CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-355

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA	**21-355**
Submission Date	March 31, 2005
Brand Name	Angeliq™
Generic Name	Drospirenone/Estradiol Tablets
Reviewer	Julie M. Bullock, Pharm.D.
Team Leader	Ameeta Parekh, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation II
ORM Division	Division of Reproductive & Urologic Drug Products
Sponsor	Berlex, Inc.
Submission Type; Code	Complete Response, BZ
Dosing regimen	Once Daily
Indication	Hormone Replacement Therapy

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1 Executive Summary

NDA 21-355 was submitted on December 14, 2001 for Angeliq Tablets (Drospirenone (DRSP) and 17β-estradiol (E2)) for hormone replacement therapy. The dosage submitted for approval in the original submission was [redacted] of DRSP and 1mg of E2 and a non-approvable letter was submitted on October 16, 2002. The sponsor re-submitted a complete response to the non-approvable letter on March 18, 2004 where a lower dose of Angeliq (DRSP [redacted] E2 1 mg) tablets was proposed, and 9 days before the action date the sponsor submitted labeling for Angeliq containing a 0.5 mg DRSP dose. The Division granted approvable status to Angeliq on September 14, 2004 citing deficiencies in the CMC section of the application for the 0.5mg DRSP dose. A type A (End of Review) meeting was held in October 2004 in which questions from the sponsor regarding the approvable action were answered by the Division. At this meeting Clinical Pharmacology requested information on the following:

- Information verifying that the clinical and to-be-marketed formulations of the 1 mg estradiol/0.5 mg drospirenone product are the same
- Information verifying that the PK studies of the 0.5 drospirenone dose involve the same formulation as the to-be marketed product.

On March 31, 2005 Berlex provided a complete response in order to satisfy the deficiencies cited in the September 14, 2004 approvable letter and the address the comments contained in the October 27, 2004 meeting response for the End of Review meeting.

To address the Clinical Pharmacology requested information Berlex provided comparative data on the Clinical formulation and the to-be-marketed formulation. They also included dissolution data that verifies the clinical supply formulation and the to-be marketed formulation are similar according to SUPAC requirements.

Berlex also provided a Phase I drug-drug interaction study to evaluate the interaction potential of DRSP to inhibit CYP3A4 using midazolam as a marker substrate for CYP3A4.

After reviewing the complete response, it can be concluded that the to-be-marketed formulation and the clinical trial formulation are the same, and that there is no meaningful clinical interaction between DRSP and midazolam.

1.1 Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-II) has reviewed the complete response to NDA 21-355 submitted on March 31, 2005. The overall Human Pharmacokinetic Section is *acceptable.*

Julie M. Bullock, Pharm.D.

Ameeta Parekh, Ph.D., Team Leader

2 Question Based Review

2.1 Are the clinical and to-be-marketed formulations of the 1 mg E2/0.5mg DRSP the same?

The film-coated tablet formulation SHT00641AA was used in the clinical studies 96097A and 96081 of the Angeliq development program. The tablet composition is identical to the to-be-marketed film-coated tablet formulation SHD00641A except for the color. Table 1 depicts the composition of the clinical trial tablet (SHT00641AA) to the to-be-marketed tablet (SHT006411A)

TABLE 1: Composition of Angeliq clinical trial and to-be-marketed tablet formulation

Compound	Clinical Trail SH T 00641AA	To-be-marketed SH T 00641A
Drospirenone	0.500 mg	0.500 mg
Estradiol	1.000 mg	1.000 mg
Lactose monohydrate		
Maize starch		
Modified starch		
Polyvidone 25000		
Magnesium stearate		
[redacted]		
Macrogol 6000		
Talc		
Titanium dioxide		
Ferric oxide pigment, [redacted]		

In order to demonstrate that the TBM formulation was equivalent to the CT formulation, dissolution profiling comparing both formulations in different media were performed (Working report No. A26093). Since the original batch of the CT formulation was manufactured in 1996, it was not possible to directly compare with a batch manufactured in 2004. A new batch of CT tablets (Batch #AH037) was manufactured at pilot scale, and compared to one batch of the TBM formulation (Batch #WEA7P3).

Multi-point dissolution profiles were performed in [redacted] ph 4.5, phosphate buffer pH 6.5, phosphate buffer pH 7.5 and water using USP dissolution apparatus II (paddles) with [redacted] The buffer solutions were prepared according to USP. Sampling points were 10, 15, 20, 30, 45 and 60 minutes. All profiles were conducted using 12 individual specimens. The test conditions for the of DRSP and E2 were:

Equipment: Apparatus II (paddles)
Temperature: 37 ± 0.5 °C
Stirring Speed:50 rpm
Volume: 900 mL

Time Intervals:10, 15, 20, 30, 45, 60 minutes

The TBM batch showed a slightly faster dissolution rate for estradiol in all media examined, but the difference and similarity factors calculated from the results were within the requirements outlined in the FDA Guidance for Industry "Dissolution Testing of Immediate Release Solid Oral dosage forms". The active ingredient DRSP was rapidly dissolved in all batches under all conditions investigated. All measurements at 15 minutes were above —— Therefore, the requirements of an immediate release dosage form were fulfilled and no further calculations with respect to the difference and similarity factor had to be performed. The results for estradiol are in Table 2.

TABLE 2: Difference and similarity factors for estradiol.

Dissolution medium	**number of time points**	f_1	f_2
0.1 N HCl	5	5.6	70.2
Buffer pH 4.5	5	5.6	69.1
Buffer pH 6.5	5	1.4	91.3
Buffer pH 7.5	5	1.6	90.6
Water	4	3.7	76.6

2.2 Do the PK studies of the 0.5mg drospirenone dose involve the same formulation as the to-be marketed product?

Two studies (Study 096097A, and Study 96081) used the product containing DRSP 0.5mg. Summaries of the studies and the results pertaining to DRSP can be found in Appendix 1. Both studies used the clinical batch SHT00641AA. In-vivo dissolution proves the clinical trial formulation be the same as the to-be-marketed formulation.

2.3 Does DRSP inhibit Cytochrome P450 3A4?

In vitro DRSP has demonstrated weak to moderate inhibition of model substrate turn over of different cytochrome P450 enzymes. Out of all the CYP enzymes investigated DRSP greatest in vitro inhibitory effect was seen for CYP2C19 and to a lesser extent 2C9 and 3A4. In vivo DRSP did not significantly influence the systemic clearance of omeprazole (substrate of 2C19) or, its 2C19 and CYP3A4 metabolites (see Yasmin NDA 21-098 reviewer: V Jarugula).

Another DDI study using simvastatin as a marker substrate for CYP3A4 did not indicate a clinically relevant inhibition (see Angeliq Original NDA review). In this study 40mg of simvastatin was given as a single dose alone or following multiple dose administration of 3 mg DRSP for 14 days. A mean change of about 15% in $AUC_{0\text{-tlast}}$ for simvastatin was observed with concomitant administration of DRSP and simvastatin compared to simvastatin alone. The confidence intervals did not mean pre-specified equivalence criterion set by the sponsor (70-143%). It was concluded in this study that an absence of a PK interaction between simvastatin and DRSP could not be concluded.

In the current submission a study using the marker substrate midazolam was conducted to study again DRSP's ability to inhibit 3A4. The full review of Study 306946 (report A11620) can be found in Appendix 1.

The study was a placebo controlled steady state crossover study to assess drospirenone's potential to inhibit CYP3A4. Each subject received DRSP 3mg or placebo to steady state and a single dose of midazolam was given on Days 7 and 9. The primary target variable was the mean of Days 7 and Day 9 AUC for Midazolam and its hydroxy-metabolite, 1-hydroxy-midazolam. The 90% confidence intervals for the geometric mean fell with the 70-143% confidence intervals set by the sponsor for bioequivalence, as well as the Agency's 80-125% confidence intervals needed for bioequivalence (see table 3).

TABLE 3: 90% confidence intervals for assessment of bioequivalence

Primary target variable	Mean ratio	Lower confidence limit	Upper confidence limit
Mean of AUC(0-tlast) of MDZ at Day 7 and Day 9	97.9%	90.9%	105.4%
Mean of AUC(0-tlast) of 1'OH-MDZ at Day 7 and Day 9	96.1%	87.4%	105.8%

Analysis of non-averaged Day 7 and Day 9 data was not included in the submission. However, looking at the mean PK from Day 7 to Day 9 (see table 6) there does not appear to be any statistically significant differences (less than 10% difference in Cmax and AUC between Day 7 and 9) in pharmacokinetic parameters within treatment groups. There was also less than 10% difference for AUC and Cmax between MDZ treatment group Day 7 compared to placebo group Day 7, and less than 10% difference between MDZ treatment group Day 9 compared to placebo group Day 9.

In addition to the simvastatin study that provided only marginal increases in simvastatin $AUC_{0\text{-tlast}}$ it would be safe to conclude that DRSP at doses up to 3 mg per day does not potently inhibit CYP3A4 and that dose reductions for substrates of CYP3A4 would be clinically un-necessary.

3 Labeling

The final sponsor agreed upon labeling can be found posted in DFS.

4 Appendix 1

Studies 96097A and 96081 were submitted with the Original NDA submission in 2001. Only the PK details with regards to the DRSP 0.5 mg dose were summarized in this submission. Please see Original NDA DFS reviews by Venkat Jarugula, Ph.D. and Leslie Furlong, M.D. for more details regarding these studies.

4.1 Summary of Study 96097A

Study 96097A (report A02827) was submitted with the Original NDA and was a phase 3, double blind, randomized study comparing the effect of continuous oral estradiol/DRSP combinations and continuous oral estradiol on the endometrium, symptoms, and bleeding patterns in post menopausal women. 1142 women were analyzed for safety and efficacy and the following dosage groups (formulation) were studied:

- 1 mg E2/day (SHT546KB)
- 1 mg E2 + 0.5 mg DRSP/day (SHT00641AA)
- 1 mg E2 + 1.0 mg DRSP/day (SHT00641BA)
- 1 mg E2 + 2.0 mg DRSP/day (SHT00641CA)

- 1 mg E2 + 3.0 mg DRSP/day (SHT00641DA)

Concentrations of estradiol, estrone and DRSP in serum were measured at pre-determined times at baseline, prior to treatment, at the end of the third (day 84), seventh (day 196), and thirteenth (day 364) treatment cycle at predose and 2 hours after dosing. Multiple sampling throughout the study was preformed in order to investigate weather DRSP steady-state levels remain constant over a treatment period of one year.

DRSP serum concentrations increased as expected from predose to 2 hours after administration in all DRSP treatment groups. DRSP serum concentrations showed considerable inter-individual variation between 34 and 72% with no trend with regard to dose and timepoints. Mean DRSP concentrations increased approximately dose-proportionally with increasing DRSP doses.

TABLE 4: Mean DRSP concentrations (ng/dL) at the end of treatment cycles 3, 7, and 13 after daily oral administration of different DRSP doses in combination with 1mg E2.

DRSP dose	Treatment cycle 3		Treatment cycle 7		Treatment cycle 13	
	0 h	2 h	0 h	2 h	0 h	N 2 h
0.5	4.6	6.4	4.2	6.7	3.7	5.9
1.0	9.3	12.2	9.5	12.7	7.1	11.2
2.0	18.4	23.5	19.3	25.3	14.2	24.6
3.0	26.2	37.4	29.6	40.4	24.2	35.2

4.2 Summary of Study 96081

Study 96081 (Report AP01) was submitted with the Original NDA and was a phase 1 single, center, open-label, randomized, intra-individual cross-over study investigating the PK of DRSP and E2 after daily oral administration of different DRSP/E2 combinations over a period of 28 days to healthy postmenopausal women. 36 women were randomized to one of the following dosage groups.

- 1mg E2 + 1 mg DRSP (SHT000641BA)
- 1mg E2 + 4mg DRSP (SHT000641EA)
- 2mg E2 + 1mg DRSP (2 tablets SHT00641AA, 1mg E2 + 0.5 mg DRSP each)
- 2mg E2 + 4mg DRSP (2 tablets SHT00641CA, 1mg E2 + 2.0 mg DRSP each)

Pharmacokinetic parameters were determined after the first and last tablet intake for DRSP, E2 and estrone. The results of the study showed that DRSP reached steady state levels within the treatment period. Dose linearity of the PK was demonstrated for DRSP for doses of 1 to 4mg.

TABLE 5: Mean ± SD steady-state pharmacokinetic parameters of DRSP after daily oral administration of E2 + DRSP.

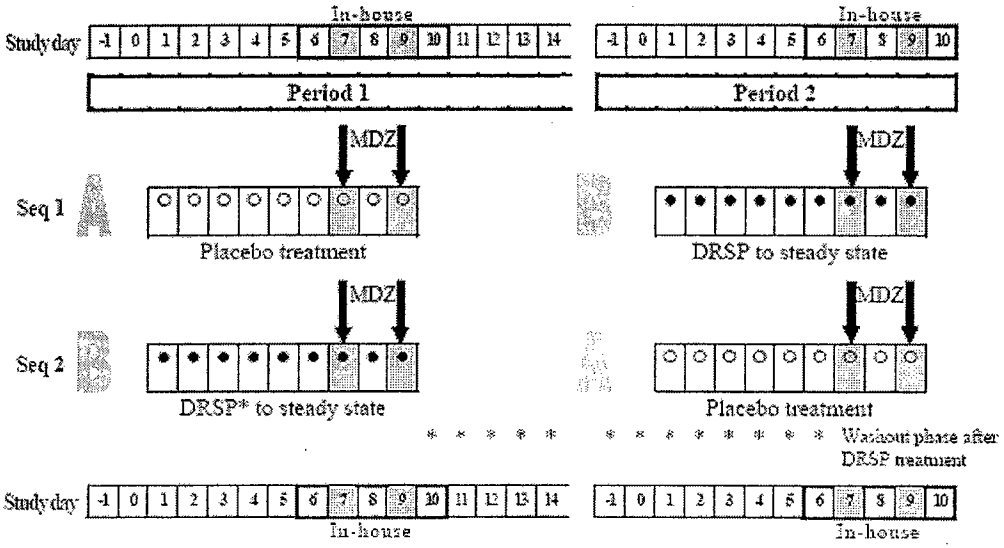
Dose	No. of Subjects	C_{max} (ng/mL)	t_{max} (h)	AUC(0-24h) (ng·h/mL)	$t_{1/2}$ (h)
1mg E2/1mg DRSP	14	18.3±5.55	1.07±0.27	208±83	42.3±21.3
2mg E2/1mg DRSP	15	20.0±6.14	1.03±0.44	210±62	41.1±12.7
1mg E2/4mg DRSP	16	74.2±16.3	1.34±0.89	865±258	35.6±6.30
2mg E2/4mg DRSP	17	93.2±22.2	1.26±0.69	1004±255	38.0±7.30

4.3 Study 036946 (Report no. A11620) review

4.3.1 Study Design

A double-blind, randomized, placebo controlled crossover study in 24 healthy post menopausal women who received midazolam with and without co-administration of DRSP was submitted to investigate the potential effect of DRSP on the in vivo PK of a model substrate for CYP3A4. A schematic of the overall study design is provided below.

FIGURE 1. Study design schematic.



- Test: Treatment B consisted of 2 tablets of 3 mg DRSP in the evening of Day 1, followed by 3 mg DRSP in the morning of Days 2-9. 4mg of Midazolam was given on Days 7 and 9.
- Reference: Treatment A consisted of 2 placebo tablets in the evening of Day 1, followed by 1 placebo tablet daily in the morning of Days 2-9. 4mg of Midazolam was given on Days 7 and 9.

The rationale for administering Midazolam two times (Days 7 and 9) was to reduce the influence of intra-individual variability.

Pharmacokinetic samples were drawn at pre-dose, 0.25, 0.5, 1, 1.5, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours post-dose on Days 7 and 9 for Midazolam and 1'-hydroxy-midazolam. Predose samples for DRSP were taken on Day 1, 6, 7, 8 and 9. Concentrations of MDZ and its 1-hydroxy metabolite in plasma were determined using a validated LC-MS method.

The primary pharmacokinetic variables were

- 1/2 × (AUC of MDZ Day 7 + AUC MDZ Day 9) and
- 1/2 × (AUC of 1'OH-MDZ Day 7 + AUC of 1'OH-MDZ Day 9).

Cmax, Tmax, Thalf and AUC0-tlast (last time point with a concentration above LLOQ) for MDZ and 1'OH-MDZ metabolite were secondary variables.

4.3.2 Results

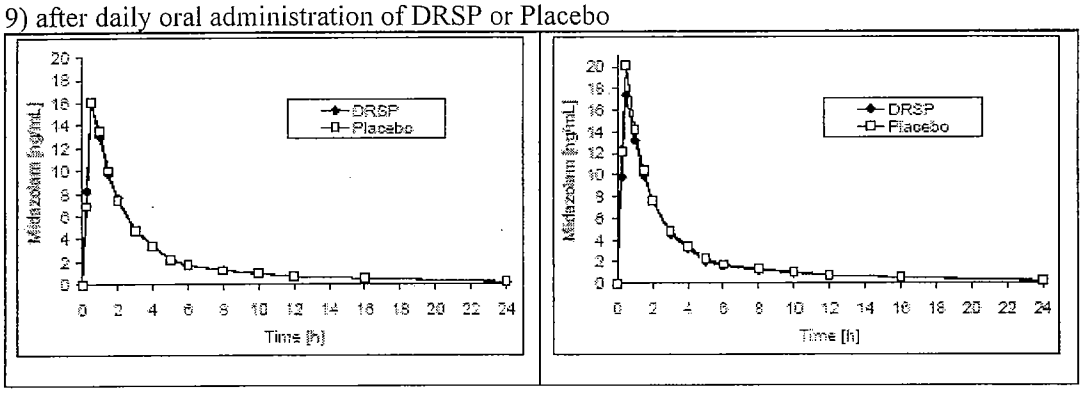
Seventy-seven Caucasian female volunteers were screened and 25 volunteers were recruited and included for randomization at one center. Of these, 24 completed the study, 1 dropped out of the study prematurely (subject received the wrong treatment on Day 7 period 2).

The mean pharmacokinetic parameter results are presented in Table 5 and Figure 2. The mean ratio ($AUC_{0\text{-tlast}}$ Day 7/ $AUC_{0\text{-tlast}}$ Day 9) of the MDZ $AUC_{0\text{-tlast}}$ determined on Day 7 and 9 was 0.986 after DRSP + MDZ treatment and 0.930 after placebo + MDZ treatment. The individual ratios varied between a minimum of 0.812 and a maximum of 1.27 after treatment with MDZ + DRSP. In the placebo treatment the individual ratios ranged from 0.364 to 1.18. Only one subject in the placebo treatment showed a more than two fold increase of the MDZ $AUC_{0\text{-tlast}}$ on Day 9 compared to Day 7 and three other subjects showed 1.3 to 1.5 fold increases. Only two subjects in the DRSP group showed a 1.3 fold higher MDZ $AUC_{0\text{-tlast}}$ on Day 7 as compared to Day 9.

TABLE 6: Mean ± SD Pharmacokinetic parameters for midazolam on Days 7 and 9 after daily oral administration of placebo or DRSP.

	N	Cmax (ng/mL)	tmax (h)	t1/2 (h)	$AUC_{0\text{-tlast}}$ (ng h/mL)	AUC_{inf} (ng h/mL)
MDZ + DRSP Day 7	24	18.3 ± 7.8	0.8 ± 0.4	6.4 ± 1.1	48.2 ± 17.1	52.4 ± 19.0
MDZ + DRSP Day 9	24	19.3 ± 6.92	0.57 ± 0.25	6.69 ± 1.08	48.6 ± 15.1	51.3 ± 16.5
MDZ + Placebo Day 7	24	16.7 ± 6.16	0.69 ± 0.29	6.50 ± 1.23	48.2 ± 19.8	50.4 ± 20.1
MDZ + Placebo Day 9	24	21.3 ± 11.9	0.53 ± 0.2	6.45 ± 1.32	52.7 ± 21.2	55.6 ± 22.9

FIGURE 2. Mean concentration time curves of single doses of MDZ (left: Day 7; right: Day 9) after daily oral administration of DRSP or Placebo

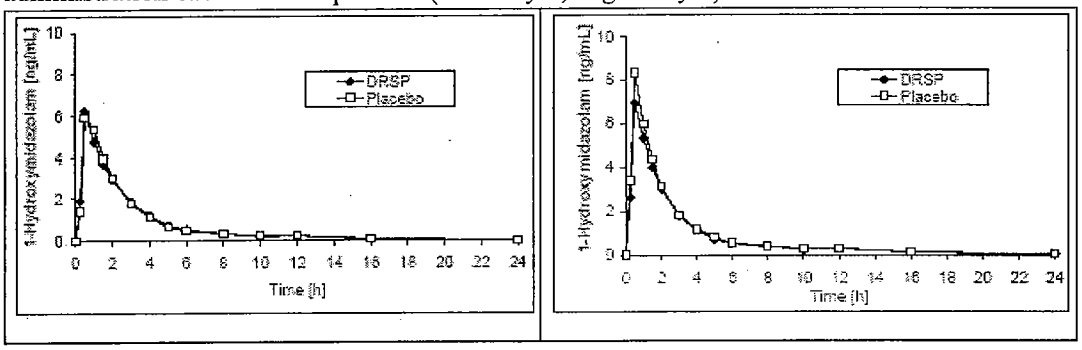


The individual pharmacokinetic parameters of 1-hydroxy-midazolam (1'OH-MDZ) determined on Day 7 and Day 9 are summarized in Table 5. Mean concentration-time values are shown in Figure 3. All pre-dose samples obtained on Day 7 and 9 were below the lower limit of quantification (LLOQ: 0.1ng/mL) indicating absence of carry over from the previous treatment on Day 7. The maximum concentration of 1'OH-MDZ was reached around 0.5 hours in all groups. After oral administration of MDZ with placebo, the 1'OH-MDZ profile results were similar to that obtained after DRSP treatment. The mean metabolic ratios between Days 7 and 9 for both DRSP and placebo were similar concluding that the rate of MDZ biotransformation to 1'OH-MDZ was consistent during treatment and was almost identical in the presence of DRSP and placebo.

TABLE 7: Mean ± SD Pharmacokinetic parameters for 1'hydroxy-midazolam on Days 7 and 9 after daily oral administration of placebo or DRSP.

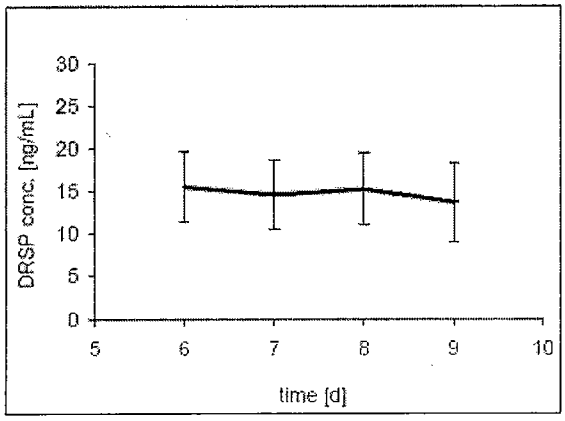
	Cmax (ng/mL)	tmax (h)	t1/2 (h)	$AUC_{0\text{-tlast}}$ (ng h/mL)	AUC (ng h/mL)
MDZ + DRSP Day 7	7.32 ± 3.98	0.79 ± 0.44	2.79 ± 1.03	15.7 ± 5.58	15.0 ± 3.31
MDZ + DRSP Day 9	7.24 ± 3.23	0.65 ± 0.26	3.70 ± 2.31	16.5 ± 6.58	18.4 ± 7.24
MDZ + Placebo Day 7	6.60 ± 2.58	0.75 ± 0.29	5.57 ± 0.77	15.7 ± 6.25	22.9 ± 7.05
MDZ + Placebo Day 9	8.78 ± 5.37	0.66 ± 0.29	4.02 ± 1.84	18.0 ± 7.52	18.5 ± 7.72

FIGURE 3. Mean Concentration-time curve profiles of 1'OH-MDZ after daily administration of DRSP and placebo (Left Day 7, Right Day 9).



The individual serum concentrations of DRSP determined on Days 1, 6, 7, 8 and 9 prior to oral administration of DRSP were about 15.6 ng/mL and remained constant indicating that DRSP concentrations were at steady-state on the days of MDZ treatment (Figure 4).

FIGURE 4. Mean (± SD) DRSP concentration after daily oral administration of DRSP.



The estimate of the mean ratios and their confidence limits for both primary target variables are shown in Table 3. The sponsor used geometric means and bioequivalence confidence limits of 70% to 143% for both primary target variables. The bioequivalence confidence limits set forth in the FDA drug-drug interaction guidance (and bioequivalence guidance) are 80-125% which the sponsor fulfills (See Table 3).

4.3.3 Conclusions

The Pharmacokinetics of midazolam are not influenced by co-administration of DRSP at clinically relevant doses, therefore DRSP does not affect the activity of CYP3A4 enzymes and a metabolic interaction between DRSP and drugs which are predominately metabolized by CYP3A4 is highly unlikely.

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Julie Bullock
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Ameeta Parekh
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BIOPHARMACEUTICS

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA	21-355
Product Trade Name	Angeliq™
Active Ingredients	Drosperinone ___ / estradiol hemihydrate [or estradiol (E2)]1 mg
Formulation	Oral tablet
Indications	Treatment of moderate to severe vasomotor symptoms; vulvar and vaginal atrophy
Sponsor	Berlex
Relevant Submission Dates	18 March 2004; 16 July 2004
Type of Submission	Resubmission; complete response to an NA letter
Reviewer	Leslie Kenna, Ph.D.
Team Leader	Ameeta Parekh, Ph.D.
OCPB Division	DPE-II
ORM Division	Reproductive and Urologic Drug Products

I. Executive Summary

This submission is a complete response to a non-approvable letter dated October 17th, 2002.

The Sponsor is seeking approval of Angeliq™ tablets for the indications "treatment of moderate to severe vasomotor symptoms associated with the menopause" and "treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause", The efficacy of Angeliq™ for the above two indications was established during the first review cycle based on single dose and multiple dose bioequivalence studies, supportive data from other biostudies, and comparative dissolution data relative to Estrace—an approved product for these two indications in postmenopausal women. Product safety concerns regarding the risk of hyperkalemia, thromboembolic events and unreliable endometrial biopsy results were deficiencies identified in the original NA action letter for Angeliq™. It was recommended that the safety concerns be addressed via clinical trials.

In this complete response, the Sponsor has provided the results of two large clinical trials, global postmarketing information, endometrial safety data and an amended package insert.

During the initial review cycle, NDA 21355 was deemed acceptable from the Clinical Pharmacology and Biopharmaceutics perspective. In this resubmission, the Sponsor has not made any changes which could impact the Clinical Pharmacology and Biopharmaceutics review. For example, there has been no change in dose administered nor has there been any change in drug formulation. Refer to the original NDA review in DFS (reviewer: Venkateswar Jarugula) for detailed information on the product's clinical pharmacology and biopharmaceutics characteristics.

This review explores the relation between drospirenone and potassium concentrations.

Recommendation

As during the original review cycle, NDA 21-355 for Angeliq tablets is acceptable from the Clinical Pharmacology and Biopharmaceutics perspective.

Phase IV Commitments

None

II. Table of Contents

III. Summary of Clinical Pharmacology and Biopharmaceutics

Refer to the original NDA review by Venkateswar Jarugula.

IV. Question Based Review

What is the relation between potassium and drospirenone concentration?

Based on data collected in N=113 subjects, potassium concentration has a small dependency on drospirenone concentration in the range of concentrations measured. A mixed effects model for the data predicts a mean change in potassium concentration from 4.354 to 4.508 across the range of drospirenone concentrations observed (0-100 ng/mL). This change is statistically significantly different than zero, however, there may be little clinical significance of this mean change. This change in potassium concentration represents a 3.4% change in concentration—a value that is considerably less than can be attributable to the residual error.

V. Detailed Labeling Recommendations

No revised labeling was sent to the sponsor due to significant clinical issues preventing approval. No labeling recommendations are being made at this time.

VI. Appendices

A. Proposed Package Insert

Refer to sponsor proposed version submitted to Electronic Document Room on March 18, 2004.

B. Cover Sheet and OCPB Filing / Review Form

Does not apply to this resubmission.

C. Individual Study Reviews

• Protocol #305471 (Study Report A08460)

A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety of the Hormone Replacement Therapy Combination Drug Product Drospirenone/Estradiol in Postmenopausal Women With Concomitant Disease and Medication Known to Potentiate the Risk of Hyperkalemia

The data from this study were used to explore the relation between drospirenone and potassium concentration. The protocol for measuring drospirenone and potassium levels in Protocol #305471 was provided in Study Report A08460.

Design

*Dose: 1 mg estradiol hemihydrate [or estradiol (E2)] + 3 mg Drospirenone (DRSP)
*N=231 have measured potassium concentration
*N=113 with potassium (K^+) and drospirenone (DRSP) concentration
*DRSP and K^+ measured in each subject on day: 1, 4, 7, 10, 12, 15, 17, 20, 22, 25, 28
*N=75 non-diabetic; N=48 diabetic

Model Fitting

Based on the saturable behavior of biological systems, a nonlinear mixed effects Emax model was fit to the data.

The K^+ - DRSP relation was evaluated using the following model:

$$C^{K+}_{i,j} = \frac{C^{K+}_{MAX\,i} * C_{Drospirenone}}{C_{50\,i} + C_{Drospirenone}} + \varepsilon_{i,j}$$

Where

$C^{K+}_{i,j}$ = Each potassium concentration in each subject

$C^{K+}_{MAX\,i}$ = Each subject's maximum potassium concentration

$C_{Drospirenone}$ = Drospirenone concentration

$C_{50\,i}$ = Each subject's $C_{Drospirenone}$ at 50% C^{K+}_{MAX}; $N(0,\sigma_{50}^2)$

εij = residual error; $N(0,\sigma^2)$

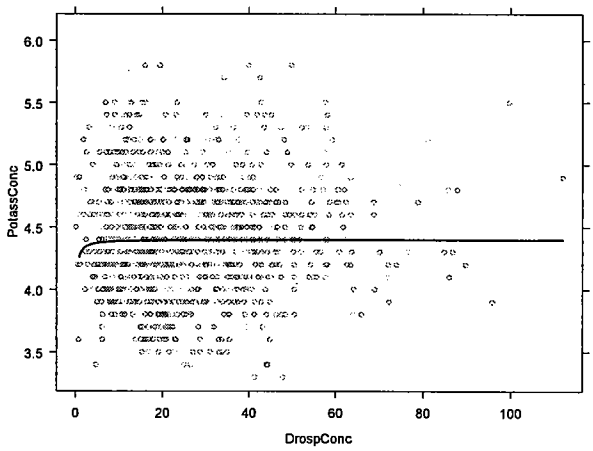
• Table 1 shows that the C^{K+}_{MAX} and C_{50} for Drospirenone are significantly different than zero. It also shows that there is great uncertainty in C_{50} and a large residual error in estimates.

Table 1. Model Parameters for a Nonlinear Mixed Effects Model Relating Drospirenone and Potassium Concentrations.

	Value	sd	p-value
C^{K+}_{MAX}	4.40	$0.274 = \sigma_{K+}$	<0.0001
C_{50}	0.0326	$0.0284 = \sigma_{50}$	0.0097
Residual		$0.273 = \varepsilon_{i,j}$	

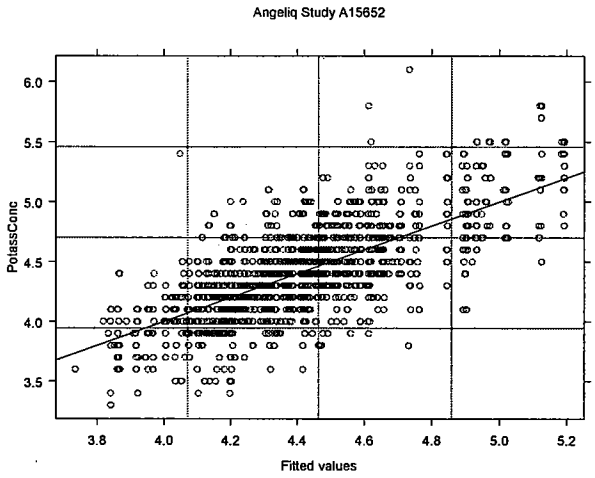
• Figure 1 illustrates the large variability in potassium concentrations observed at a given drospirenone concentration. It also suggests why C_{50} may be hard to estimate. There are few points measured at low concentrations; effect seems to have reached a plateau at the values of drospirenone achieved in the study.

Figure 1. Expected Value of Population Model.



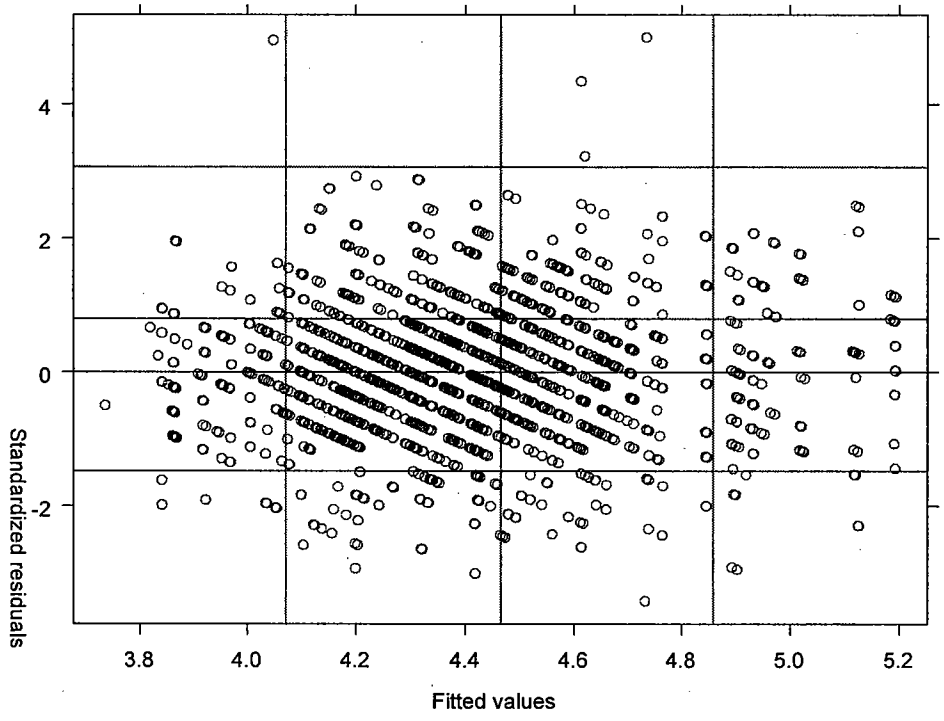
• Figure 2 suggests a poor fit of the model to the data, particularly at low concentrations. The nonlinear model overestimates low concentrations and underestimates high concentrations.

Figure 2. Predicted Versus Measured Potassium Concentration for the Nonlinear Mixed Effects Model.



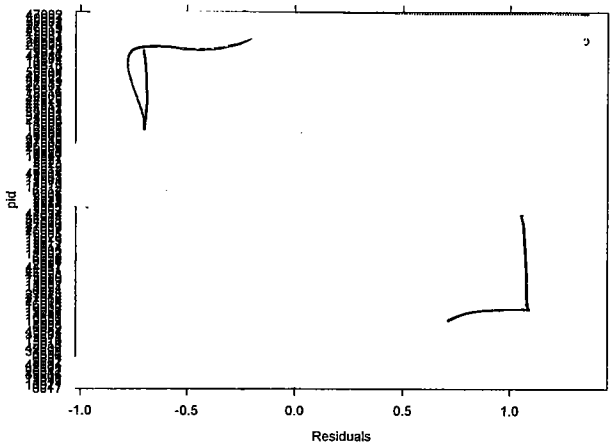
• Figure 3 reveals skewness in the distribution of residual error, indicating model misspecification.

Figure 3. Standardized Residuals Versus Fitted Values.



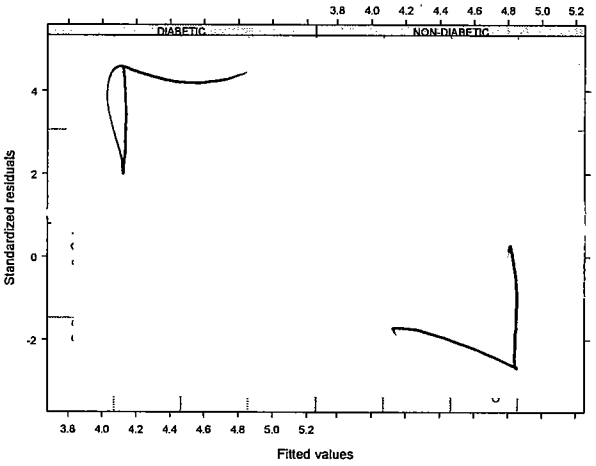
• Figure 4 illustrates the wide variability in each subject's measures.

Figure 4. Residuals for Each Patient (PID).



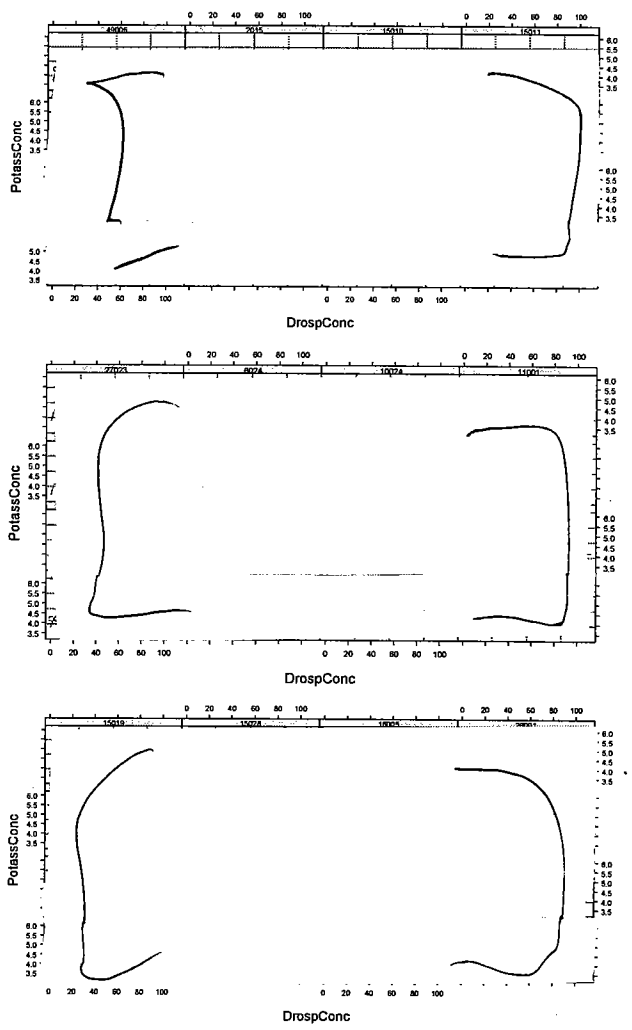
• Figure 5 suggests that there is no difference in variability for diabetic versus non-diabetic subjects.

Figure 5. Standardized Residuals Versus Fitted Values for Diabetic Versus Non-Diabetic Subjects.



• Figure 6 illustrates why it may be so difficult to estimate the Cmax in the model; there are few data points measured in the region of C50.

Figure 6. Individual Observations and Predicted Concentrations for the Linear Mixed Effects Model.



A linear mixed effects model was also fit to the data.
The relation beween K^+ and DRSP concentration was evaluated using the following mixed effects model:

$$C_{Potassium\ i,j} = a + b_i * C_{Drospirenone} + \varepsilon_{i,j}$$

Where:

$C_{Potassium\ i,j}$ = each subject's potassium concentration at a given time
a = intercept; $N(0,\sigma_a^2)$
bi = each subject's slope; $N(0,\sigma_b^2)$
εij = residual error; $N(0,\sigma^2)$
σ_b^2= covariance of observations within an individual; correlation of $\sigma_b^2/(\sigma_b^2+\sigma^2)$

Results:

$$C_{Potassium\ i,j} = 4.354 + 0.00154 * C_{Drospirenone} + 0.2716$$

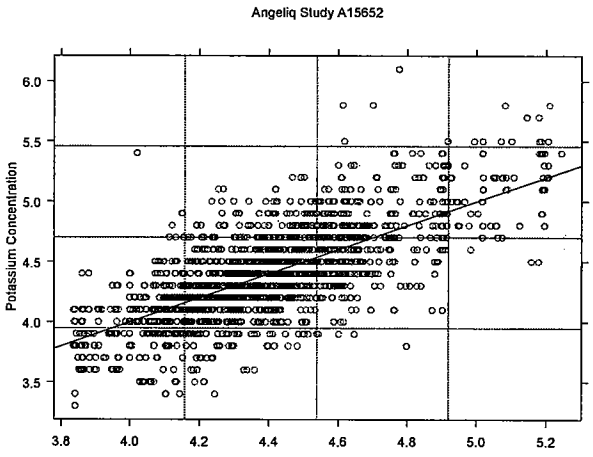
Table 2. Model Parameters for a Linear Mixed Effects Model Relating Drospirenone and Potassium Concentrations.

	Expected Value	Standard Deviation	95% CI	p-value
Intercept	4.354	0.2825 = σ_a	(4.294, 4.413)	<0.001
Slope	0.00154	0.00319 = σ_b	(0.000272, 0.00280)	0.0173
Residual		0.2716 = $\varepsilon_{i,j}$		

Although there is a statistically significant slope for the relation between drospirenone concentration and potassium concentration, the residual error is quite large.

Diagnostic plots for the linear mixed effects model:
• Figure 7 suggests a poor fit of the model to the data. The linear model overestimates low concentrations and underestimates high concentrations.

Figure 7. Measured Versus Predicted Potassium Concentration for the Linear Mixed Effects Model.



• Figure 8 suggests homoscedastic error—error is of a constant value across the range of predictor values.

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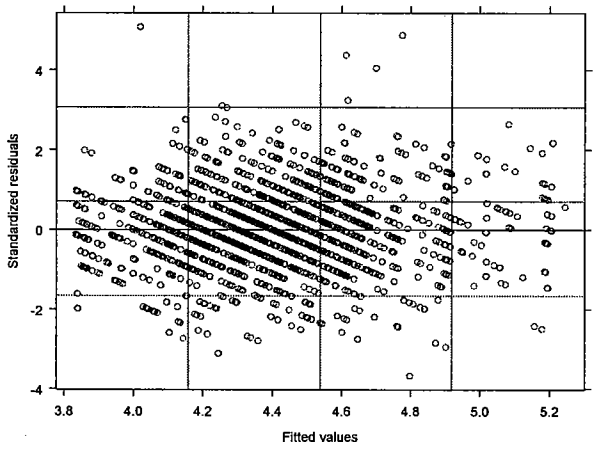
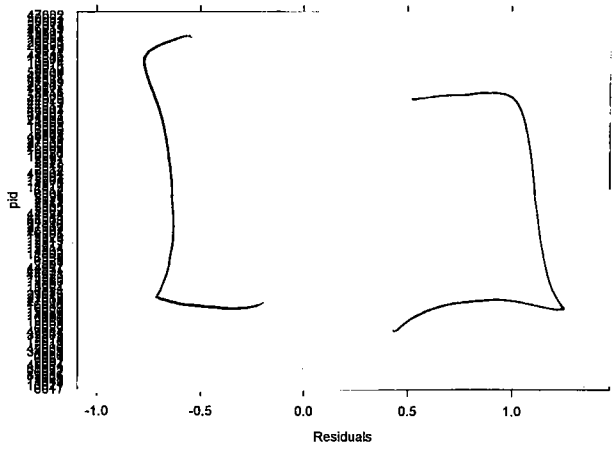
Figure 8. Standardized Residuals Versus Fitted Values



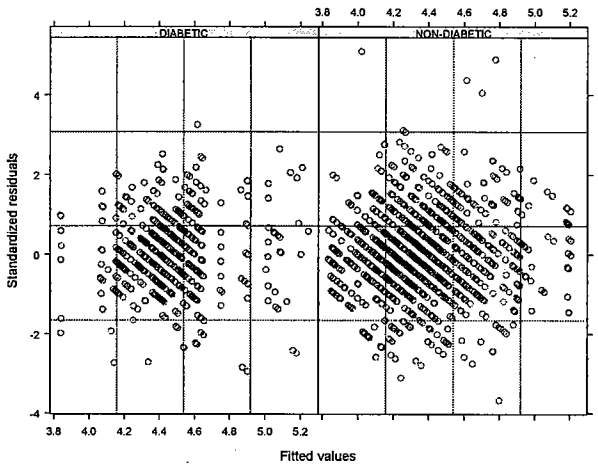
• Figure 9 illustrates the wide variability in each subject's measures.

Figure 9. Residuals for Each Patient (PID).



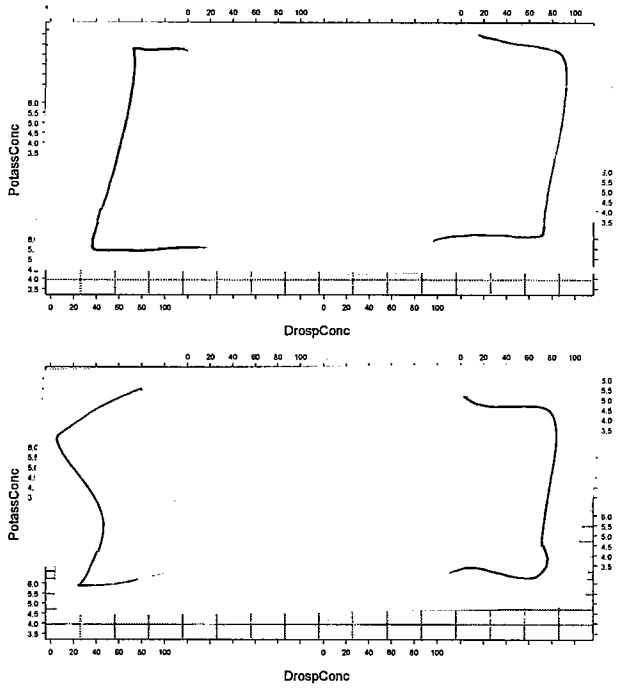
• Figure 10 suggests that there is no difference in variability for diabetic versus non-diabetic subjects.

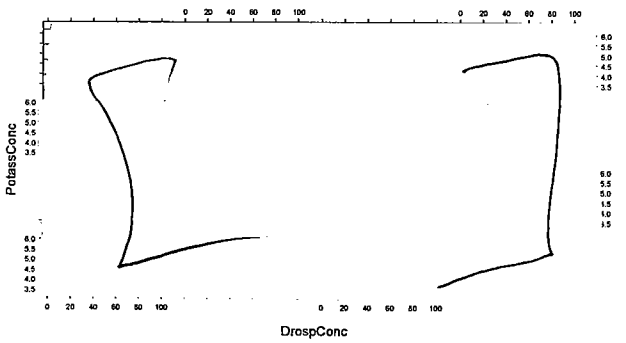
Figure 10. Standardized Residuals Versus Fitted Values for Diabetic Versus Non-Diabetic Subjects.



• Figure 11 illustrates why the model may have difficulty fitting the data. There is wide variability in measures of potassium concentration at a given drospirenone concentration.

Figure 11. Individual Observations and Predicted Concentrations for the Linear Mixed Effects Model.





Across the range of drospirenone concentrations observed (0-100 ng/mL), the model predicts an expected change in potassium concentration from 4.354 to 4.508. This is only a 3.4% change in concentration—a value that is considerably less than can be attributable to the residual error.

Due to such variability, it was not possible to distinguish between a linear or a saturating model.

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/s/

Leslie Kenna
9/14/04 02:25:10 PM
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Ameeta Parekh
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Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA: 21-355

Drug: Angeliq (mg Drospirenone/1 mg Estradiol tablets)

Sponsor: Berlex

Date of Submission: 12/1/4/01, 5/8/02, 7/3/02, 09/05/03 and 09/30/02

Type of Submission: Original NDA (1S)

Reviewer: Venkateswar R. Jarugula, Ph.D.

1 Executive Summary

Angeliq tablets contain drospirenone (DRSP), a synthetic progestin with progestational and antimineralocorticoid activity, in combination with 17β-estradiol (E_2). The proposed indication for Angeliq is hormone replacement therapy (HRT) in postmenopausal women for the treatment of moderate to severe vasomotor symptoms, , and vulvar and vaginal atrophy. The proposed dosing is DRSP/1 mg E_2 tablet once a day. Previously, drospirenone in combination with ethinyl estradiol (Yasmin tablets) was approved as oral contraceptive.

Sponsor submitted a total of seven new pharmacokinetic/pharmacodynamic studies in the Human Pharmacokinetics and Biovailability section of the NDA. In addition, sponsor also resubmitted all the studies (dealing with DRSP and DRSP/EE combination) of previously approved Yasmin in the current electronic NDA. Since these studies have already been reviewed in the NDA for Yasmin (NDA 21098), only new studies regarding combination of DRSP and E_2 have been reviewed here. Synopsis of Clinical Pharmacology and Biopharmaceutics review of Yasmin is included in Attachment 1.

In support of the clinical indication of HRT, the sponsor has not performed a VMS/VVA trial. The sponsor has proposed to acquire the efficacy claims by demonstrating bioequivalence of estrogens from Angeliq to an approved product for HRT indication, Estrace. The clinical division has agreed to this bioequivalence approach during the IND stage. In order to demonstrate bioequivalence of Angeliq Vs Estrace, sponsor has submitted a single dose and a multiple dose bioequivalence studies and comparative dissolution data.

In support of endometrial protection, a Phase III study was conducted to assess the optimal dose of DRSP in combination with 1 mg estradiol (please refer to Medical review).

1.1 Review Comments

Based on the single dose and multiple dose bioequivalence studies, supportive data from other bio-studies and the comparative dissolution data, it can be concluded that estrogens from Angeliq are bioequivalent to Estrace, an approved product for hormone replacement therapy in postmenopausal women. Therefore, the efficacy claims of treatment of vasomotor symptoms and vulvar and vaginal atrophy of Estrace can be extrapolated to Angeliq (please refer to page 9 of this review for more discussion on bioequivalence).

DRSP is rapidly absorbed with plasma concentrations reaching peak level at approximately 1 hour following single oral administration of Angeliq tablets and eliminated rather slowly with a mean terminal half-life of about 36 hours. Peak serum estradiol concentrations were reached at 8-9 hours after single dose administration of Angeliq. The oral relative bioavailability of estradiol and DRSP from Angeliq tablets compared to a combination oral microcrystalline suspension is 101% and 104%, respectively. For more information on ADME of DRSP, please refer to the synopsis of Yasmin review (Attachment 1).

Following multiple administration of Angeliq tablets, steady state concentrations were reached for DRSP and estradiol by 13 days of daily dosing. The steady state pharmacokinetics of DRSP were dose proportional within the range of 1 – 4 mg.

The exposure of DRSP in moderate hepatic impairment subjects is about three times higher compared to normal subjects. There was one subject in the moderate impairment group who experienced hyperkalemia beginning at 72 hours following DRSP administration. This subject had the highest AUC of DRSP in the group. It should be noted that this subject was taking K-Dur and her potassium levels were in the normal range until 72 hours after DRSP administration indicating that DRSP administration might have increased her serum K.
Although no significant difference in serum potassium levels was found between normal subjects group and moderate impairment group, the number of subjects (n=10) may be too small to detect significant difference. The effect of severe hepatic impairment has not been studied. Since there is already a clinical concern for hyperkalemia with DRSP and the exposure of DRSP is higher in moderate hepatic impairment, the labeling for Angeliq should recommend contraindication for liver dysfunction. Clinical division should evaluate the feasibility of clinicians following this labeling recommendation before prescribing Angeliq to postmenopausal women, who will be older than the population that DRSP is currently approved for.

The serum DRSP levels were on average 37% higher in female subjects with moderate renal impairment compared to normal renal function. Moderate renal impairment did not significantly affect the potential of DRSP to cause hyperkalemia. However, the number of subjects may be too small to detect significant effects of hyperkalemia. The effect of severe renal impairment on PK/PD of DRSP has not been studied. Yasmin is contraindicated for subjects with renal dysfunction because of clinical concern for hyperkalemia.

subjects. The feasibility of clinicians following this recommendation in their practice for the patient population should be considered by the Clinical Division.

No pharmacokinetic interaction was found between DRSP and E_2 when these two drugs were administered in combination at doses ranging from 1mg to 4mg of DRSP and 1 mg to 2 mg of E_2.

Pharmacodynamic interaction study with indomethacin showed that there was no significant effect of concomitant administration of DRSP and indomethacin on serum potassium levels. However, it should be noted that more women in DRSP + indomethacin treatment group had serum potassium levels above the upper normal range (4.4 mmol/L) than in the indomethacin alone treatment group. The labeling should caution appropriately for concomitant use of NSAID with Angeliq.

No food effect study was conducted with Angeliq. Sponsor stated that clinical studies with formulations containing DRSP (Yasmin) or E_2 (literature article on E_2/norgestimate tablet) have shown that the bioavailability of both drugs is not affected by concomitant food intake. Since Yasmin formulation is similar to Angeliq, food effect results of Yasmin can be applicable to DRSP component of Angeliq. However food effect results of E_2 in combination with norgestimate from literature article may not be applicable to Angeliq, since the formulation used in the literature study is unknown. Therefore, the labeling should mention that the effect of food on the absorption and bioavailability of Angeliq has not been investigated and state the results of DRSP from Yasmin.

2 RECOMMENDATION

NDA 21355 for Angeliq tablets is acceptable from the clinical pharmacology and biopharmaceutics perspective. Above labeling comments should be considered at the time of approval action.

Venkateswar R. Jarugula, Ph.D.

RD initialed by Ameeta Parekh, Ph.D. , Team Leader _____

FT signed by Ameeta Parekh, Ph.D., Team Leader _____

cc: NDA , HFD-580 (Furlong, Reddy), HFD-870 (Malinowski, Parekh, Jarugula), CDR (B.Murphy for Drug).

CPB Briefing Date: 09/30/02

CPB Briefing attendees: Drs. John Hunt, Ameeta Parekh, Myong Jin Kim, and Lesley Furlong.

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4. Question Based Review

4.1 General Attributes

1. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product? What is the proposed mechanism of drug action and therapeutic indications? What is the proposed dosage and route of administration?

Angeliq tablets contain two steroid hormones: a synthetic progestin, drospirenone (DRSP) and a natural estrogen,17β-estradiol (E_2). DRSP is a synthetic derivative of 17α-spiranolactone, with progestational, and antimineralocorticoid activity. This novel progestin is currently in an approved oral contraceptive called Yasmin (3 mg DRSP + 30 µg Ethinyl estradiol tablets). E_2 is the primary endogenous female sex hormone and has been approved (either alone or in combination with a progestin) in many hormone replacement therapy products for postmenopausal women. Formulation is presented in Biopharmaceutics section of the review.

Scientific rationale and Mechanism of action
The endogenous production of female sex hormones declines during menopause. Estrogen replacement therapy is known to reduce the number of hot flushes, improve urogenital symptoms, and prevent progression of osteoporosis in postmenopausal women. Since, estrogen alone treatment of postmenopausal women with intact uterus has been shown to increase the risk of endometrial hyperplasia and cancer, a progestin is usually added to protect the endometrium against the deleterious effects of estrogen.

Proposed indication and dosage
Angeliq is indicated in women with an intact uterus for the:
- Treatment of moderate to severe vasomotor symptoms associated with menopause
- Treatment of vulvar and vaginal atrophy

The marketing approval is sought for [redacted] DRSP [redacted] in combination with 1 mg estradiol to be taken orally once a day. Sponsor did not specify in the label how to [redacted]

2. What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology and biopharmaceutics study data (e.g., if disparate efficacy measurements or adverse event reports can be attributed to intrinsic or extrinsic factors that alter drug exposure/response relationships in patients)?

The submission contains one phase III study investigating the protective effects on endopmetrium with 1mg estradiol alone and DRSP at four different doses (0.5, 1, 2, and 3 mg) in combination with 1 mg estradiol. The primary purpose of this study is to evaluate the endometrial protection by progestin and the primary endpoint in this study is endometrial hyperplasia. In addition, the relief of vasomotor symptoms such as hot flushes was also studies as secondary objective. However, none of these endpoints were correlated with drug exposure. The effect of hepatic and renal disease on pharmacokinetics of DRSP and on DRSP's potential to increase serum potassium levels have been investigated in two separate clinical pharmacology

studies (please see section on extrinsic factors).

4.2 CLINICAL PHARMACOLGY

4.2.1 How is the efficacy of Angeliq evaluated in the submission?

Bioequivalence
Sponsor has not conducted a separate randomized, placebo-controlled clinical trial for showing efficacy of relief in hot flashes. Rather, sponsor proposed to acquire the relief of vasomotor symptoms indication by showing estrogen bioequivalence of Angeliq to a marketed estradiol alone product (Estrace). This proposal has been discussed with the Division several times and has been accepted (refer to the meeting minutes dated 08/11/98).

In support of bioequivalence, the following was submitted:

- A single dose bioequivalence study that demonstrated bioequivalence of the E_2 from a Berlex single component 2-mg E_2 test tablet with 2- mg Estrace (containing E_2) tablet (Report 94045)

- A multiple dose bioequivalence study that demonstrated the bioequivalence of the E_2 from a tablet containing 2 mg DRSP and 1 mg E_2 with Estrace containing 1 mg E_2 (Report B274)

- In vitro dissolution data linking Berlex single component E_2 formulation to DRSP/E_2 combination tablet (Angeliq).

The above mentioned two bioequivalence studies in combination with comparative dissolution data were used to demonstrate bioequivalence of estrogens in DRSP+E2 and Estrace tablets. This approach was accepted by the Division (refer to FDA meeting minutes dated 8/11/98) and consisted of linking Berlex single component 2 mg E_2 tablet (used in single-dose bioequivalence study) to the E2 component of the 2 mg DRSP+1 mg E2 tablet (used in the multiple dose bioequivalence study) through comparative dissolution data.

Single dose BE study:

This was a single center, open label, single-dose, randomized, 2-period crossover study in 36 healthy female subjects between the ages of 48 and 64 years. The bioavailability of 17β-estradiol (E_2) from a Berlex tablet formulation containing 2 mg E_2 (2x2mg E_2) was evaluated relative to that from Estrace (2x2 mg E_2), the marketed estradiol product, manufactured by Mead Johnson Laboratories, a Bristol-Myers Squibb Company.

Table 1. Mean PK (SD) parameters and bioequivalence

	Test	Reference	Ratio*	90% CI*
Estradiol (baseline corrected)				
Cmax (pg/ml)	95(39)	100 (58)	0.988	89.7 – 108.7
AUC (pg.h/ml)	2721 (1216)	2852 (1315)	0.965	91.5-101.8
Tmax (h)	7.2 (3.3)	7.0 (2.9)		
Free Estrone (baseline corrected)				
Cmax (pg/ml)	911 (325)	842 (310)	1.09	103.5 – 114.6
AUC (pg.h/ml)	18376 (7943)	17821 (8124)	1.04	100.0 – 108.0
Tmax (h)	5.9 (2.2)	6.6 (2.3)		
Total Estrone (baseline corrected)				
Cmax (ng/ml)	108 (29)	78 (22)	1.39	129.5 – 148.7
AUC (ng. h/ml)	843 (283)	814 (276)	1.04	100.3 – 107.2
Tmax (h)	0.9 (0.6)	2.3 (1.6)		

*90% CI and ratios are based on log transformed data

Both estradiol and free estrone (baseline corrected) were bioequivalent between test and reference. However, the total estrone that includes estrone sulfate peak concentration was not bioequivalent. Considering that estrone sulfate (a conjugate) is not active and only serves as a reservoir for actives such as estradiol and estrone (which are bioequivalent), these results are acceptable.

Multiple dose BE study

This was a single center, open label, randomized, multiple dose, 2-period, crossover study in thirty six postmenopausal women (45-65 years). The bioequivalence of estrogens from two tablets of Berlex formulation (2x 2 mg DRSP/1 mg E_2) with that from two tablets of Estrace (2x1 mg E_2) was evaluated in the study following multiple dosing (once a day) for 13 days with a 14 days washout period between treatments.

Table 2. Bioequivalence analysis of pharmacokinetic parameters

	Test (A)	Reference (B)	Ratio (A/B)	90% CI*
Estradiol (baseline corrected)				
Cmax (pg/ml)	148.5 (72.2)	162.6 (67.4)	0.93 (0.23)	83.4 – 96.7
$AUC_{(0\text{-}24h)}$ (pg.h/ml)	2377 (1093)	2595 (1104)	0.91 (0.12)	87.3 – 94.2
Free Estrone (baseline corrected)				
Cmax (pg/ml)	1076 (513)	1111 (525)	0.98 (0.18)	91.8 – 101.4
$AUC_{(0\text{-}24h)}$ (pg.h/ml)	15607 (8149)	17337 (9123)	0.91 (0.15)	86.4 – 94.4
Estrone Sulfate (baseline corrected)				
Cmax (ng/ml)	24.9 (12.6)	23.5 (13.3)	1.12 (0.32)	99.7 – 117.0
$AUC_{(0\text{-}24h)}$ (ng.h/ml)	281 (162)	286 (178)	1.01 (0.24)	91.8 – 104.7

*90% CI based on log transformed parameters.

Steady state conditions for E_2, estrone (E_1), and estrone sulfate (E_1SO_4) serum levels were reached by Day 12 after multiple dose administration. As shown in the above table, at steady state following multiple dosing, estrogens are bioequivalent between Berlex combination product and estradiol alone product.

At steady state, serum SHBG levels did not significantly differ between 2mg DRSP/1 mg E_2 combination and 1mg Estrace administrations. The mean change from baseline (Day 1) serum SHBG levels was 27.1 (SE: 1.27) nmol/L for reference treatment versus 28.3 (SE: 1.37) nmol/L for the test treatment.

Bridging between single dose and multiple dose BE studies:

In the single dose BE study Berlex's single component 2 mg E2 tablets were assessed in comparison to 2 mg Estrace tablets where as in the multiple dose BE study, 2mg DRSP/1 mg E2 combination tablet was evaluated with reference to 1mg Estrace tablets.
The DRSP/E2 combination tablet and the Berlex's single component E2 tablet have identical compositions except for the active components, which are substituted for lactose (see Attachment 3). In an agreement reached with FDA, sponsor proposed to provide dissolution data to link the formulations used in single dose and multiple dose studies. In vitro dissolution data comparison in three media of different pH were provided to link the E_2 component from 2 mg DRSP/1 mg E2 tablet to the Berlex's single component 1 mg E2 tablet.

Table 3. F2 values for dissolution comparison of E2

Comparison	Method	0.1 N HCl	Water	SIF without enzymes
2mg DRSP/1 mg E2 Vs. Berlex 1mg E2 tablets	USP2, 100 rpm, 500 ml	70.4	62.3	58
Berlex E2 2-mg Vs Berlex E2 1-mg tablets	USP2, 100 rpm, 500 ml*		52.7	
Berlex E2 2-mg Vs Berlex E2 1-mg tablets	USP 2, 75 rpm, 500 ml*		60.6	

* medium: 500 ml 0.3% sodium lauryl sulfate.

In vitro dissolution data shows similarity of the dissolution profiles for E2 from the 2 mg DRSP/1 mg E2 combination tablet and the Berlex's single component 1-mg E2 tablet. In addition similarity of the dissolution profiles for the single component 1-mg E2 tablet and the single component 2-mg E2 tablet was also shown. Thus, the results of the single dose BE study with E2 alone formulation can be applicable to the DRSP/E2 combination product.

In summary, Angeliq is shown to be bioequivalent to Estrace based on the following results:

- Following single dose administration, Berlex's 2 mg E_2 tablet is bioequivalent to 2 mg Estrace tablets.

- Following multiple dose administration to steady state conditions, a 2 mg DRSP/ 1mg E_2 combination tablet is bioequivalent to a 1mg Estrace tablet.

- Berlex's 2 mg E_2 tablet formulation (used in single dose BE study) is identical to the Angeliq formulation (used in the multiple dose BE study, 2mg DRSP/1 mg E_2) except for the addition of 2 mg DRSP and change of amount of E_2 by substituting corresponding amounts of lactose (See Attachment 3).

- The 2 mg DRSP/1 mg E_2 tablet formulation (used in multiple dose BE study) is identical to the proposed [redacted]s of 1 mg DRSP/1 mg E_2 and 3 mg DRSP/1 mg E_2 tablets except for DRSP amount that was replaced with lactose.

- The addition of DRSP to Berlex's single component E_2 tablet formulation did not affect the pharmacokinetics of estradiol based on the bioequivalence shown between DRSP/E_2 combination Vs Estrace in the multiple dose BE study. Furthermore, a pharmacokinetic drug interaction study (discussed later in Section 4.4.3 of this review) also showed that DRSP at doses ranging from 1 mg to 4 mg in combination tablets containing E_2 did not affect the PK of estradiol.

- In vitro dissolution of E_2 is similar between the 2 mg DRSP/1mg E_2 combination tablet and Berlex's 1 mg E_2 tablet formulation (see Table 3).

- In vitro dissolution of 2 mg DRSP/1 mg E_2 tablet (used in multiple dose BE study) is similar (based on F2 test) to the proposed ——— strengths of 1mg·DRSP/ 1mg E_2 and 3 mg DRSP/1 mg E_2 Angeliq tablets.

In addition to the bioequivalence approach, sponsor also provided efficacy data regarding the relief of hot flash symptoms in the Phase III study as supporting information. Please refer to the clinical review of the NDA for details. In general this data shows that there is no significant difference between the estradiol (1 mg) alone group and other treatment groups with combination of DRSP (0.5 1, 2, 3 mg) + estradiol (1 mg). However, it should be noted that the entry criterion for subjects did not meet the required baseline weekly hot flash criterion of 50 to 60 hot flashes per week and there is no placebo control group in the study. Therefore, this study was not considered pivotal for efficacy. Nevertheless, this information is supportive of the bioequivalence data.

4.3 Intrinsic Factors
How is PK/PD of DRSP affected by intrinsic factors?

4.3.1 Effect of liver impairment

The pharmacokinetics and safety of DRSP in female volunteers with normal hepatic function or moderate liver impairment (Child-Pugh B) were investigated following single dose administration of a film coated tablet containing 3 mg DRSP and 1 mg E_2. This was an open-label, parallel group, non-randomized study in twenty female volunteers (10 subjects in each group) between the ages 18 and 75 years. Mean serum concentrations of DRSP are illustrated in the following figure.

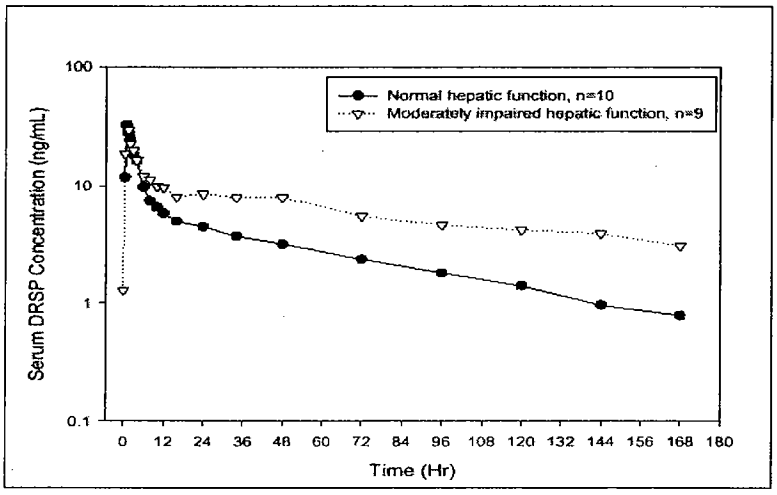

Fig 1. Serum DRSP concentrations in subjects with normal or moderately impaired hepatic function.

Table 4. Effect of hepatic function on arithmetic mean (SD) pharmacokinetic parameters of DRSP:

Hepatic function	C_{max} (ng/ml)	AUC(0-tlast) (hr*ng/ml)	AUC (hr*ng/ml)	Cmaxu (ng/ml)	AUC(0-tlast)u (hr*ng/ml)
Normal (n=10)	35.7 (15.9)	505 (106)	584 (157)	1.19 (0.52)	16.8 (3.54)
Moderate (n=9)*	35.0 (19.3)	1043 (545)	1737 (1508)	1.42 (0.946)	41.1 (23.2)

Hepatic function	t1/2 (hr)	CL/f (ml/min)	Vz/f (L)	CLu/f (ml/min)	Vzu/f (L)
Normal	56 (25)	90 (19)	421 (173)	2725 (634)	12461 (3789)
Moderate	100 (72)	48 (31)	281 (119)	1208 (700)	7233 (2872)

*One subject (#20203) excluded because she took K-Dur during the study.

Based on the above results, the absorption phase of DRSP was not affected by hepatic function. However, the elimination was significantly lower in moderate hepatic impairment group (half-life was double in this group compared to normal). The extent of absorption (AUC of unbound as well as total) was on average about three times higher in moderately impaired subjects compared to subjects with normal hepatic function. Pharmacokinetic analysis was performed with and without subject #20303 data (who took K-Dur) and this subject did not make any difference in the pharmacokinetic results.

It should be noted that severe hepatic impairment has not been investigated in this study. However, the increase of DRSP exposure in subjects with severe hepatic impairment would likely be even higher than those observed in moderate impairment group. Sponsor has recommended contraindication in subjects with severe liver dysfunction.

Pharmacodynamics (Serum potassium)

Individual serum potassium profiles following drug administration in normal and moderate hepatic impairment are shown below:

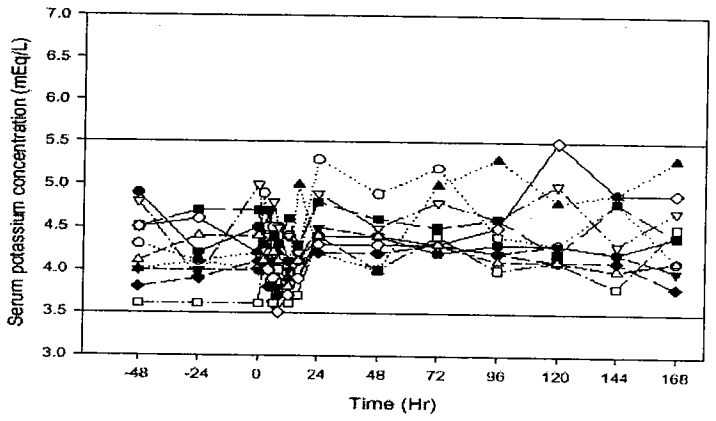

Fig 2A). Individual serum potassium profile for normal hepatic function group

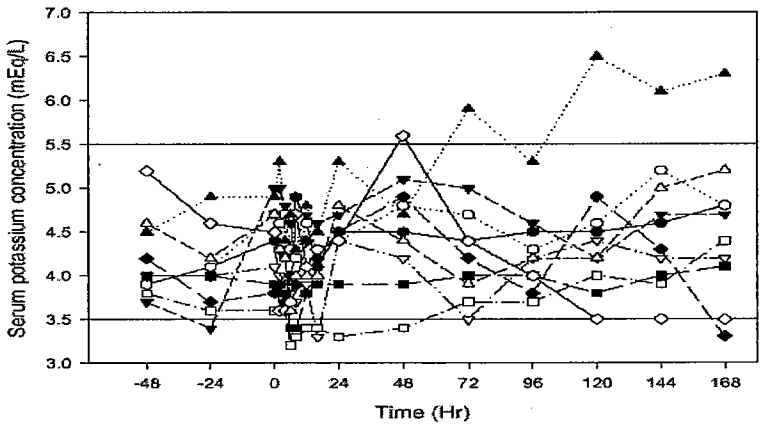

Fig 2B). Individual serum potassium profile for moderate hepatic impairment group

Table 5. Statistical analysis of serum potassium levels

Parameter	Geometric Mean		Impaired/ Normal	p-Value	90% Confidence Limits
	Group 1 Normal Hepatic Function (N = 10)	Group 2 Moderate Hepatic Impairment (N = 9)			
AUC(0-168h) (mEq*h/L)	739.9	716.3	0.968	0.3166	0.917,1.023
Cmax (mEq/L)	4.813	4.845	1.007	0.88	0.934,1.085

As can be seen from the above table, there was no significant effect of hepatic impairment on serum potassium levels following DRSP administration. However, there were two individuals (one in each group) serum potassium levels ≥5.5 mEq/L.

Sponsor excluded subject 20203 from the moderate impairment group because this subject was taking K-Dur in addition to spiranlolactone because K-Dur was an excluded drug in the protocol. This subject had normal serum potassium levels before DRSP administration and her serum potassium levels were raised above 5.5 mEq/L from 72 hours after dosing and the levels were as high as 6.5 mEq/L at 120 hrs following dosing with DRSP. This subject also had highest AUC of DRSP in the group suggesting that hyperkalemia may be associated with DRSP administration.

There were four other subjects in moderate impairment group who also received spiranolactone, but their serum potassium levels did not reach 5.5 mEq/L (hyperkalemic level).

Relationship between maximum serum K levels and the exposure to DRSP is shown in the following figure.

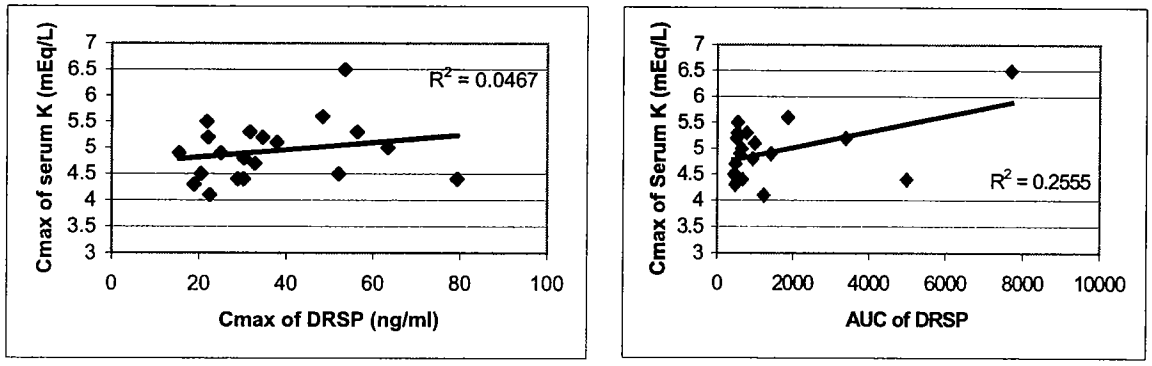

Fig 3. Relationship between DRSP exposure and serum potassium levels

Although there is a weak linear trend, there is insufficient data at high exposure (AUC) of DRSP to conclude a relationship between DRSP exposure and increase in serum K levels. However, subject #20203 who had elevated serum K (hyperkalemia) also had the highest exposure of DRSP in the study, suggesting association between DRSP exposure and hyperkalemia.
Overall, the number of subjects in each group (n=10) is not sufficient to detect any significant differences in serum potassium levels.

4.3.2 Effect of renal impairment

The effect of renal impairment on the pharmacokinetics of DRSP was investigated in female subjects (n = 28, age 30 - 65) with normal renal function and mild and moderate renal impairment. Following multiple daily dosing of DRS 3mg/E1 mg tablets for 14 days, serum DRSP levels in the group with mild renal impairment (creatinine clearance CLcr, 50-80 mL/min) were comparable to those in the group with normal renal function (CLcr, >80 mL/min). The serum DRSP levels were on average 37 % higher in the group with moderate renal impairment (CLcr, 30 - 50 mL/min) compared to those in the group with normal renal function. This study was reviewed in NDA 2109 for Yasmin (please refer to the CPB review of renal impairment study in Attachment 2).

DRSP treatment did not show any clinically significant effect on serum potassium concentration. Hyperkalemia was not observed in the study, in five of the seven subjects who continued use of potassium sparing drugs during the study. However, individual mean serum potassium levels increased by up to 0.33 mEq/L (to 4.67 mEq/L). Therefore, there exists potential for hyperkalemia in subjects with renal impairment whose serum potassium is in the upper normal range, and who are concomitantly using potassium sparing drugs. This information is reported in the labeling for Yasmin and it applies to the Angeliq label also.

4.4 Extrinsic factors
How is PK/PD affected by extrinsic factors?

4.4.1 Pharmacokinetic drug interaction with Simvastatin

An open label, randomized, single center, two period crossover study was conducted in 24 healthy postmenopuasal women to investigate the effect of DRSP on the pharmacokinetics of Simavstatin, used as model substrate for CYP 3A4. Simvastatin (Zocor 40 mg) was given as a single dose alone or following multiple dose administration of 3 mg DRSP for 14 days. The washout period was 7 days in Sequence 1 where Simvastatin was given first and 14 days in sequence 2 where Period one started with DRSP + Simvastatin.

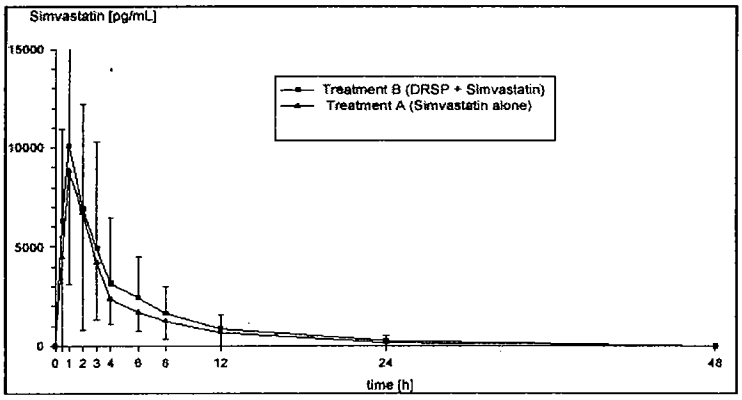

Fig 4. Mean simvastatin concentration time curves with or without DRSP administration.

Table 6. Mean pharmacokinetic parameters of simvastatin and simvastatin acid (metabolite)

PK Parameter	Simvastatin(A)	DRSP + Simvastatin(B)	Ratio(B/A)	Confidence intervals
Simvastatin				
Cmax (ng/ml)	10.9 (6.8)	10.8 (5.7)		
AUC(0-tlast) (ng.h/ml)	35.2 (15.3)	44.7 (31.7)	1.15	89.8% - 146.6%
AUC (ng.h/ml)	38.9 (17.4)	50.9 (34.9)		
T1/2 (h)	3.93 (1.6)	4.98 (1.48)		
Simvastatin acid				
Cmax (ng/ml)	4.3 (2.1)	4.3 (2.0)		
AUC(0-tlast) (ng.h/ml)	26.8 (14.2)	31.9 (21.2)	1.12	90.4% - 138.9%
AUC (ng.h/ml)	31.3 (13.7)	34.9 (24.8)		
T1/2 (h)	4.49 (2.02)	5.5 (2.1)		

Multiple dose administration of 3 mg DRSP with a single dose of simvastatin resulted in slightly higher serum concentrations of simvastatin compared to simvastatin alone administration. A mean change of about 15% in AUC0-tlast was observed with concomitant administration of DRSP. Based on the small magnitude of change in serum concentrations, it can be concluded that there is no clinically significant interaction effect of DRSP administration on simvastatin (CYP450 3A substrate) pharmacokinetics. However, since the confidence intervals did not meet prespecified criterion (70 –143%), sponsor stated that the equivalence of both treatments, i.e. the absence of a pharmacokinetic interaction between simvastatin and DRSP could not be concluded. Nevertheless, DRSP does not seem to cause potent inhibition of Simvastatin, CYP3A4 substrate, as predicted by in vitro inhibition experiments, which were reviewed in Yasmin NDA.

4.4.2 Pharmacodynamic interaction with indomethacin

An open-label, randomized, crossover study was conducted in 32 healthy postmenopausal women, (age 45- 75 years) to evaluate the potential of 1mg E2/3 mg DRSP combination to cause hyperkalemia after repeated oral coadministration with 150 mg (50 mg tid) indomethacin. Because DRSP is similar to spiranolactone, the study also looked at the effect of E2/DRSP on the renal excretion of calcium.
Thirty two healthy postmenopuasal women were randomly assigned to one of the two sequences (AB, BA) and received the following two treatments:

Treatment A: 1 capsule of 50 mg indomethacin, 3 times daily on Days 1 – 5
Total treatment phase : 8 days

Treatment B: 1 tablet of 1 mg E2/3 mg DRSP QD on Days 1- 17
Total treatment phase : 19 days.

Table 7. Statistical analysis of serum potassium measurements

Parameter	Treatment A		Treatment B		Ratio	95% Confidence
	Day 1	Day 5	Day 13	Day 17	(B/A)	intervals
Cmax (mmol/l)	4.31 (0.29)	4.34 (0.26)	4.44 (0.24)	4.37 (0.33)	1.03	98.2% - 100.6%
AUC(0-24h) (mmol.h/l)	95.09 (3.80)	96.07 (4.36)	95.93 (3.57)	96.07 (5.03)	1.01	98.6% - 99.98%

In the current study, serum potassium levels are similar between the two treatments indicating that multiple dose administration of 1mg E2/3 mg DRSP combination concomitant with 150 mg/day of indomethacin do not cause hyperkalemia.

Based on individual observations, twelve volunteers (36.4%) had at least one potassium level above the upper limit of normal (4.4 mmol/l) with E2/DRSP + indomethacin in contrast to one volunteer (3.0%) with indomethacin alone and fourteen volunteers (42.4%) with both the treatments. More individuals with increased serum K values above normal range with E2/DRSP + indomethacin treatment were noted. There was only one volunteer (her value: 5.82 mmol/l)

who had a single potassium level above 5.5 mmol/l (hyperkalemic). This sample was hemolytic (plasma hemoglobin was 157.7 µmol/l).

Based on the results of this study, concomitant administration of Angeliq and indomethacin does not appear cause hyperkalemia in postmenopausal women.

4.4.3 Pharmacokinetic interaction between E2 and DRSP

An open-label, randomized, crossover multiple dose drug interaction study was conducted to evaluate the interaction between estradiol and DRSP. Thirty six (36) healthy postmenopausal women, aged 45-75 years, received the following treatments in randomized fashion:

Treatment A: 1mg E2 + 1mg DRSP/day for 28 days
Treatment B: 1mg E2 + 4mg DRSP/day for 28 days
Treatment C: 2mg E2 + 1mg DRSP/day for 28 days
Treatment D: 2mg E2 + 4mg DRSP/day for 28 days

Each volunteer was randomly assigned to one of 12 treatment sequences in a factorial design; each sequence consisted of an initial treatment phase 1 (treatment A, B, C, or D), a 4-week washout phase and a second treatment phase with alternate treatment.

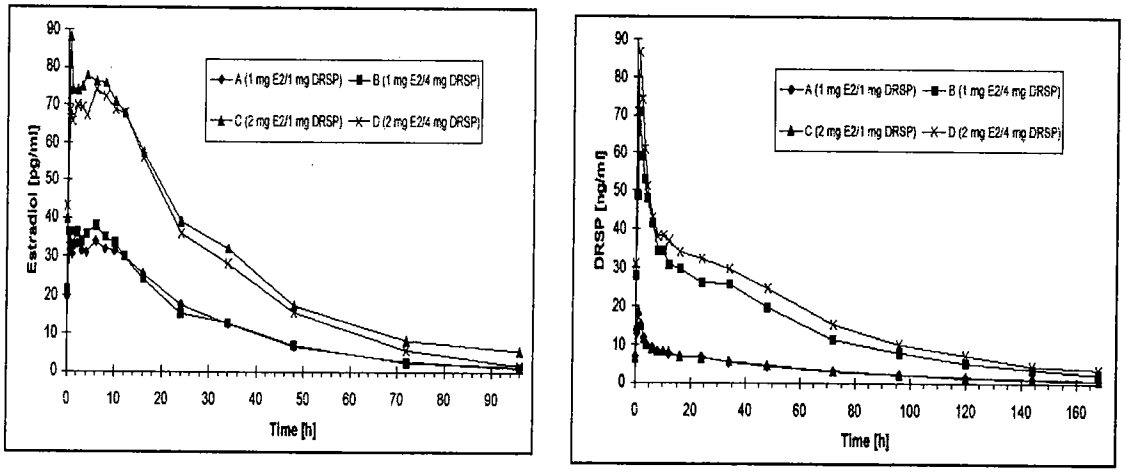

Fig 5. Mean serum estradiol (left) and DRSP (right) concentrations after 28 days of E2/DRSP administration.

Table 8. Mean pharmacokinetic parameters of estradiol

Pharmacokinetic Parameter	Unit	Treatment A	B	C	D
Day 1					
C_{max}	pg/ml	22.3 (1.3)	21.8 (1.5)	40.5 (1.6)	37.1 (1.4)
t_{max}	h	8.0 (0.5-24)	6.0 (0.5-12)	6.0 (0.5-16)	6.0 (0.5-12)
AUC(0-24h)	pg·h/ml	339 (1.3)	346 (1.4)	614 (1.5)	623 (1.4)
Day 28					
C_{max}	pg/ml	42.5 (1.3)	40.8 (1.6)	90.7 (1.7)	78.5 (1.5)
t_{max}	h	2.5 (0.5-12)	4.0 (0.5-8.0)	2.0 (0.5-12)	6.0 (0.5-12)
AUC(0-24h)	pg·h/ml	641 (1.3)	602 (1.8)	1356 (1.7)	1322 (1.6)
AUC(0-tlast)	pg·h/ml	939 (1.6)	835 (2.2)	2222 (2.0)	2010 (1.8)

Table 9. Mean pharmacokinetic parameters of DRSP

Pharmacokinetic Parameter	Unit	Treatment A	B	C	D
Day 1					
C_{max}	ng/ml	11.6 (1.4)	42.5 (1.4)	11.5 (1.4)	50.4 (1.3)
t_{max}	h	1.0 (0.5-2.0)	1.0 (1.0-3.0)	1.0 (0.5-3.0)	1.0 (0.5-3.0)
AUC(0-24h)	ng·h/ml	82.1 (1.2)	319 (1.2)	79.0 (1.3)	337 (1.2)
Day 28					
C_{max}	ng/ml	17.6 (1.3)	72.4 (1.3)	19.2 (1.3)	90.8 (1.3)
t_{max}	h	1.0 (1.0-2.0)	1.0 (0.5-4.0)	1.0 (0.5-2.0)	1.0 (0.5-3.0)
$t_{½}$	h	38.7 (1.5)	35.1 (1.2)	39.3 (1.4)	37.7 (1.2)
AUC(0-24h)	ng·h/ml	194 (1.5)	837 (1.3)	200 (1.4)	975 (1.3)
AUC	ng·h/ml	548 (1.9)	2027 (1.3)	584 (1.7)	2689 (1.4)

Based on the results reported above, DRSP at doses administered (2 mg and 4 mg) did not significantly affect the pharmacokinetics of estradiol of either 1 mg or 2 mg doses. Similarly, E2 at 1 and 2 mg doses did not significantly affect the pharmacokinetics of 2 mg or 4mg DRSP.

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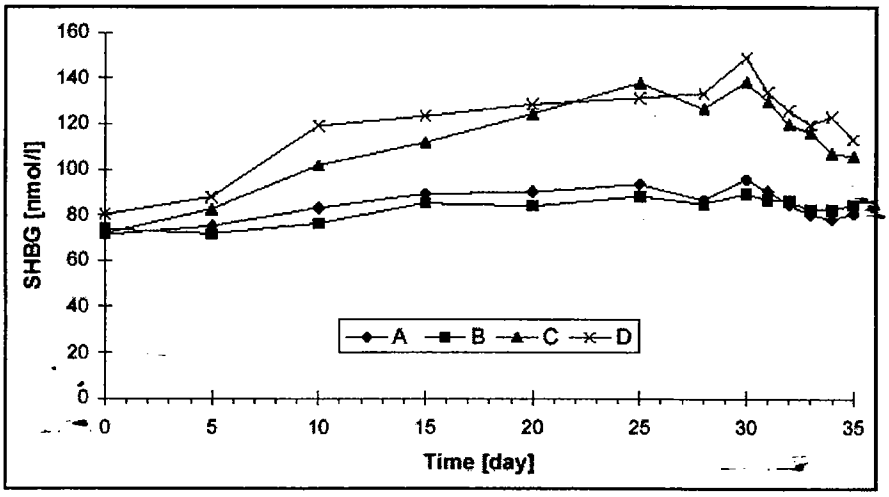

Fig 6. Change in serum SHBG concentrations with E2/DRSP administration.

As expected, estradiol increased the serum SHBG concentrations in a dose dependent manner. Mean serum SHBG levels increased from pretreatment values of 71.3 and 73.8 nmol/l in treatment groups A and B respectively, to 86.7 and 85.1 nmol/l on the last day of the treatment. The increase with Treatment groups C and (2 mg estradiol) was even greater from 71.8 and 80.8 nmol/l to 126.9 and 133.5 nmol/l, respectively.

At steady state, estradiol and DRSP pharmacokinetics were shown to be dose dependent. As expected, there were also dose dependent increases in SHBG with increasing doses of estradiol.

4.5 BIOPHARMACEUTICS

4.5.1 Effect of food

The effect of food on the bioavailability of Angeliq tablets has not been investigated. Sponsor stated that clinical studies with formulations containing DRSP (Yasmin) or E_2 (literature article on E_2/norgestimate tablet) have shown that the bioavailability of both drugs is not affected by concomitant food intake.

A food effect study was submitted in NDA 21-098 for Yasmin and this study showed that there was no significant effect of food on the bioavailability of DRSP, even though the Cmax was decreased (refer to the Yasmin review of NDA 21098). Since Yasmin formulation is similar to Angeliq, food effect study results can be applicable to DRSP component of Angeliq. For E2 component, sponsor referred to a literature article by Gisclen et al (2000) which showed lack of effect on the bioavailability of 17β-estradiol/norgestimate. Since the formulation in the literature article is not reported, these results may not be applicable to E_2 component of Angeliq. Therefore, the label of Angeliq should state that food effect has not been studied and state the results of DRSP from Yasmin food effect study. It should be noted that the Phase III clinical study was conducted without regard to the food intake.

4.5.2 Relative Bioavailability

An open label, randomized, cross over study was conducted to evaluate the relative bioavailability of E2, estrone (E1), and drospirenone (DRSP) from two film coated tablets containing either 1 mg E2 +1 mg DRSP or 1 mg E2 + 3 mg DRSP in comparison with a microcrystalline suspension of 2 mg E2 + 6 mg DRSP after single dose oral administration in healthy post menopausal women.

Table 10. Mean (SD) pharmacokinetic parameters (n=16)*

Parameter	Test 1	Test 2	Ref (solution)
Estradiol#			
C_{max} (pg/ml)	45.8 (14.5)	41.8 (11.3)	59.2 (25.3)
T_{max} (h)	9.2 (4.7)	8.4 (4.3)	2.9 (4.8)
$AUC_{0\text{-}tlast}$ (pg.h/ml)	1324 (617)	1257 (670)	1251 (588)
DRSP			
C_{max} (ng/ml)	29.9 (8.01)	83.6 (14.3)	79.8 (22.4)
T_{max} (h)	1.1 (0.5)	1.4 (0.6)	1.4 (0.5)
$AUC_{0\text{-}tlast}$ (ng.h/ml)	425 (77)	1296 (228)	1244 (241)
$AUC_{0\text{-}inf}$ (ng.h/ml)	473 (98)	1430 (273)	1287 (218)
$T_{1/2}$ (h)	36.4 (6.04)	34.5 (6.42)	33.1 (6.39)

* Two volunteers were excluded from total of 18 subjects because baseline E2 levels were >20 pg/ml.

T1/2 and AUC0-inf of E2 were not determined because of lack of sufficient data points in terminal linear portion

The relative bioavailability of E_2 from Test 1 and Test 2 was 105% and 97% compared to the reference solution. In contrast to the mean E_2 concentration-time curve following treatments Test 1 and Test 2 (tablet formulations), the E_2 concentration profile after reference treatment (microcrystalline suspension) showed a pronounced initial peak (rapid absorption) which was followed by rapid decline and a second peak.

The relative bioavailability of DRSP from Test 1 (dose adjusted) and Test 2 compared to the suspension was 103% and 104%, respectively.

4.5.3 Formulation

The composition of clinical and the [redacted] formulations is included in Attachment 1. Two strengths of combination (1 mgDRSP/ 1 mg E2 and 3 mg DRSP/ 1 mg E2) [redacted] The to be marketed tablet formulations had color change in the coating formulation and all other components of the formulation were identical to the clinical trial formulations. Sponsor stated that the color change was necessary for blinding purposes in clinical investigations. As demonstrated by F2 values >50, the color change in coating formulation did not affect the dissolution characteristics.

The commercial product will be manufactured with scale up at Weimar, Germany, where as pilot batches of clinical trial formulation were manufactured at Berlin, Germany. Dissolution comparison between the pilot and scale up batches in three media and water are provided in Attachment 4. As demonstrated by F2 values between 50 and 100, the dissolution of scale up batches made at Weimar is similar to that of pilot batches manufactured at Berlin except for DRSP 3mg/E2 1mg strength where the dissolution profile at pH 6.5 for pilot batch is significantly lower than for scaled up batch. Sponsor reported a high F2 value (>50) for this comparison. Sponsor was requested to provide an explanation regarding this discrepancy and also to provide justification for dissimilar dissolution profiles of DRSP between pilot and scale up batches. In response, sponsor sent in information (two amendments dated 09/05/02 and 09/30/02) stating that an in valid profile of different formulation was mistakenly incorporated into the report, but the F2 values corresponds to the data of correct formulation. The final comparison data shows that the pilot and scaled up batches have similar dissolution profiles.

4.5.4 In vitro Dissolution

Proposed dissolution method and specifications

Apparatus:	USP 2 (Paddle)
Medium:	Water
Volume:	900 ml
Paddle speed:	50 rpm
Temperature:	37 ± 0.5^0C

Proposed specifications: Q = ⁻ % at — minutes for estradiol and Q=—% at · — minuets for DRSP.

Based on the in vitro dissolution data for clinical trial batches (see attachment 3), specification of Q=—% at 30 minutes for estradiol and Q=— % at 30 minutes for DRSP were recommended and the sponsor agreed to adapt these specifications in their July 16, 2002 amendment.

4.6 Analytical methodology

Serum concentrations of DRSP were measured radioimmunoassay (RIA). The same method was used in the NDA for Yasmin (DRSP/EE tablets) and was reviewed previously (refer to the original Clinical Pharmacology Review of NDA 21-098). The accuracy of RIA was within accepted range of 80- 120% of the nominal DRSP concentration. The intra and inter assay coefficients of variation were below 20% for the QC at the lower limit of quantitation (LOQ = 200 pg/ml) and below 15% at higher concentrations. The cross reactivity to 17β-isomer of DRSP was about 0.2%.

A validated GC/MS method was used to measure serum concentrations of estradiol (E2) and estrone (E1). An LC/MS/MS method was used to measure estrone sulfate (E1SO4) concentrations. The LOQ of E2, and E1 were 2.5, 5.0 pg/ml, respectively and for E1SO4, it was 0.250 ng/ml. The precision and accuracy of these analytes were below 20% and the assay method was found acceptable.

It should be noted that DSI audit of pivotal bioequivalence was requested and the DSI concluded that the study conduct and the analytical methodology was acceptable (please see DSI report in attachment).

Attachment 1
(Clinical Pharmacology and Biopharmaceutics Review of Yasmin, NDA 21098)

APPEARS THIS WAY
ON ORIGINAL

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-098

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

I SYNOPSIS

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

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

The results submitted in the NDA showed that:

Drospirenone (DRSP) and ethinyl estradiol were rapidly absorbed from the tablet formulation with maximum plasma concentrations occurring between 1 and 3 hours after oral administration.
The absolute bioavailability of DRSP (from DRSP alone tablets) was 76 ± 13%. Following single dose administration of Yasmin, the relative bioavailability of DRSP and EE was 107% and 117%, respectively, compared to a suspension.
The pharmacokinetics of DRSP was dose proportional in the range of 1 – 10 mg, following oral

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

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

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

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

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

Reviewer Comments

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

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

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

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

II RECOMMENDATION

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

Reviewer	Date	Reviewer	Date
_____	_____	_____	_____

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

Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

Final version signed by Ameeta Parekh, Ph.D., Team Leader _____

cc NDA 20-713:

HFD-870:	Shiew-Mei Huang Ameeta Parekh Monique Wakelkamp-Barnes Venkat Jarugula
HFD-580:	Jeanine Best Dena Hixon
CDR:	Barbara Murphy

Attachment 2
(CPB review of Renal Impairment study)

APPEARS THIS WAY
ON ORIGINAL

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

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

Synopsis

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

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

Renal Impairment Study (B682):

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

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

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

In total 28 subjects were enrolled. Subjects were classified in various renal function groups based on their creatinine clearance (CrCL) values. For screening, a preliminary classification was carried out using the Cockroft-Gault formula to estimate CrCL value. The final group allocation

was based on 24-hour CrCL measured in the pretreatment phase (baseline). In cases where the CrCL estimated at screening differed from the 24-hour clearance at baseline, the value measured at baseline in 24-hour urine was used for group assignment. Each subject was administered one tablet (batch # SH T00470R) containing 3 mg DRSP daily for 14 days (see the attached study synopsis for more details on the design and methods).

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

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

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

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

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

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

The exposure for DRSP in normal renal function group of this study is found to be lower (approximately 30% lower) than that observed in other multiple dose studies that were previously reviewed in the original NDA. Since, Yasmin is contraindicated in patients with renal insufficiency, this may not be an issue.

Bioequivalence analysis of serum potassium levels from ACE inhibitor drug interaction study (98106):

Yasmin tablets contains 3 mg DRSP and 35 μg ethinyl estradiol (EE) and have been developed for contraceptive indication. Berlex is currently developing another drug product containing DRSP and estradiol (E2) for hormone replacement therapy under IND 53,842. As part of the development program for this IND, Sponsor conducted a double-blind, randomized, two-parallel groups, placebo controlled study to evaluate the potential for developing hyperkalemia when DRSP is administered as DRSP 3mg /estradiol 1 mg (for hormone replacement therapy indication) in 24 postmenopausal women who were on ACE inhibitor (enalapril maleate, 10 mg twice daily). Twenty-four hour serum potassium levels were measured at baseline (pretreatment Day 1) and on Day 14. Predose serum levels of DRSP were measured on Day 12, 14 and 15 by radioimmunoassay.

The primary variables were $AUC_{0\text{-}24h}$ and C_{max} of serum potassium on Pretreatment Day 1 (baseline) and after administration of DRSP/E2 or placebo on Day 14. These primary variables were analyzed using analysis of covariance (ANCOVA) with baseline values as covariates. It was assumed that the variables were lognormally distributed. The 90% confidence intervals were determined for the ratios of log transformed Cmax or AUC for DRSP treatment and placebo treatment.

Parameter for serum potassium	Adjusted geometric mean		D/P ratio*	P-value	90% confidence intervals
	Placebo N=12	DRSP/E2 N=12			
Cmax (mEq/L)	4.448	4.248	0.955	0.091	0.914, 0.999
$AUC_{(0\text{-}24h)}$ (mEq*h/L)	88.32	89.16	1.010	0.809	0.944, 1.080

*D=DRSP/E2; P=placebo

The 90% confidence intervals for ratio of DRSP/E2 treatment and placebo treatment for both Cmax and AUC were well within the 80 to 125% limits, the agency set criterion for the bioequivalence of pharmacokinetic endpoints. However, it should be noted that the serum potassium measured in this study is a pharmacodynamic endpoint for which the confidence interval limits of bioequivalence may be different. Therefore, for the clinical significance of the differences in potassium levels of this study, please refer to the clinical review.

There were also differences in the design and statistical analysis of results in this study when compared to a typical bioequivalence study. This study was a parallel design with one period whereas the typical bioequivalence study would be a two sequence, two period, crossover design. Typically ANOVA is performed in bioequivalence analysis, whereas ANCOVA was done (with baseline serum potassium as covariate) in this study. Since serum potassium is pharmacodynamic marker with a variable baseline, ANCOVA is deemed adequate for statistical analysis.

The formulation and the drug combination used in this study (DRSP/E2) are different from that of Yasmin. However, the serum trough concentrations of DRSP at steady state from this study

were approximately 25 ng/ml (as reported in IND 53,842 serial No. 045) and are comparable to the levels reported in the original NDA for Yasmin. Therefore, the results (DRSP effects on serum potassium) from this study have been extrapolated to Yasmin.

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

Recommendation

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

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

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

___1___ Page(s) Withheld

___X___ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Clin Pharm/Bio-*___1___

Attachment 4 (Dissolution (F2) comparison of scale up versus pilot batches)

Text Table 34: Difference and similarity factor for comparison of SH T00641B and SH T00641BA in different dissolution media

Media	Difference factor f_1 in %		Similarity factor f_2 in %	
	Drospirenone	Estradiol	Drospirenone	Estradiol
0.1 N HCl	2.6	7.0	77.2	60.3
buffer pH 4.5	0.5	8.3	95.8	58.5
buffer pH 6.5	1.5	4.8	79.0	68.5
buffer pH 7.5	8.7	2.0[1]	51.3	68.9[1]
Water	1.0	5.1	89.4	66.8

[1]The coefficient of variation is greater than 20% at the 10-minute timepoint and greater than 10% at the 20- and 30-minute timepoint for estradiol in SH T00641BA and greater than 20% at the 10-minute timepoints for estradiol in SH T00641B.

Text Table 35: Difference and similarity factor for comparison of SH T00641C and SH T00641CA in different dissolution media

Media	Difference factor f_1 in %		Similarity factor f_2 in %	
	Drospirenone	Estradiol	Drospirenone	Estradiol
0.1 N HCl	1.0	5.8	88.4	63.0
buffer pH 4.5	1.1	2.1	75.4	82.6
buffer pH 6.5	2.4[1]	4.6	75.0[1]	65.7
buffer pH 7.5	0.7	0.9[1]	68.0	80.2[1]
Water	0.3	2.4	97.1	78.3

[1]The coefficient of variation is greater than 10% at the 20-minute timepoints for drospirenone in SH T00641C and greater than 20% at the 10-minute timepoints for estradiol in SH T00641CA.

Text Table 36: Difference and similarity factor for comparison of SH T00641D and SH T00641DA in different dissolution media

Media	Difference factor f_1 in %		Similarity factor f_2 in %	
	Drospirenone	Estradiol	Drospirenone	Estradiol
0.1 N HCl	4.2	0.0	62.9	91.7
buffer pH 4.5	1.9	2.0	74.5	72.9
buffer pH 6.5	1.4	2.7	87.5	73.4
buffer pH 7.5	1.4	4.7	89.7	67.5
Water	1.0	4.4	85.8	64.7

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Attachment 5 (Dissolution data for clinical batches)

Text Table 31: Drug Product Dissolution Testing

Batch No. (Report No./Study No.)	Dosage Form, Strength, and Schering AG Batch No. (Berlex Lot No.) Formulation	Date of Test	Dissolution Apparatus	Volume/ Media/ Temperature	Speed of Rotation (rpm)	Time (min.)	No. of Units	Active	Range (%)	Mean % Label Claim Dissolved	% CV
B274 (97071)	Test FC[1] tablet DRSP[2]=2 mg E2[3]=1 mg 6421 (CL2149) SH T641 CA	07/21/97	USP Apparatus 2	500 mL Water 37°C	100	5	12	E2		64.1	17.2
						10	12	E2		98.2	3.8
						20	12	E2		99.8	1.2
						30	12	E2		99.7	1.4
						60	12	E2		100	0.9
	Reference Estrace® Tablet E2[3]=1 mg A7J032 (CL2155)	6/4/98	USP Apparatus 2	500 mL Water 37°C	100	5	12	E2		50.4	16.8
						10	12	E2		71.0	6.18
						20	12	E2		83.1	2.25
						30	12	E2		85.4	2.17
						60	12	E2		88.5	2.04
94045 (307-11)	Test Tablet E2[3]=2 mg A219/340031 (CL1869) SH T546L	NA	USP Apparatus 2	500 mL Water 37°C	100	10	12	E2		41.4	15.7
						20	12	E2		51.2	3.96
						30	12	E2		54.7	2.43
						60	12	E2		58.3	1.49
	Reference Estrace ® tablet E2[3]=2 mg MCA24 (CL1885)	NA	USP Apparatus 2	500 mL Water 37°C	100	10	12	E2		22.5	10.0
						20	12	E2		31.8	7.36
						30	12	E2		37.4	5.67
						60	12	E2		47.2	3.67

[1]Film coated, [2]Drospirenone, [3]Estradiol, NA=Not available

Text Table 32: Drug Product Dissolution Testing

Batch No. (Report No./Study No.)	Dosage Form and Strength Schering AG Batch No. Formulation	Date of Test	Dissolution Apparatus	Volume/ Media/ Temperature	Speed of Rotation (rpm)	Time (min.)	No. of Units	Active	Range (%)	Mean % Label Claim Dissolved	% CV
AP01 (ME96081)	Treatment A Tablet DRSP[1]=1 mg E2[2]=1 mg 6421 SH T641 BA	02/1997	USP Apparatus 2	900 mL, 0.3% SDS in water, 37°C 900 mL Water	100	60	6	DRSP E2		102.8 99.4	2.2 1.5
	Treatment B Tablet DRSP[1]=4 mg E2[2]=1 mg AA005 SH T641 EA	03/1997	USP Apparatus 2	900 mL, 0.3% SDS in water, 37°C	100	60	6	DRSP E2	NA	92.2 93.9	4.0 2.0
	Treatment C Tablet DRSP[1]=0.5 mg E2[2]=1 mg 6421 SH T641 AA	02/1997	USP Apparatus 2	900 mL, 0.3% SDS in water 37°C	100	60	6	DRSP E2	NA	103.2 99.7	0.5 0.6
	Treatment D Tablet DRSP[1]=2 mg E2[2]=1 mg 6421 SH T641 CA	02/1997	USP Apparatus 2	900 mL, 0.3% SDS in water 37°C	100	60	6	DRSP E2	NA	99.9 98.7	1.4 1.3

[1]Drosperione; [2]Estradiol; NA=Not available

Text Table 33: Drug Product Dissolution Testing

Batch No. (Report No./Study No.)	Dosage Form and Strength Schering AG Batch No. Formulation	Date of Test	Dissolution Apparatus	Volume/ Media/ Temperature	Speed of Rotation (rpm)	Time (min.)	No. of Units	Active	Range (%)	Mean % Label Claim Dissolved	% CV
AX19 (ME97066)	Test 1 Tablet DRSP[1]=1 mg E2[2]=1 mg 80303 SH T641 B	02/1999	USP Apparatus 2	900 mL/ Water/ 37°C	50	5	6	DRSP		44.6	14.3
								E2		34.9	15.7
						10	6	DRSP		69.3	6.2
								E2		68.4	7.2
						20	6	DRSP		99.3	1.8
								E2		85.3	2.8
						30	6	DRSP		98.5	1.6
								E2		89.9	1.7
						45	6	DRSP		98.8	1.4
								E2		93.6	2.0
						60	6	DRSP		98.6	1.2
								E2		94.7	1.3
	Test 2 Tablet DRSP[1]=3 mg E2[2]=1 mg 80301 SH T641 D	02/1999	USP Apparatus 2	900 mL Water 37°C	50	5	12	DRSP		41.6	11.9
								E2		37.4	12.8
						10	12	DRSP		83.8	7.7
								E2		73.2	8.4
						20	12	DRSP		97.6	2.0
								E2		89.2	4.6
						30	12	DRSP		97.3	1.8
								E2		92.3	4.5
						45	12	DRSP		96.8	1.5
								E2		96.0	3.9
						60	12	DRSP		96.2	1.6
								E2		96.2	4.1

Attachment 5
(DSI audit report of multiple dose BE study)

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MEMORANDUM

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

DATE: August 20, 2002

FROM: Martin K. Yau, Ph.D.
Pharmacologist
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. _____
Associate Director, Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 21-355
Angeliq® (Drospirenone/17ß-Estradiol) Tablets
Sponsored by Berlex Laboratories

TO: Daniel Shames, M.D.
Director, Division of Reproductive and Urologic Drug Products (HFD-580)

At the request of HFD-580, the Division of Scientific Investigations conducted an audit of the following bioequivalence study:

Protocol 97071: Study for the Evaluation of the Bioequivalence of 17ß-Estradiol from a Tablet, Containing Drospirenone (2 mg) and 17ß-Estradiol (1 mg), Relative to Estrace® (1 mg) Tablet, a Marketed 17ß-Estradiol Product.

The clinical portion of the study was conducted by [redacted] The analytical portion of the study was conducted by [redacted].

Following the inspection of the clinical site (6/10-14/02) and the analytical site (5/13-15/2002), Form 483 was issued at each site. The objectionable items and our evaluation of the findings are as follow:

Clinical Site: [redacted]

1. **The screening ECG for subjects 027 and 028 were annotated to indicate that the sponsor was notified of abnormal findings and approved their inclusion in the study. However, there is no documented evidence showing that the sponsor approved the enrollment of these subjects.**

2. **ECG for subject 19 at discharge showed premature ventricular contractions not present at screening ECG. Both ECGs were reported as normal to the sponsor on the case report form.**

The site should correct the above objectionable observations that involved safety of study subjects. The above observations, however, should not have a significant impact on the study

outcomes. [Note: Item 2 was discussed in the EIR but not listed on the Form FDA-483]

Analytical Site: [redacted]

5. **An [redacted] was used for the quantitation of estrone ([redacted]) and estrone sulfate [redacted]. The [redacted] used is a theoretical value and is not confirmed by experiment. Limited experimental data was generated during the inspection to confirm the theoretical [redacted]**

In the written 483 response, the site provided additional experimental data to confirm the theoretical [redacted] (see Attachment 1). These additional data were reviewed by DSI and found to be adequate.

Conclusion:

The Division of Scientific Investigations recommends that Angeliq® Study 97071 be accepted for Agency review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Martin K. Yau, Ph.D.

Attachment

Final Classification:

[redacted] **VAI**

VAI

cc:
HFA-224
HFD-45/Rhoads
HFD-48/Yau/O Shaughnessy(2)/cf
HFD-580/Reddy
HFD-870/Jarugula/Parekh
HFR-CE2545/Cortes
HFR-CE250/Salisbury
HFR-SE2575/Collado
HFR-SE250/Torres
Draft: MKY 8/20/02
Edit: MFS 8/20/02
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FACTS 2

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

/s/

Venkateswar Jarugula
10/10/02 12:25:42 PM
BIOPHARMACEUTICS

Ameeta Parekh
10/11/02 12:52:28 PM
BIOPHARMACEUTICS
I concur