulation is described in Item 6 in Volume 39 on page 6 00100. (A replacement page for this page was provided in Attachment 3. The composition of the formulation did not change but, as discussed in the response to Comment 1 above, clinical studies using this formulation were added to the table on this page.)

3. Please provide a complete report on the analytical method validation for drospirenone assay, including cross reactivity information.

A complete separate assay validation was not performed for the DRSP-RIA method. The performance of the assay, particularly with respect to assay specificity, accuracy and precision, was demonstrated in the individual studies. The latter data are summarized as mean values in the individual study reports provided in the original NDA. The individual data have been compiled and are provided in the response to Comment 4 below.

The specificity as well as its own metabolites was assessed in a separate study (Report 6632 – provided in Item 5 of the original NDA and here in Attachment 5). Pooled plasma samples obtained at different times after oral administration of 10 mg of drospirenone to healthy volunteers , using the . At early time points after drug administration (5 to 36 h), the contribution of cross-reacting metabolites was about 2 to 3 % and at later sampling points (72 h), a maximum contribution of cross-reacting metabolites of about 11 % was observed. Therefore, the specificity of the antiserum was regarded as satisfactory for the analysis of drospirenone in pharmacokinetic studies.

The recovery of the extraction procedure of drospirenone from human serum samples was not assessed explicitly during method development. It was shown that the structurally closely related 1,2-dehydro analogue of drospirenone, which was used as antigen for the antiserum production, was almost completely extracted at four different concentrations (0.125, 5, 10 and 1000 ng/ml). The corresponding recoveries were 88.6 %, 84.9 %, 85.2 % and 98.9 %, respectively. Complete recovery of drospirenone after extraction is also confirmed indirectly by the fact that in the actual assays, the included quality controls which were prepared from human serum and evaluated against a standard curve prepared in buffer showed good accordance (deviation less than ± 20%) between nominal concentration values and those actually measured.