CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-355

MEDICAL REVIEW

DIVISION OF REPRODUCTIVE AND UROLOGIC PRODUCTS (DRUP)

CLINICAL TEAM LEADER MEMORANDUM

NDA	NDA 21-355/N-000
Type of Application	Original NDA (complete response to Approvable Action)
Applicant	Berlex Laboratories, Inc. Montville, NJ
Proprietary Drug Name	Angeliq™
Established Drug Name	(Drospirenone/17β-estradiol) tablets
Dosage Form	Oral tablet
Dosage Strength	0.5 mg drospirenone and 1 mg 17β-estradiol per tablet
Dosing Regimen	One tablet daily
Indications	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause.
Intended Population	Postmenopausal women with a uterus
PDUFA Goal Date	October 1, 2005
Date of Memorandum	September 28, 2005
Team Leader	Scott E. Monroe, MD Clinical Team Leader, DRUP

1 RECOMMENDATIONS

1.1 Recommendation regarding Approvability

It is recommended that (0.5 mg drospirenone/1 mg 17β-estradiol) tablets be approved for marketing for the indications of (1) "treatment of moderate to severe vasomotor symptoms associated with the menopause" and (2) "treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered." (0.5 mg drospirenone [DRSP]/1 mg 17β-estradiol [E_2]) tablets (also referred to as Angeliq™ in this Memorandum) are recommended only for postmenopausal women who have a uterus.

In the present submission, the Applicant has satisfactorily addressed all of the deficiencies and provided all of the requested updated safety information listed in the Division's Approvable Letter of September 14, 2004.

1.2 Basis for Recommendation

This recommendation for approval is based on (1) the Division's previous finding that (0.5 mg drospirenone/1 mg 17β-estradiol) tablets are safe and effective for the recommended indications, (2) the Applicant's addressing all issues listed in the Division's Approvable Letter of September 14, 2004, and (3) the Applicant's commitment to conduct additional Phase 4 investigations to define the lowest effective doses of E_2 and DRSP for treatment of vasomotor symptoms and protection of the endometrium from estrogen stimulation, respectively.

1.3 Recommendation on Phase 4 Studies and Risk Management Steps

1.3.1 Phase 4 Studies and Commitments

The Applicant has not demonstrated that (0.5 mg DRSP/1 mg 17β estradiol) tablets contain the lowest doses of 17β estradiol and DRSP that will effectively reduce the frequency and severity of hot flushes (E_2) and protect the endometrium from adverse stimulatory effects of estrogen (DRSP). Therefore, the Applicant should conduct Phase 4 investigations of lower doses of both E_2 and DRSP.

A postmarketing active surveillance study (The European Active Surveillance Study of Women Taking HRT [EURAS-HRT] that compares the safety of the European formulation of Angeliq (2 mg DRSP/1 mg E_2) to the safety of other hormonal therapies for menopausal symptoms is ongoing. The Applicant should submit to the NDA annual (or more frequent) interim reports and the final report for the EURAS-HRT in a timely manner.

1.3.2 Risk Management Program

No risk management program beyond approved product labeling and routine monitoring of spontaneously reported adverse events is warranted. Labeling should include all contraindication, warning, and precautions as recommended in the draft Labeling Guidance for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms as well as additional warning and/or precautions regarding the potential risk of hyperkalemia (similar to those in the label for Yasmin) because of the anti-mineralocorticoid properties of DRSP.

2 BACKGROUND

2.1 Original NDA submission

Original NDA 21-355 for (DRSP/E_2) tablets (DRSP/1 mg E_2 and DRSP/1 mg E_2) was submitted in December 2001 and received a Not Approvable Letter in October 2002 because of 3 safety concerns:

- Concerns about an increased risk for thrombotic and thromboembolic adverse events in women using Yasmin (an oral contraceptive containing DRSP), relative to other combination oral contraceptives (COCs), based on spontaneous postmarketing safety reports

- Uncertainty about the risk of developing hyperkalemia because of the anti-mineralocorticoid properties of DRSP
- Unreliable endometrial biopsy readings

Original NDA 21-355 did not include clinical data indicating that (———)RSP/1 mg E_2) tablets reduced the frequency and severity of vasomotor symptoms associated with the menopause. Rather, by prior agreement with the Division, the efficacy of (DRSP/1 mg E_2) tablets was inferred by the Applicant successfully showing bioequivalence between the E_2 component of their combination drug product and Estrace oral tablets (a product approved for the treatment of menopausal vasomotor symptoms that contains E_2 but no progestin).

2.2 First Complete Response

According the clinical review of the primary Medical Officer and the Division Director's Memorandum, the 3 safety concerns listed in the Division's Not Approvable Letter of October 2002 were satisfactorily resolved in the Applicant's Complete Response of March 2004 (see the primary Medical Review of Dr. Furlong [dated September 13, 2004] and the Division Director's Memorandum [dated September 14, 2004]). In the first Complete Response, the Applicant sought approval to market only (——— DRSP/1 mg E_2) tablets. However, based on the data provided in the submission, the primary FDA medical reviewer concluded that 0.5 mg DRSP also was adequate to protect the endometrium from adverse estrogenic stimulatory effects. Although the Applicant agreed with the Division's assessment, the Applicant did not have adequate chemistry data to support the marketing of (0.5 mg DRSP/1 mg E_2) tablets; consequently, the Application received an Approvable Letter on September 14, 2004.

3 CONTENT OF PRESENT SUBMISSION (SECOND COMPLETE RESPONSE)

The present submission (second Complete Response) included the following components:

- Chemistry data to support the marketing of (0.5 mg DRSP/1 mg E_2) tablets. These data were found to be acceptable and sufficient to support marketing of the proposed formulation.
- A pharmacokinetic study to evaluate the potential for drug-drug interaction between DRSP and midazolam, a CYP 3A4 substrate. The study did not detect a drug-drug interaction.
- A safety update for (DRSP/1 mg E_2) tablets that covered the reporting interval from January 1, 2004 through January 31, 2005 The safety update included:
  - Study Report A07028 – a Phase 2 study of the effects on coronary flow reserve in angina patients
  - Study Report A11620 – a Phase 1 drug-drug interaction study using midazolam as marker substrate for CYP 3A4
  - Summaries of safety data from six ongoing clinical studies, including serious adverse events and discontinuations
  - A brief postmarketing safety update for (2 mg DRSP/1 mg E_2) tablets that are marketed outside of the U.S.
  - Relevant safety information for Yasmin (a combination oral contraceptive that also contains 3 mg DRSP)
- Physician and patient labeling

4 OVERVIEW OF SAFETY FINDINGS IN PRESENT SUBMISSION

In this Memorandum, the review of safety for DRSP/E_2 tablets is limited, for the most part, to safety information contained in the Applicant's Complete Response of March 31, 2005 and other safety information submitted by the Applicant during the current review cycle. Previously submitted safety data that resulted in the Division's Approvable Letter of September 14, 2004 for (0.5 mg DRSP/1 mg E_2) tablets are not re-reviewed.

4.1 Safety Update for Drospirenone/Estradiol Tablets

The reporting period for the Safety Update in the present submission was January 1, 2004 to January 31, 2005. The Division requested that the following elements be included in the Safety Update:

- Significant changes in the safety profile.
- Tables showing
  - Discontinuations due to adverse events
  - Serious adverse events
  - Common adverse events
- Updated tabulations of reasons for premature study discontinuation.
- Case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event.
- Information that suggested a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
- A summary of worldwide experience on the safety of this drug.
- English translations of currently approved foreign labeling not previously submitted.

According to the primary Medical Reviewer, "the Applicant adequately addressed each of the requested elements for the safety update. In addition, the Applicant provided updated safety information about Yasmin, the oral contraceptive that contains DRSP."

4.2 Safety Data from Clinical Studies, Completed or Ongoing during the Reporting Interval

Eight studies were completed or ongoing during the reporting interval. During the reporting period, there were no deaths in these studies. The primary Medical Reviewer stated "the adverse events in clinical studies during the reporting interval do not raise any new safety issues. Bleeding and breast pain were also the 2 most common reasons for discontinuation in the data submitted with the original NDA."

4.3 Postmarketing Experience with Drospirenone/Estradiol Tablets

Drospirenone/estradiol tablets are approved for marketing in more than 30 countries including Australia, France, Germany, Ireland, Netherlands, and the United Kingdom. According to the Applicant, approximately ——— packs, corresponding to ——— women-years of use, had been distributed as of December 10, 2004. The Applicant reports having received four spontaneous reports of serious adverse drug reactions as of January 31, 2005. These include one case each of optic neuritis, intraductal papilloma of breast, thrombosis, and elevated liver function.

In response to a query by the Division to provide an update regarding any regulatory actions in other countries that occurred after January 31, 2005 (the cutoff date for the safety update), the Applicant provided on September 8, 2005 the following information:

> "There have been no post approval actions taken by any regulatory agency because of a safety issue since January 31, 2005." ... " There have been no denials of approval or marketing application withdrawals since January 31, 2005."

4.4 Relevant Postmarketing Safety Experience with Yasmin (Risk of Thrombotic and Thromboembolic Adverse Events)

The postmarketing safety of Yasmin is germane to the likely safety of (0.5 mg DRSP/1 mg E_2) tablets because Yasmin is the only U.S.-approved product that contains the progestin DRSP. Although typical users of Yasmin are likely to be younger and therefore healthier than typical users of (0.5 mg DRSP/1 mg E_2) tablets, Yasmin tablets contain 6 times more DRSP (3 mg).

4.4.1 Interim Report of the European Active Surveillance (EURAS) Study

Following review of the submission of the original NDA 21-355, the application received a Not Approvable action because of safety concerns in October 2002. One of these concerns was related to a potential increased rate of serious thrombotic and thromboembolic adverse events, based on spontaneously reported postmarketing adverse events in women using Yasmin. At that time, only limited data were available from the European Active Surveillance (EURAS) Study. EURAS is a prospective postmarketing surveillance study being performed in Europe chiefly to evaluate the cardiovascular risks in three cohorts of women using combination oral contraceptives containing different progestins: users of Yasmin, users of levonorgestrel (LNG)-containing contraceptives, and users of oral contraceptives containing other progestins. As of June 9, 2004, quality controlled data sets with follow-up were available on 49,342 women representing 64,103 women-years of observation.

As shown in Table 1, the rates per 10,000 women years for venous thrombotic events (VTEs) and arterial thrombotic events (ATEs) are similar across the 3 treatment groups. According to the Applicant, the results for all thromboembolic events are robust enough to exclude a 1.8-fold greater thromboembolic risk for Yasmin users compared to users of LNG-containing oral contraceptives (OCs) and other progestin-containing OCs (Other OCs). The only deaths related to thrombotic events (N=2) occurred in the LNG cohort.

Table 1 Confirmed Thromboembolic Adverse Events per 10,000 Women Years of Exposure

Event category	Yasmin (19,530 WY)			LNG-containing OCs (18,476 WY)			Other OCs (26,097 WY)			Total
	n	per 10^4 WY	95% CI	n	per 10^4 WY	95% CI	n	per 10^4 WY	95% CI	
All VTE/ATE	**13**	**6.7**	**3.5 - 11.4**	**14**	**7.6**	**4.1 – 12.7**	**23**	**8.8**	**5.6 – 13.2**	**50**
All VTE	**12**	**6.1**	**3.2 - 10.7**	**11**	**6.0**	**3.0 – 10.7**	**19**	**7.3**	**4.4 – 11.4**	**42**
of which PE	3	1.5	0.3 – 4.5	2	1.1	0.1 – 3.9	2	0.8	0.1 – 2.8	7
All ATE	**1**	**0.5**	**0.0 – 2.9**	**3**	**1.6**	**0.3 – 4.8**	**4**	**1.5**	**0.4 – 3.9**	**8**
of which AMI	0	0.0	0.0 – 1.9	1	0.5	0.0 – 3.0	2	0.8	0.1 – 2.8	3
CVA	1	0.5	0.0 – 2.9	2	1.1	0.1 – 3.9	2	0.8	0.1 – 2.8	5
Fatal VTE/ATE	**0**	**0.0**	**0.0 – 1.9**	**2**	**1.1**	**0.1 – 3.9**	**0**	**0.0**	**0.0 – 1.4**	**2**

WY = women year; VTE = venous thrombotic event; ATE = arterial thrombotic event; PE = pulmonary embolus; AMI = acute myocardial infarction; CVA = cerebral vascular accident.

Source: Table 8, p.22, primary Medical Review of September 9, 2005 for submission of March 31, 2005 (Complete Response No. 2).

Team Leader Comment

- *These data are reassuring in that they indicate (within the limitations of the power of the study) that women using a combination oral contraceptive (COC) containing DRSP plus estrogen are not at greater risk of developing thrombotic or thromboembolic adverse events than women using COCs containing a different progestin. These data, by extrapolation, further suggest that postmenopausal women using (0.5 mg DRSP/1 mg E_2) tablets (i.e., Angeliq) would not be at a greater risk for developing thrombotic or thromboembolic adverse events than women using other (progestin/1 mg E_2) products for treatment of vasomotor symptoms.*

4.4.2 Interim Report for Ingenix Study

The Ingenix Study is a U.S. prospective cohort study based on claims data from United Health Care. The study is part of a Phase 4 commitment for Yasmin. The original objective of the study was to assess the risk of hyperkalemia in women using Yasmin. The protocol was amended to also assess thrombotic risk. Table 2 summarizes the data related to thrombotic events from the Ingenix Interim Report that was included in the Applicant's present submission. To date, the Ingenix Study has not detected a difference between Yasmin users and users of other OCs with respect to the incidence of thrombotic events.

Table 2. Ingenix Study: Chart-Confirmed VTE and ATE Events from Third Quarter 2001 to Third Quarter 2003

Outcome[a]	Number of Women					
	Yasmin Initiators (N = 14,295)			Other OC Initiators (N = 28,590)		
	Claims-Based	Chart Confirmed	Chart Not Found	Claims-Based	Chart Confirmed	Chart Not Found
All VTE/ATE events[b]	44	15	4	86	32	8
Pulmonary embolism	7	4	0	11	8	1
Venous thrombosis	14	10	0	31	20	5
Arterial embolism	0	0	0	9	0	0
Stroke	11	1	2	15	3	1
TIA[c]	5	0	1	6	0	0
Thrombotic thrombocytopenic purpura	0	0	0	1	1	0
Other diagnoses	5	0	0	9	0	1
Not specified[d]	2	0	0	4	0	0

ATE = arterial thrombotic event; TIA = transient ischemic attack; VTE = venous thrombotic event.

[a] A woman can have events in multiple categories. The 15 Yasmin events are contributed by 14 women; the 32 Other OC events are contributed by 28 women. The multiple events share the same event date, e.g., VT and PE diagnosed during the same admission. Multiple charts may have been requested for a given event, leading to a higher count of Charts Not Found.

[b] Potential VTE/ATE events identified after clinical review of the claims data.

[c] TIA outcomes also counted in stroke.

[d] Women with claims for procedures or anticoagulant therapy only.

Source: Table 3, p.13, primary Medical Review of September 9, 2005 for submission of March 31, 2005 (Complete Response No. 2).

Team Leader Comment

- *The present power of the Ingenix Study to detect a difference in incidence of thrombotic adverse events in Yasmin users compared to users of other COCs is less than that of the EURAS Study. However, the results of the Ingenix Study are reassuring and support the findings of the EURAS Study.*

4.5 Safety Experience with (DRSP/E_2 Tablets) and Yasmin (Risk of Hyperkalemia)

4.5.1 Clinical Trial Findings

During the clinical development of both Yasmin (3 mg DRSP/30 mcg EE) for contraception and (DRSP/E_2) tablets for treatment of vasomotor symptoms, the Applicant conducted several clinical trials to assess the effect of DRSP (generally at a dose of 3 mg/day) on serum potassium concentrations. These studies were conducted in generally healthy reproductive-aged or postmenopausal women, women with mild to moderate renal impairment, and women taking concomitant medication that are known to decrease the excretion of potassium and increase the risk of hyperkalemia (e.g., NSAIDs, angiotensin converting enzyme [ACE)] inhibitors, or angiotensin receptor blockers). The findings from these studies are presented in the reviews of the primary Medical Reviewer (dated September 12, 2002 and September 13, 2004). The primary Medical Reviewer made the following statements in her earlier reviews of the NDA: "In general under the controlled conditions of clinical trials, women exposed to DRSP have had small, insignificant, mean increases in serum potassium and decreases in serum sodium consistent with antimineralocorticoid effect." ... "Clinically significant

hyperkalemia was detected in one high risk 46-year old woman in a Phase I trial (reviewed in the original Angeliq submission). This woman took a single dose of DRSP 3 mg. She had an unusually high serum concentration of DRSP, likely related to hepatic dysfunction and concomitant medications. Otherwise, although there have been other instances of hyperkalemia, there have been no serious adverse events related to hyperkalemia in the clinical trials of Angeliq."

4.5.2 Postmarketing Safety Findings for Yasmin

Spontaneous Adverse Event Reporting. In the primary Medical Review of the present submission, the Reviewer states "There have been no clinically significant cases of hyperkalemia reported since the introduction of Yasmin in November 2000 through December 31, 2004. During this time period, the Applicant estimates that there were [redacted] women-years of use globally."

Ingenix Postmarketing Study. In the primary Medical Review of the present submission, the Reviewer states "There have been no clinically significant cases of hyperkalemia detected by the Ingenix Study."

Team Leader Comment

- *Among the studies specifically conducted to assess the effects of DRSP on serum potassium levels, the primary Medical Reviewer reported that only one subject developed clinically serious hyperkalemia. In these studies, the subjects received 3 mg DRSP per day. According to the Applicant, 3 mg DRSP per day has anti-mineralocorticoid activity comparable to 25 mg spironolactone (the lowest marketed dose). The Applicant also reports in the present safety update that no cases of clinically significant hyperkalemia have been reported for women using Yasmin (3 mg DRSP/30 mcg EE) in either the Ingenix Study or spontaneous postmarketing safety reports. Based on these observations, the risk of (0.5 mg DRSP/1 mg E_2) tablets producing clinically significant hyperkalemia is low and acceptable for the proposed indications.*

5 NON CLINICAL REVIEW RECOMMENDATIONS

5.1 Chemistry (CMC)

The Chemistry Reviewer (Suong Tran, Ph.D.) recommended approval of the Application without any Phase 4 commitments. She stated the following in her review:

> "All chemistry issues were previously resolved satisfactorily for the higher dosage strengths (Chem. Reviews #1-4), and there is no chemistry issue in this current review of the to-be-marketed dosage strength."
>
> "A recommendation from the Office of Compliance is "Acceptable" (11-APR-2005 by S. Adams)."
>
> "On 31-MAR-2005, new packaging labels (mock-ups) were submitted. The new labels (including the proprietary name) are acceptable per chemistry perspective...."

5.2 Clinical Pharmacology and Biopharmaceutics

The primary Clinical Pharmacology and Biopharmaceutics Reviewer (Julie M. Bullock, Pharm.D.) stated the following in her review:

"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."

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

5.3 Toxicology and Preclinical Pharmacology

The primary Toxicology Reviewer (Krishan Raheja, Ph.D.) stated the following in his review of the present submission:

"From the P/T prospective there are no issues and there is nothing to review."

Dr. Raheja stated the following in his review of the original submission:

"Since all pre-clinical pharmacology/toxicology is referred to the sponsor's approved NDA 21-098 for Yasmin (3 mg drospirenone plus 0.030 mg ethinyl estradiol) as an oral contraceptive and as the dosage of drospirenone in Angeliq is equal or lower than that approved for Yasmin and 1 mg 17-B-estradiol is an approved dosage, Pharmacology recommends approval of NDA 21-355 for oral hormone replacement therapy."

5.4 Statistics

The Statistical Reviewer (Sonia Castillo, Ph.D.) stated the following in her review of this submission:

"Since the purpose of this application is to address chemistry and labeling issues cited in an approvable letter from the agency, no efficacy studies are submitted. Thus, no statistical review for efficacy is required.

5.5 Division of Scientific Investigation (DSI)

Four clinical sites were inspected during the original review cycle. Two of these sites were inspected for the bioequivalence trial and two for the endometrial protection trial. Data from all 4 sites were determined to be acceptable for inclusion in the NDA.

5.6 Office of Drug Safety/Division of Drug Risk Evaluation (DDRE)

A meeting was held with DDRE on September 13th to discuss the need for a risk management program (RMP) for Angeliq. At the meeting, it was agreed that a RMP beyond labeling would not be warranted for this product.

5.7 Division of Drug Marketing, Advertising, and Communications (DDMAC)

DDMAC made several suggestions regarding the Applicant's proposed Package Insert (PI) and Patient Package Insert (PPI). All suggestions were considered in the Division's revision of the Applicant's proposed label.

5.8 Office of Drug Safety/Division of Medication Errors and Technical Support (DMETS)

In their consultation of August 18, 2005, DMETS stated that they had no objections to the use of the proprietary name, Angeliq™, provided Angeliq™ is approved prior to the

approval of another drug product with a similar sounding name. DMETS also communicated the information that DDMAC did not recommend approval of the proposed trade name "Angeliq" because [redacted] The review team considered DDMAC's concern but does not concur with DDMAC regarding the name "Angeliq" and does not consider it to be [redacted]

5.9 Division of Surveillance, Research, and Communication Support (DSRCS)

DSRCS had reviewed the patient package insert (PPI) during the previous review cycle and made no specific recommendations other than that the PPI should follow class labeling for menopausal hormone products.

6 LABELING

For the most part, product labeling for (0.5 mg DRSP/1 mg E_2) tablets (Angeliq™) reflects class labeling for "Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms." In additional, labeling includes specific warnings related to the anti-mineralocorticoid activity of DRSP. These include statements about the potential risk of hyperkalemia in women who may choose to use (0.5 mg DRSP/1 mg E_2) tablets and contraindications to its use in women with renal or adrenal insufficiency. The following bolded warning, not found in other progestin/estrogen products for the treatment of vasomotor symptoms appears in labeling at the beginning of the section on Warnings:

Product labeling (PI and PPI) submitted on September 23, 2005, in conjunction with the editorial revisions submitted on September 28, 2005, are acceptable.

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

/s/

Scott Monroe
9/28/2005 02:06:17 PM
MEDICAL OFFICER

Daniel A. Shames
9/28/2005 03:29:51 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA Complete Response
Submission Number	21-355/N000
Submission Code	BZ
Letter Date	31-Mar-2005
Stamp Date	01-Apr-2005
PDUFA Goal Date	01-Oct-2005
Reviewer Name	Lesley-Anne Furlong
Review Completion Date	9-Sep-2005
Established Name	Drospirenone/17β-estradiol Tablets
(Proposed) Trade Name	Angeliq™
Therapeutic Class	Hormonal agents
Applicant	Berlex
Priority Designation	S
Formulation	Tablets containing drospirenone 0.5 mg and 17β-estradiol 1 mg
Dosing Regimen	One tablet orally every day
Indication	Hormone therapy
Intended Population	Menopausal women

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

From a clinical perspective, I recommend approval of Angeliq™ for the requested indications:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.
2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause.

Angeliq is a tablet for once daily oral dosing. It contains the estrogen, 17β-estradiol, for treatment of menopausal symptoms, and the progestin, drospirenone, for protection of the endometrium from estrogen-induced hyperplasia.

This will be the third NDA action on Angeliq™. The first action was a nonapproval based on the following clinical concerns:

1. Uncertainty about thrombotic risk related to postmarketing reports from Yasmin, the oral contraceptive containing drospirenone
2. Uncertainty about risk of hyperkalemia related to the antimineralocorticoid properties of drospirenone
3. Unreliable endometrial biopsy readings

The nonapproval issues were adequately addressed in the Applicant's second submission. However, a re-reading of endometrial biopsies showed that the lowest dose of drospirenone studied (0.5 mg) was sufficient to provide endometrial safety. The Applicant, however, did not have adequate chemistry information to support approval of the 0.5 mg dose, and the submission received an Approvable action. Labeling was not negotiated.

From a clinical perspective, the present submission is a safety update and labeling review. The Applicant has successfully addressed efficacy and safety of Angeliq™ in clinical trials that are summarized in the Executive Summary of the two previous clinical reviews. (See pages 23 and 30 in the Appendix.)

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The European Active Surveillance Study of Women Taking HRT (EURAS-HRT), the European Active Surveillance Study (EURAS), and routine postmarketing surveillance should be adequate for postmarketing risk management.

EURAS-HRT is an ongoing study that compares the safety of European Angeliq to the safety of other hormonal therapies for menopausal symptoms. The study focuses mainly on cardiovascular outcomes and death. Because the European formulation of Angeliq™ contains a *higher* dose of drospirenone than the American formulation (2 mg versus 0.5 mg) with the same dose of estradiol, a demonstration of safety for the European formulation will support the safety of the American formulation.

In addition, there is an ongoing surveillance study called EURAS that compares Yasmin, an oral contraceptive containing drospirenone, to other oral contraceptives. For reasons discussed in the review, the safety assessment of Yasmin is relevant to the safety assessment of Angeliq™.

1.2.2 Required Phase 4 Commitments

The Applicant should

1. Send interim reports and the final report of the European Active Surveillance Study (EURAS) to the NDA. The expected completion date for EURAS is 2006.

2. Send interim reports and the final report of the European Active Surveillance Study of Women Taking HRT (EURAS-HRT) for Angeliq™ to the NDA. The expected completion date for the EURAS-HRT study is 2008.

1.2.3 Other Phase 4 Requests

The Applicant should study lower doses of both components. There is evidence in the oral contraceptive literature that decreasing the estrogen dose in oral contraceptives decreases thrombotic risk. Since there is an estradiol 0.5 mg tablet approved for menopausal symptoms, it is reasonable to develop an Angeliq™ formulation containing 0.5 mg estradiol, and assess whether a lower dose of drospirenone protects the endometrium from the adverse effects of estrogen.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The present submission is a complete response to an approvable action taken on September 14, 2004. Two issues identified in the approvable action letter included:

1. Inadequate information in the Chemistry, Manufacturing, and Controls section of the application to support approval of the 0.5 mg/1 mg drospirenone/estradiol tablets.
2. Labeling was not negotiated.

The overall clinical program is summarized the Executive Summary of previous clinical reviews. (See pages 23 and 30 in the Appendix.)

The clinical data in the present submission consists of a safety update that covers the reporting interval from January 1, 2004 through January 31, 2005. Included in the safety update are:

1. Study Report A07028 - Phase 2 study of the effects on coronary flow reserve in angina patients
2. Study Report A11620 - Phase 1 drug-drug interaction study using midazolam as marker substrate for CYP3A4
3. Summaries of safety data from six ongoing studies, including serious adverse events, and discontinuations
4. An update of ongoing safety evaluation of Yasmin, the oral contraceptive containing drospirenone
5. Articles from a literature search

1.3.3 Safety

The information provided in the safety update did not introduce any new safety issues or change the adverse event profile for labeling purposes.

2 INTRODUCTION AND BACKGROUND

2.5 Presubmission Regulatory Activity

The first new drug application for Angeliq™ received a non-approval on October 17, 2002, based on three concerns:

1. Uncertainty about thrombotic risk related to postmarketing reports from Yasmin, the oral contraceptive containing drospirenone
2. Uncertainty about risk of hyperkalemia related to the antimineralocorticoid properties of drospirenone
3. Unreliable endometrial biopsy readings

The Applicant satisfactorily addressed all three issues in a complete response. However, the re-reading of the endometrial biopsy slides supported that the lowest dose of drospirenone (DRSP) studied (0.5 mg) adequately protected the endometrium from endometrial hyperplasia. The Applicant had not provided sufficient chemistry information for the tablet containing DRSP 0.5 mg [redacted] Therefore, the Division took an approvable action on September 14, 2004 because of inadequate chemistry information to support Angeliq™ containing DRSP 0.5 mg. Labeling was not negotiated.

On October 27, 2004, the Division faxed responses to the Applicant's questions intended for an end-of-review meeting. The questions and answers addressed chemistry and biopharmaceutic issues. The end-of-review meeting was canceled by mutual agreement.

The current submission is a complete response to the approvable action taken on September 14, 2004.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

There are no outstanding chemistry or microbiology issues that affect approvability. A facilities inspection conducted by the Office of Compliance found the NDA to be acceptable.

3.2 Animal Pharmacology/Toxicology

According to the Applicant, there were five new nonclinical reports and two publications during the review period of January 1, 2004 to January 31, 2005, and there were no new findings that adversely affect the safety assessment.

5 CLINICAL PHARMACOLOGY

The present submission includes two clinical pharmacology studies:

1. Study A11620, a study to evaluate the potential for drug-drug interaction between DRSP and midazolam, a CYP 3A4 substrate. The study did not detect a drug-drug interaction. (See page 19.)
2. Study Report A26093, an in vitro dissolution study to show bioequivalence of the to-be-marketed formulation with the formulation used in the clinical trial. According to the FDA's biopharmaceutical reviewer, bioequivalence was demonstrated.

7 INTEGRATED REVIEW OF SAFETY

7.2.2.2 Postmarketing experience

Drospirenone/estradiol tablets are approved in the countries in Table 1 under the trade names Angeliq™, Allurene, Visanne, or Angemin.

Table 1. Countries in which Drospirenone/Estradiol Tablets Are Approved

Country	Approval Date MM/DD/YYYY	Country	Approval Date MM/DD/YYYY	Country	Approval Date MM/DD/YYYY
Argentina	12/16/2004 (a)	Guatemala	06/18/2004 (a)	Portugal	10/03/2003 (b) 05/25/2004 (a)
Australia	11/30/2004 (a)	Honduras	02/12/2004 (a)	Russian Federation	11/17/2004 (a)
Austria	11/27/2003 (a,b)	Hungary	04/30/2004 (a)	South Africa	05/28/2004 (a)
Belgium	09/22/2003 (a,b)	Iceland	11/05/2003 (d)	Spain	09/11/2003 (a) 10/29/2003 (c)
Bolivia	01/11/2005 (a)	Indonesia	10/15/2004 (a)	Sweden	11/14/2003 (b,d)
Columbia	08/17/2004 (a)	Ireland	03/05/2004 (a,b)	Thailand	09/01/2004 (a)
Denmark	09/11/2003 (b,d)	Luxembourg	09/30/2003 (a,b)	Turkey	03/17/2004 (a)
Finland	10/14/2003 (a,b)	Mexico	01/11/05 (a)	Ukraine	12/03/2004 (a)
France	03/16/2004 (a,b)	Netherlands	02/07/2003 (b) 12/11/2002 (a)	United Kingdom	03/10/2004 (a)
Germany	08/29/2003 (a,b)	Paraguay	01/14/2005 (a)	Uruguay	10/20/2004 (a)
Greece	03/31/2004 (a,b)	Peru	01/18/2005 (a)		

a= Angeliq, b= Allurene, c= Visanne, d=Angemin
Source: Page 9 of Safety Update in NDA submission, 31-Mar-2005

As of December 10, 2004, about [redacted] packs had been distributed, corresponding to [redacted] women-years of treatment. Berlex has received four spontaneous reports of serious adverse drug reactions as of January 31, 2005. These include one case each of:

1. Optic neuritis
2. Intraductal papilloma of breast
3. Thrombosis
4. Elevated liver function

At the request of the FDA medical team leader, the Applicant was asked to update safety by providing information about regulatory actions in other countries that may have occurred after the cutoff date of the safety update (January 31, 2005). On September 8, 2005, the Applicant provided the following statements:

> "There have been no post approval actions taken by any regulatory agency because of a safety issue since January 31, 2005. There have been no denials of approval or marketing application withdrawals since January 31, 2005."

Comment: Spontaneous reporting has not detected a new safety concern for Angeliq™.

7.2.2.3 Literature

The Applicant identified and provided 56 new publications containing clinical information published during the reporting period (January 1, 2004 through January 31, 2005.) There was no new safety information that would change the previous assessments of safety and efficacy.

In addition, since March 2003, I have requested weekly email alerts through EMBASE on any article detected by the search "drospirenone OR Yasmin OR petibelle". I have identified no new safety issues among 155 articles detected in this manner.

7.2.9 Additional Submissions, Including Safety Update

The reporting period for the Safety Update is January 1, 2004 to January 31, 2005. The Division requested the following routine elements for the safety update:

1. Describe any significant changes in the safety profile
2. Provide tables showing
    - Discontinuations due to adverse events
    - Serious adverse events
    - Common adverse events
3. Updated retabulation of reasons for premature study discontinuation and describe new trends.
4. Case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Comment: The Applicant adequately addressed each of the requested elements for the safety update. In addition, the Applicant provided updated safety information about Yasmin, the oral contraceptive that contains DRSP.

7.2.9.1 Safety Data from Clinical Studies, Completed or Ongoing during the Reporting Interval

Table 2 lists the eight studies that were completed or are ongoing during the reporting interval.

Table 2. Clinical Studies of Angeliq™, Completed or Ongoing during the Reporting Period 1Jan04 to 31Jan05

Protocol Number	Goal	N	Status
303967	Effects of DRSP 2 mg/estradiol 1 mg on skin and hair	N=94 (46 active, 47 placebo)	Ongoing
303966	Coronary flow reserve	N=60 (30 active, 30 placebo)	Complete
306743	Treatment of hypertension	N=417	Ongoing
308381	Vasomotor symptoms in Korean women	N=86	Ongoing
308660	Vasomotor symptoms in Belgian women (open-label)	N=1,540	Ongoing
306946	Drug-drug interaction study	N=25	Complete
306753	Effects on hemostasis	N=59 (29 Angeliq™, 30 Activelle)	Ongoing
308301	[redacted]	N=36	Ongoing

Source: prepared by reviewer from text in the Safety Update, NDA submission dated 31-Mar-2005

There were no deaths reported during the reporting interval in any study.

There were two treatment phase SAEs during the reporting interval:

1. A transient ischemic attack in a subject taking DRSP 2 mg/E2 1 mg in Study 308660. This was a 58 year old woman with hypertension who developed a TIA after 2 weeks on therapy.
2. New onset of angina in a subject whose treatment assignment remains blinded in Study 306743.

There were 108 discontinuations due to adverse events during the reporting interval, including 9 in Study 306743 (N=473), 3 in Study 308381 (N=86), and 96 in Study 308660 (N=1,540). The studies are ongoing, and treatment assignment remains blinded. Three subjects discontinued Study 308660 for serious adverse events, including a transient ischemic attack (briefly described in the preceding paragraph), breast cancer in situ, and a hysterectomy. The most common reasons for discontinuation in Study 308660 were vaginal bleeding (34 subjects) and breast pain or engorgement (17 subjects).

The reasons for discontinuation in the remaining Studies 306743 and 308381 by subject included:

1. Pedal edema and elevated serum potassium (to 5.4 mEq/L)
2. Myocardial ischemia
3. Exacerbation of retrosternal pain
4. Hypertriglyceridemia
5. Genital bleeding (2 subjects)
6. Stiff neck
7. Flu
8. Negative attitude
9. Nausea
10. Gastrointestinal problems
11. Abdominal discomfort

The Applicant states that "there was not unusually high frequency of a less serious event in any of the ongoing studies during the reporting period".

Comment: The adverse events in clinical studies during the reporting interval do not raise any new safety issues. Bleeding and breast pain were also the 2 most common reasons for discontinuation in the data submitted with the original NDA.

7.2.9.2 Epidemiological Studies

The NDA describes a prospective cohort study called the "European Active Surveillance Study of Women Taking HRT" (EURAS-HRT). The primary objective of the study is to compare incidence rates of serious adverse events in users of Angeliq™ and users of other hormone therapies for symptoms of menopause, with special emphasis on cardiovascular outcomes. At least 90,000 women-years of observation are expected. A pilot phase of the study started in 2002, but, because of delayed launch of Angeliq™ in Europe, women using Angeliq™ were enrolled starting in September 2004. The study will end in 2008. The first interim outcome information on Angeliq™ is expected in the second quarter of 2006. The study will compare incidence rates of myocardial infarction, stroke, sudden death, and venous thromboembolism in the following cohorts:

- Women using Angeliq™
- Women using other oral continuous combined hormone therapies for menopause
- Women using other hormone therapies for menopause symptoms

The study is powered to detect a three-fold increase in cardiovascular events if Angeliq™ reaches a 10% or greater market share in Europe.

Comment: This study is similar in design to the EURAS study that has been useful in defining the risk of rare events in users of Yasmin compared to users of other contraceptives. The Applicant should submit all interim analyses and the final study report to the NDA as they become available.

7.2.9.3 Postmarketing Safety of Yasmin

The postmarketing safety of Yasmin is germane to Angeliq™ because Yasmin is the only U.S.-approved product that contains the progestin DRSP. Although typical users of Yasmin are likely to be younger and therefore healthier than typical users of Angeliq™, Yasmin exposes its users to 6 times more DRSP and *roughly* 7 times more estrogen than Angeliq. (Yasmin contains a more potent estrogen, ethinyl estradiol (EE), than Angeliq. By some measures, EE is 250 times more potent than estradiol, the estrogen in Angeliq. Therefore, although the mg dose of ethinyl estradiol in Yasmin is lower than the dose of estradiol in Angeliq™, the estrogen potency of Yasmin is roughly 7-fold greater than the estrogen potency of Angeliq™.) Although the typical Yasmin user is younger than the typical Angeliq™ user, the greater hormone exposure in Yasmin users makes its safety record useful to consider when evaluating Angeliq™. Brief reviews of three "actual use" postmarketing studies of Yasmin follow.

7.2.9.3.1 EURAS Study (Yasmin)

The European Active Surveillance Study (EURAS) is a large postmarketing study of Yasmin in Europe. The latest interim report of EURAS is reviewed in the Appendix, page 21. To date, the EURAS study had not detected an increased risk of thromboembolic events or death in women using Yasmin compared with women using oral contraceptives (OCs) containing levonorgestrel (LNG). According to the Applicant, the results for all thromboembolic events are robust enough to exclude a 1.8-fold difference in thromboembolic risk for Yasmin users compared with users of LNG-containing OCs.

7.2.9.3.2 Ingenix Study (Yasmin)

The Ingenix study is a U.S. prospective cohort study based on claims data from United Health Care. The study is part of a Phase 4 commitment for Yasmin, and it was started in response to concern about the potential for electrolyte abnormalities in Yasmin users. The protocol was amended to add a study of thrombotic risk. A final study report is expected in January 2006.

Table 3 summarizes the data related to thrombotic events from the most recent interim report. To date, the Ingenix study has not detected a difference between Yasmin users and users of other OCs with respect to incidence of thrombotic events. There have been no clinically significant cases of hyperkalemia detected by the study.

Table 3. Ingenix Study: Chart-Confirmed VTE and ATE Events from 3rd Quarter 2001 to 3rd Quarter 2003

	Number of Women					
	Yasmin Initiators (N = 14,295)			Other OC Initiators (N = 28,590)		
Outcome[a]	Claims-Based	Chart Confirmed	Chart Not Found	Claims-Based	Chart Confirmed	Chart Not Found
All VTE/ATE events[b]	44	15	4	86	32	8
Pulmonary embolism	7	4	0	11	8	1
Venous thrombosis	14	10	0	31	20	5
Arterial embolism	0	0	0	9	0	0
Stroke	11	1	2	15	3	1
TIA[c]	5	0	1	6	0	0
Thrombotic thrombocytopenic purpura	0	0	0	1	1	0
Other diagnoses	5	0	0	9	0	1
Not specified[d]	2	0	0	4	0	0

ATE = arterial thromboembolism; TIA = transient ischemic attack; VTE = venous thromboembolism.
[a] A woman can have events in multiple categories. The 15 Yasmin events are contributed by 14 women; the 32 Other OC events are contributed by 28 women. The multiple events share the same event date, e.g., VT and PE diagnosed during the same admission. Multiple charts may have been requested for a given event, leading to a higher count of Charts Not Found.
[b] Potential VTE/ATE events identified after clinical review of the claims data.
[c] TIA outcomes also counted in stroke.
[d] Women with claims for procedures or anticoagulant therapy only.
Source: Data from Table 2 Ingenix Report dated February 9, 2005, in Safety Update of NDA submission 31-Mar-2005

7.2.9.3.3 Prescription-Event Monitoring Study (Yasmin)

Prescription-Event Monitoring (PEM) studies are observational, uncontrolled studies conducted in large cohorts in the UK to monitor the safety of recently marketed medicines. A PEM study was conducted by the Drug Safety Research Unit, a registered charity in the UK that receives unconditional grants from pharmaceutical companies. The purpose of the study was to evaluate safety events after 6 to 12 months of Yasmin use. A total of 13 women with VTEs were identified: 8 cases of PE and 5 cases of DVT. The crude incidence rate was 13.7 cases per 10,000 women-years (95%CI: 7.3 to 23.4). Each woman had one or more risk factors for VTE.

Although the incidence of VTE was higher in the PEM study than expected, the authors cautioned that, "Taking into account nonresponse bias and the potential effect of other bias, it should be borne in mind that the incidence rate for this cohort may well be an overestimate and should be interpreted with caution. Further research is required into the association between the use of Yasmin and DVT or PE."

Among other problems, this study

- Had a 49% nonresponse rate
- Was uncontrolled
- Covered only the time period of greatest risk for VTE (the first 6 to 12 months)

- Did not control for prescribing to higher risk women

Comment: The lack of controls and high nonresponse rate make this the weakest of the 3 postmarketing studies of Yasmin.

7.2.9.3.4 Spontaneous VTE reporting rates for Yasmin

The spontaneous reporting rate for VTE from the time of launch of Yasmin to Dec. 31, 2004 has been less than the expected incidence for women using oral contraceptives, but the extent of underreporting is unknown. Table 4 shows the spontaneous reporting rates for VTE's based on estimated exposure of [redacted] women-years from time of launch in November 2000 through December 31, 2004.

Table 4. Spontaneous Reporting Rates for VTEs for Yasmin as of Dec. 31, 2004

Thromboembolic Event	World (per 100,000 WY)	US (per 100,000 WY)
VTE	4.79	4.4
PE	2.3	2.7
Fatal VTE	0.17	0.23

Source: Page 18 of Safety Update in NDA submission 31-Mar-2005

FDA's Office of Drug Safety (ODS) has provided the Division with a series of consults related to thromboembolic events in Yasmin users at the Division's request. The initial request was prompted by a concern about the number of reports of thrombotic events in the early months after launch.

In the most recent consult dated 31-Aug-2004, ODS reviewers concluded that "The reporting rates for all thromboembolic and thrombotic events and those for pulmonary embolism (PE) continue to be higher for Yasmin when compared to Alesse and Ortho Tri-Cyclen but are similar when compared to Mircette and Ortho Evra." Furthermore, "It should be noted that AERS data cannot provide definitive answers as to why one product has more reports than another, nor whether there may be increased thrombogenicity associated with one product compared to others."

7.2.9.3.5 Spontaneous Reporting of Electrolyte Abnormalities for Yasmin

There have been no clinically significant cases of hyperkalemia reported since the introduction of Yasmin in November 2000 through December 31, 2004. During this time period, the Applicant estimates that there were [redacted] women-years of use globally.

Of note, there have been 2 U.S. cases of hyponatremia reported postmarketing, both of which resulted in hospitalization. The MedWatch reports for these 2 cases provided too few details to assess whether Yasmin was a factor. However, clinical trials of Yasmin have detected small decreases in mean serum sodium and occasional cases of hyponatremia. Furthermore,

hyponatremia is a plausible adverse event for a drug with antimineralocorticoid properties. Although not mentioned on the Yasmin package insert, hyponatremia is discussed in the "Precautions" section of the spironolactone label.

Comment: It would be reasonable to mention hyponatremia as a plausible electrolyte disturbance in the Angeliq™ label.

9 OVERALL ASSESSMENT

9.1 Conclusions

The safety data in this submission raise no new issues for Angeliq™.

Based on the best available postmarketing studies of Yasmin (EURAS and Ingenix), the incidence of thrombotic events in women using Yasmin™ is similar to the incidence of thrombotic events in women using other combination oral contraceptives containing estrogen and progestin. The ongoing EURAS-HRT will address this issue as well.

The risk of electrolyte abnormalities should be small because the dose of drospirenone in Angeliq™ is low. The ongoing EURAS-HRT study will indirectly address the hyperkalemia issue by collecting data about death rates and cardiac events. It is reassuring that serious hyperkalemia has not been detected postmarketing among women using Yasmin, an oral contraceptive containing a 6-fold higher mg dose of DRSP. However, women using Angeliq™ will be older and more likely to take other medications that increase the risk of electrolyte problems. The label should contain language similar to the language in the Yasmin label, cautioning prescribers and patients about the potential for electrolyte abnormalities.

9.2 Recommendation on Regulatory Action

I recommend approval of Angeliq™ when labeling is satisfactorily negotiated.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Routine risk management should be adequate.

9.3.2 Required Phase 4 Commitments

The Applicant should

1. Send interim reports and the final report of the European Active Surveillance Study (EURAS) for Yasmin to the NDA. The expected completion date for the Study is 2006.

2. Send interim reports and the final report of the EURAS-HRT Study for Angeliq™ to the NDA. The expected completion date for the Study is 2008.

9.3.3 Other Phase 4 Requests

The Applicant should explore lower doses of both components. There is evidence in the literature that decreasing the estrogen dose in oral contraceptives decreases the risk of thrombotic events. It is reasonable to surmise that the same may be true for women who use estrogen for menopause symptoms. Although Angeliq™ exposes its user to an amount of estradiol that is bioequivalent to an approved estradiol *1 mg* tablet, there is also an estradiol *0.5 mg* tablet approved for menopausal symptoms. To reduce hormone exposure, the Applicant could develop an Angeliq™ formulation containing 0.5 mg estradiol, and assess whether a lower dose of drospirenone would suffice to protect the endometrium from adverse effects of estrogen.

9.4 Labeling Review

Much of the labeling for Angeliq™ reflects class labeling for estrogen-containing products indicated for menopausal symptoms. FDA's recommendations regarding class labeling for these products have changed in the past three years in response to the publication of large clinical studies, particularly the Women's Health Initiative. To address these changes, I used the FDA's most current labeling guidance (written by other FDA reviewers). This was supplied by Dr. Theresa Van der Vlugt, the FDA medical officer who has been working closely with sponsors to keep labeling on these products current with scientific knowledge.

Also, I consulted the Yasmin label to ensure that language regarding electrolyte effects of drospirenone and clinical studies was consistent between labels. FDA's Division of Surveillance, Research, and Communication Support provided comments about the patient package insert in a consult dated June 16, 2004. In addition, FDA's Division of Drug Marketing, Advertising, and Communications provided a consult dated July 14, 2004, regarding the package insert. My review addressed these comments. FDA's Division of Medication Errors and Technical Support (DMETS) found the proposed brand name acceptable and provided comments about the container label and carton label. The comments about the container label and carton label were considered by the chemistry reviewer. The Applicant provided, and I considered, the European core labeling for Angeliq™ during the labeling review. And finally, I removed a number of promotional claims inserted by the Applicant in various sections of the label because the claims were inadequately supported by data. The Appendix of this review contains a line-by-line labeling review (page 36). The labeling review is my primary review and may not be identical to final approved labeling which had not been negotiated when this review was finalized.

10 APPENDICES

10.1 Review of Individual Study Reports

The following brief reviews focus on safety.

10.1.1 Study 303966 (Study Report A07028)

Study Overview

The study was a double-blind, randomized, placebo-controlled, single center study to determine the effect of 1 mg estradiol and 2 mg drospirenone (1 tablet daily) on the coronary flow reserve of post-menopausal women with angina pectoris measured by positron emission tomography (PET) and echocardiography. Treatment duration was 6 weeks. The study site was in Finland, and 60 patients were randomized (30 in each treatment arm). Women were between 50 and 70 years old at baseline, had angina for at least 1 year, and had no other serious cardiovascular risks.

Disposition

Ninety subjects were screened and 30 failed screening. The study report did not provide reasons for screening failures beyond "other inclusion/exclusion criteria not met" for 26 subjects, and "ovarian cyst", "ovarian tumor", "asthma", and "no medication available" for other patients. Four patients never took any study medication, 3 from active treatment arm and 1 from the placebo arm. The remaining subjects completed study medication.

Baseline Characteristics

All subjects were Caucasian. At baseline, the mean weight was 66.3 kg, mean BMI was 24.7, and the mean age was 60.1 years old.

Efficacy

The primary efficacy value was myocardial perfusion reserve measure by 15-oxygen PET. Cardiac perfusion increased in the active treatment arm at 6 weeks by 14% (N=26). Perfusion decreased in the placebo arm at 6 weeks by 15% (N=23). According to the Applicant, the results met pre-specified statistical margins for a significant difference between treatment groups in favor of active treatment.

Safety

There were no deaths, SAEs, or discontinuations for adverse events. Thirteen of 27 subjects in the active treatment arm reported AEs (48.1%), whereas 9 of 29 subjects on placebo reported AEs (31.0%).

The most frequent AES are shown in Table 5. There were no noteworthy findings.

Table 5. Most Frequently Reported AEs (>3% of Subjects)

	Active Treatment		Placebo	
AEs by HARTS term	N = 27		N = 29	
AEs by HARTS term	**n**	**%**	**n**	**%**
Headache	3	11.1	2	6.9
Upper respiratory infection	2	7.4	2	6.9
Arthralgia	1	3.7	1	3.4
Gastrointestinal disorder	1	3.7	1	3.4

N: Total number of patients per treatment group
n: Number patients with AE
Source: TT87, p.147 of Final Clinical Study Report

Laboratory findings were clinically insignificant. Shifts in sodium and potassium were slight and consistent with antimineralocorticoid effect. There were decreases from baseline serum sodium of 2.1 mmol/L in the active group and 1.2 mmol/L in the placebo group, and increases from baseline in serum potassium of 0.08 mmol/L in the active group, and 0.06 mmol/L in the placebo group.

Conclusions

This study provided no unexpected safety findings.

10.1.2 Study 306946 (Study Report A11620)

Study Overview

The study was a double-blind, randomized, crossover study to assess the potential of drospirenone to inhibit cytochrome P450 3A4 by looking for interaction between DRSP and midazolam. Twenty-five healthy postmenopausal women participated at a single center in Germany. Treatment in the active treatment arm was 2x3mg DRSP on the evening of Day 1, followed by 3 mg DRSP daily on Days 2 though 9, and 4 mg midazolam on Days 7 and 9. In the placebo arm, placebo replaced DRSP. The route of therapy was oral.

Disposition

Seventy-seven subjects were screened. Twenty-eight did not meet inclusion/exclusion criteria; 21 were reserve volunteers; 2 withdrew consent; 1 withdrew for logistic reasons, and 25 subjects received treatment. One subject (#9) discontinued therapy because she received the wrong treatment on Day 7 (placebo instead of DRSP). Twenty-four of 25 subjects completed therapy.

Baseline Characteristics

All subjects were Caucasian. The average age was 59.8 years old, the average weight was 67.6 kg, and the mean body mass index was 25.3 kg/m^2.

Efficacy

The primary pharmacokinetic endpoint was mean of Day 7 and Day 9 AUC for midazolam and its metabolite (1'OH-MDZ). The criteria to conclude equivalence between treatments were fulfilled. Therefore DRSP did not affect the serum concentration of midazolam, a drug primarily metabolized by CYP 3A4 enzymes.

Safety

There were no deaths, no serious adverse events, and no discontinuations related to adverse events. Overall, 25 subjects experienced 142 adverse events: 73 AEs during placebo administration and 69 AEs during DRSP administration. Ninety-six of 142 events were "sedation". The following adverse events were reported for more than 2 subjects:

- Sedation (N=25)
- Venipuncture site hemorrhage (N=4)
- Erythema (N=4)
- Diarrhea (N=3)
- Back pain (N=3)
- Headache (N=3)

Comment: Sedation is an expected reaction to midazolam.

There were no on-therapy safety laboratory evaluations. One subject had an elevated post-treatment alanine aminotransferase level to 121 U/L that resolved on follow-up.

Conclusions

There were no unexpected safety findings. DRSP did not affect the activity of CYP3A4 enzymes.

10.1.3 Interim Report of the European Active Surveillance Study (EURAS)

Study Overview

This is the latest of several interim reports for the EURAS study. Briefly, the study is a postmarketing surveillance study being performed in Europe chiefly to evaluate the cardiovascular risks in three cohorts: users of Yasmin, users of levonorgestrel (LNG)-containing contraceptives, and users of other oral contraceptives (OCs). Local physicians recruit women when they write a new prescription for an oral contraceptive. Women receive a questionnaire through the mail requesting follow-up every six months. Multiple methods of contact have kept the lost-to-follow-up rate between 1 and 2%. The study will end in 2006.

Baseline Characteristics and Disposition

The present interim report includes data collected up to June 9, 2004. At this time, quality controlled data sets with follow-up were available on 49,342 women representing 64,103 women-years of observation. Table 6 shows the number of women and women-years by cohort.

Table 6. Study Subjects by Cohort

	Yasmin		LNG-containing OCs		Other OCs		Total Study	
N (%)	15,020	(30.4)	14,630	(29.7)	19,692	(39.9)	49,342	(100)
Women-years (%)	19,530	(30.5)	18,476	(28.8)	26,097	(40.7)	64,103	(100)
Mean Age (SD)	26.3	(8.2)	25.2	(8.8)	25.1	(8.0)	25.5	(8.3)

Source: Table on p.9 of EURAS Report- Database Status: June 9, 2004, in Safety Update section of NDA submission

About 20 percent of subjects in each cohort are first-ever users of oral contraceptives. Differences in cohorts at baseline detected so far are

- The percentage of obese women is higher in the Yasmin user cohort compared to both other cohorts (6.9% for Yasmin, 4.4% for LNG, and 3.8% for Other OCs)
- A higher percentage of Yasmin users reported having had elevated cholesterol levels than LNG users (2.9% for Yasmin, 1.8% for LNG, and 2.5% for other)

Safety

No differences have been detected in death rates (Table 7), adverse event reporting rates, venous thromboembolic event rates (Table 8), or arterial plus venous thromboembolic rates (Table 8). According to the Applicant, the results for all thromboembolic events are robust enough to exclude a 1.8-fold thromboembolic risk of Yasmin users compared to users of LNG-containing

OCs or other OCs. The only deaths related to thrombotic events (N=2) occurred in the LNG cohort. Remaining deaths were related to cancer, infection, accident, and an aortic aneurysm.

Table 7. Fatal Cases – Number of Deaths, Incidence, 95% CI

	Yasmin			LNG-containing OCs			Other OCx		
	N	Incidence*	95% CI	N	Incidence	95% CI	N	Incidence	95%CI
All Deaths	2	**1**	0.1-3.7	4	**2.2**	0.6-5.5	4	**1.5**	0.4-3.9

*Incidence and 95% CI per 10,000 women-years of observation
Source: Table on p.18 of EURAS Report- Database Status: June 9, 2004, in Safety Update section of NDA submission

Table 8. Confirmed Thromboembolic Events

Event category	Yasmin (19,530 WY)			LNG-containing OCs (18,476 WY)			Other OCs (26,097 WY)			Total
	n	per 10^4 WY	95% CI	n	per 10^4 WY	95% CI	n	per 10^4 WY	95% CI	
All VTE & ATE	**13**	**6.7**	**3.5 - 11.4**	**14**	**7.6**	**4.1 – 12.7**	**23**	**8.8**	**5.6 – 13.2**	**50**
All VTE	**12**	**6.1**	**3.2 - 10.7**	**11**	**6.0**	**3.0 – 10.7**	**19**	**7.3**	**4.4 – 11.4**	**42**
of which PE	3	1.5	0.3 – 4.5	2	1.1	0.1 – 3.9	2	0.8	0.1 – 2.8	7
All ATE	**1**	**0.5**	**0.0 – 2.9**	**3**	**1.6**	**0.3 – 4.8**	**4**	**1.5**	**0.4 – 3.9**	**8**
of which AMI	0	0.0	0.0 – 1.9	1	0.5	0.0 – 3.0	2	0.8	0.1 – 2.8	3
CVA	1	0.5	0.0 – 2.9	2	1.1	0.1 – 3.9	2	0.8	0.1 – 2.8	5
Fatal VTE/ATE	**0**	**0.0**	**0.0 – 1.9**	**2***	**1.1**	**0.1 – 3.9**	**0**	**0.0**	**0.0 – 1.4**	**2**

Source: Table on p.29 of EURAS Report- Database Status: June 9, 2004, in Safety Update section of NDA submission

Conclusions

This large post-marketing study has not detected an unusual safety signal related to thromboembolic events or deaths among women using Yasmin, a contraceptive containing DRSP.

10.2 Executive Summary of Clinical Review Supporting the Non-Approval Action (17-Oct-2002)

1. Recommendations

From a clinical perspective, Angeliq is not approvable for safety reasons.

Angeliq is a once-a-day tablet, intended for women with an intact uterus. The proposed indications are:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.
2. Treatment of vulvar and vaginal atrophy.

It contains two hormones, the estrogen, estradiol (E_2), for treatment of menopausal symptoms, and the progestin, drospirenone (DRSP), for protection of the endometrium from estrogen-induced hyperplasia [redacted] The Applicant requests approval of [redacted] dosage combinations for oral use:

[redacted]

E_2 is a widely used estrogen found in many combination estrogen plus progestin (E/P) products for menopause symptoms. On the other hand, DRSP is found in only one marketed product, the oral contraceptive Yasmin, approved in the U.S. in May 2001. DRSP is unique among marketed progestins for its potent antimineralocorticoid activity, with DRSP 3 mg roughly equivalent in antimineralocorticoid potency to spironolactone 25 mg. Because of DRSP's antimineralocorticoid properties, Yasmin's approval depended on the Applicant agreeing to Phase 4 commitments to evaluate the risk of hyperkalemia.

The usual serious safety concerns for E/P products are thrombotic events and breast cancer. Estrogen is considered the cause of the increase in thrombotic events, although observational studies in recent years suggest that certain progestins may have thrombotic properties as well. Breast cancer has always been a safety concern for women using E/P products for menopause symptoms, a concern reinforced by a recent publication from the Women's Health Initiative.[1] However, the increased risk of breast cancer in the Women's Health Initiative was only significant after five years of therapy. Therefore, detection of an increased risk of breast cancer is unlikely in the typical one- to two-year clinical trials for marketing approval of E/P products.

Common side effects for E/P products, such as vaginal bleeding, headaches, and breast discomfort, are usually mild and well tolerated, but can lead to discontinuations.

[1] Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA*, 2002; 288:321-333.

In this NDA, the Applicant showed efficacy in treatment of menopausal symptoms by showing bioequivalence of E_2 in Angeliq to E_2 in the marketed product, Estrace. Although the data showed that DRSP protects the endometrium from E2-induced hyperplasia, evidence of bias and quality issues were detected in the pathology readings. That is, there was no evidence that DRSP 3 mg offered any benefit over DRSP 1 mg. More importantly, the safety data raised two concerns beyond those expected for E/P products used to treat menopause symptoms. The first concern was electrolyte abnormalities, particularly hyperkalemia. The second concern was the possibility that DRSP is a thrombogenic progestin, raised by postmarketing reports of thrombotic events for Yasmin.

In a Phase I study, a woman with preexisting risk factors developed severe hyperkalemia that appeared to be related to DRSP. Although the risk of hyperkalemia in healthy women is probably small, the risk is not shared with other E/P products for menopause symptoms.

The other safety concern is that DRSP may be a thrombogenic progestin. Although the clinical trials for Angeliq did not detect an unusual number of thrombotic events, there have been more postmarketing reports than expected in users of Yasmin, the oral contraceptive containing DRSP. Reporting may be increased because of true increased risk, because of enhanced sensitivity to this issue, or because higher risk women are receiving Yasmin.

To address the issue of thrombotic events in Yasmin users, the European Active Study Surveillance Group launched a large prospective cohort study in 2001. Investigators expect to enroll 30,000 women by 2003, and end the study in 2006. It is prudent to await the results of this study before approving Angeliq, a product intended for women who are older than the typical Yasmin user, because older women are already at risk for life-threatening thrombotic events because of age-related cardiovascular changes.

In summary, we must set a high safety bar for a product intended to treat the discomforts of a normal stage of life. There is no shortage of therapies, and little tolerance for new risks. So far, Angeliq has shown no benefit over other E/P products to justify added risk. In addition, the Applicant must show that DRSP is not a thrombogenic progestin by showing that users of Yasmin have no greater risk of thrombosis than users of other oral contraceptives. The large prospective cohort study described above may adequately address the thrombosis issue, or the Applicant may propose additional studies. And finally, the quality issues in the endometrial

biopsy readings may be addressed by a complete re-reading of the endometrial biopsy slides, by pathologists who are independent.

2. Summary of Clinical Findings

2.1 Brief Overview of Clinical Program

The three clinical trials for efficacy studied 1214 postmenopausal women, with 1142 in an endometrial protection trial, and 72 in two bioequivalence trials.

Nine clinical trials contributed to the safety database of 1893 women who took E_2 + DRSP. Most of the women (95%) were between the ages of 45 and 65.

2.2 Efficacy

The Applicant showed efficacy by showing bioequivalence of E_2 in Angeliq to E_2 in the marketed product, Estrace. The FDA biopharmaceutical reviewer reviewed these two studies.

DRSP prevented E_2-induced endometrial hyperplasia. The endometrial protection trial showed one-year hyperplasia rates of less than 2% for the DRSP 1 mg, 2 mg, and 3 mg treatment groups, with the upper bound of the one-sided 95% confidence interval less than 4%. The lowest dose tested, 0.5 mg DRSP, did not meet these criteria for prevention of endometrial hyperplasia, and therefore DRSP 1 mg was the lowest dose that protected the endometrium. However, there was evidence of bias and quality issues in the pathology readings. One pathologist appeared to have undue influence in cases of disagreement among pathologists. The same pathologist had wide discrepancies in his own readings of the biopsy slides, for example, reading three slides as "hyperplasia" (including one atypical hyperplasia) for the purpose of patient care, and re-reading them as "inactive, atrophic" for the purpose of calculating hyperplasia rates.

[redacted]DRSP 3 mg showed no advantage over DRSP 1 mg in endometrial protection, bleeding profile, or any other secondary endpoints.

2.3 Safety

Except for electrolyte abnormalities and possible increased thrombotic tendencies, Angeliq had a safety profile much like other E/P regimens.

The safety database contains 1893 women who took DRSP + E_2, with 362 women exposed to DRSP 1 mg + E_2 1 mg, 641 women exposed to DRSP 3 mg + E_2 1 mg, and the remaining women exposed to other combinations of E_2 (1 or 2 mg) and DRSP (0.5, 1, 2, 3, or 4 mg). Most women (N=1114) had 52 or more weeks of exposure. The total exposure in the safety database

met ICH guidelines for drugs intended for long-term treatment of non-life-threatening conditions.[2] The probable marketing exposure will be months to years.

There was one death unrelated to study drug. A woman who took DRSP 1 mg plus E_2 1 mg for nine months died in an auto accident. She had no medical history suggesting increased risk for electrolyte abnormalities, and had normal electrolyte levels two months before the accident.

Six women had serious thromboembolic events. However, the percentage of women with serious thromboembolic events was similar to the percentage in the clinical trials of other E/P products for menopause symptoms. Concern about thromboembolic events arose from an unexpectedly high number of postmarketing reports in users of Yasmin, the oral contraceptive that contains DRSP. Concern in Europe was sufficient to launch a large prospective cohort study to evaluate thrombotic events in women using Yasmin compared with women using other oral contraceptives. Investigators expect to enroll 30,000 women in this study, which will end in 2006.

Because of FDA concerns about potential electrolyte problems, the Applicant did four Phase I PK studies that exposed women with risk factors for hyperkalemia to Angeliq. The risk factors included kidney impairment, liver impairment, indomethacin intake, and ACE inhibitor intake. Altogether, these four trials exposed 65 women with risk factors for hyperkalemia to DRSP.

Among these 65 women, one woman had serious hyperkalemia related to DRSP use. This occurred in the liver impairment study. The subject was a 46-year-old woman with moderate liver impairment, who was included in the study despite having three exclusion criteria.[3] After a single dose of Angeliq (E_2 1 mg plus DRSP 3 mg), she developed persistent, severe hyperkalemia that required hospitalization and Kayexalate treatment. This woman illustrated not only the potential for severe hyperkalemia following DRSP exposure, but also the danger of medication errors. A second woman was removed from the indomethacin study on Day 1, after a drop in creatinine clearance following indomethacin intake, and before any exposure to DRSP. What might have happened had she not been getting daily labs will never be known. However, close scrutiny of daily labs is not feasible in actual practice.

Trial exclusions decreased the likelihood of detecting electrolyte abnormalities. Overall, the trials studied healthy postmenopausal women, with the exception of the four small safety trials mentioned above. In addition, in all trials women had to have normal baseline labs to be included. As it is not the standard of care to evaluate electrolytes, liver function, and kidney function before starting E/P products, we can expect some women with these problems to be inadvertently exposed to Angeliq in actual practice. How this would impact the risk of hyperkalemia is not known.

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2 http://www.fda.gov/cder/guidance/iche1a.pdf. Guideline for Industry. The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions.

[3] Among her exclusion criteria were insulin dependent diabetes, evidence of renal compromise at baseline, and possible vascular disease as shown by the amputated extremity, although the case report form does not give a reason for the amputation.

Breast cancer may be increased in women using E/P products for menopause,[1] although it is possible that the increase seen in the early years of E/P therapy represents earlier diagnosis, as appears to be the case with oral contraceptives.[4] The eight breast cancers detected in the safety data for Angeliq were not excessive compared to the expected incidence of breast cancer for postmenopausal women, but the mean duration of therapy, 53.8 weeks, was short for detecting breast cancer. In addition, the Angeliq trials excluded women with baseline abnormal mammograms or a history of breast cancer, so comparing Angeliq-exposed subjects to historical controls that include all postmenopausal women is problematic.

There were no clinically significant changes in weight, blood pressure, lipids, liver function tests, or complete blood counts. In one small study there was a slight decrease in glucose tolerance in women using ethinyl estradiol (EE) plus DRSP 3 mg (a 10% increase in the $AUC_{0\text{-}3hr}$ for glucose at 6 months, compared to baseline). This is consistent with the known effects of progestins on glucose tolerance.

The most frequent adverse events (AEs) resulting in discontinuation, in order of most to least frequent, were vaginal bleeding, breast pain, headache, and depression, which are all expected for this class of drugs. The following table shows AEs occurring in more than 5% of women.

Adverse Events in More than 5% of Subjects

Adverse Event	All DRSP groups n (%)	E_2 1 mg n (%)
Breast pain	369 (19.5)	35 (13.3)
Vaginal hemorrhage	205 (10.8)	44 (16.7)
Headache	181 (9.6)	29 (11.0)
URI	153 (8.1)	40 (15.2)
Abdominal pain	147 (7.8)	31 (11.8)
Flu syndrome	138 (7.3)	15 (5.7)
Back pain	121 (6.4)	15 (5.7)
Infection	115 (6.1)	3 (1.1)
Pain in extremity	98 (5.2)	16 (6.1)

Limited data did not show significant drug-drug interactions (simvastatin and omeprazole interaction studies).

2.4 Dosing

The dose of E_2 in Angeliq is the same as the lowest dose of E_2 recommended for the same indications in the approved product, Estrace. The Applicant did not do any dose ranging since

[4] Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53,297 women with breast cancer and 100,239 women without breast cancer from 54 epidemiological studies. *The Lancet*, 1996;347:1713-1727.

efficacy was shown by bioequivalence, as previously agreed between the Applicant and the FDA.

The doses of DRSP [redacted] were both effective at protecting the endometrium against endometrial hyperplasia, while a lower dose, 0.5 mg, was not. The Applicant did not show an advantage of DRSP 3 mg over DRSP 1 mg.

An unresolved dosing issue is that the effect of DRSP alone on hot flushes was never studied. Some progestins are effective in treatment hot flushes[5,6] and DRSP may have activity as well. If so, it may be possible to reduce the E_2 dose or eliminate E_2 altogether. There might be adverse consequences to this approach, such as adverse effects on bone or lipids, but without the data, we do not know. Nonetheless, the Applicant's approach, using an estrogen for efficacy and a progestin for endometrial safety, is a recognized standard for treatment of menopause symptoms.

2.5 Drug-Drug Interactions

E_2 and DRSP do not affect each other's pharmacokinetics. DRSP does not appear to induce or inhibit the cytochrome P450 enzymes 2C29 and 3A4. Estradiol drug-drug interactions were not studied in this submission. Based on what is known about the related drug, ethinyl estradiol, estradiol concentrations may vary 20-30% in the presence of hepatic enzyme inducers and inhibitors. This should not compromise safety.

2.6. Special Populations

Racial differences were not detected in the data, but the safety database was largely Caucasian (94%). There were no pharmacokinetic studies of racial differences. All ten DRSP-exposed women with endometrial hyperplasia in the endometrial protection trial were Caucasian, but so were most of the women in the trial (92%).

Too few women over 65 were studied to know if there were age-related issues in efficacy or safety. However, the limited data did not suggest a different safety profile in older women. In the endometrial protection trial, the average age of ten DRSP-exposed women who developed endometrial hyperplasia was 58 years old, not much different from the average age of trial participants, which was 56 years old.

Women with moderate liver or kidney disease have greater exposure to DRSP than women with normal liver and kidney function. DRSP exposure in women with moderate liver impairment,

[5] Lobo RA, McCormick W, Singer F, Roy S. Depo-medroxyprogesterone acetate compared with conjugated estrogens for the treatment of postmenopausal women. Obstet Gynecol. 1984 Jan;63(1):1-5

[6] Loprinzi CL, Michalak JC, Quella SK, O'Fallon JR, Hatfield AK, Nelimark RA, Dose AM, Fischer T, Johnson C, Klatt NE, et al. Megestrol acetate for the prevention of hot flashes N Engl J Med 1994 Aug 11;331(6):347-52

measured by AUC, is about twice the exposure in women with normal liver function. DRSP serum concentrations were 37% greater at steady state in women with moderate renal impairment compared with women with normal renal function.

The Applicant did not study children and requested a pediatric waiver. Since the proposed indications apply to postmenopausal women, a pediatric waiver is recommended.

10.3 Executive Summary of Clinical Review Supporting the Approvable Action (14-Sep-2004)

1.1 Recommendation on Regulatory Action

I recommend a nonapproval action for Angeliq containing drospirenone —— because the dose of drospirenone (DRSP) is higher than necessary to protect the endometrium from estrogen-induced hyperplasia.

Nine days before the action date, the Applicant submitted an amendment containing labeling for Angeliq containing DRSP 0.5 mg. The amendment did not contain CMC information to support the DRSP 0.5 mg dose. I recommend an approvable action for Angeliq containing DRSP 0.5 mg since the appropriate Chemistry, Manufacturing and Control (CMC) information for the 0.5 mg DRSP dose has not been submitted, a Phase 4 commitment has not been negotiated with the Applicant to conduct a clinical study demonstrating the lowest effective dose (LED) of DRSP, and labeling has not been negotiated.

DRSP is unique among marketed progestins for its potent antimineralocorticoid activity, with DRSP 3 mg roughly equivalent in antimineralocorticoid potency to spironolactone 25 mg. Spironolactone is associated with hyperkalemia in vulnerable patients. Although the incidence of hyperkalemia is greater with higher doses of spironolactone, even the lowest approved dose of spironolactone (25 mg) has been associated with hyperkalemia.

The risk of hyperkalemia in a postmenopausal woman exposed to DRSP 1 mg is likely to be small. In general under the controlled conditions of clinical trials, women exposed to DRSP have had small, insignificant, mean increases in serum potassium and decreases in serum sodium consistent with antimineralocorticoid effect. Studies have detected only one high risk woman who was hospitalized for hyperkalemia following a single dose of DRSP 3 mg.

However, it is unclear why a woman who simply seeks relief from menopausal symptoms should assume *any* risk of electrolyte abnormalities when she has a wide choice of hormonal preparations that do not affect electrolytes. To minimize the risk of electrolyte abnormalities, Angeliq should contain the lowest dose of DRSP that will protect the endometrium from hyperplasia induced by estradiol. As discussed in the following section, the data show that DRSP 0.5 mg protects the endometrium. The Applicant has not provided an acceptable rationale for seeking approval for the —— dose, nor has the Applicant determined the lowest effective dose of DRSP.

1.2 Recommendation on Postmarketing Action

Not applicable.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Angeliq is a once-a-day tablet intended for menopausal women who have a uterus. The proposed indications are:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.
2. Treatment of vulvar and vaginal atrophy.

Angeliq contains two hormones:

1. 17β-estradiol (E_2), an estrogen, for treatment of menopausal symptoms
2. drospirenone (DRSP), a progestin, for protection of the endometrium from estrogen-induced hyperplasia and cancer.

E_2 is widely used for menopause symptoms. In contrast, DRSP is found in only one US product, the oral contraceptive Yasmin, approved in the U.S. in May 2001.

On October 17, 2002, FDA issued a nonapproval letter for Angeliq based on 3 concerns:

1. Thrombotic risk
2. Hyperkalemia risk
3. Unreliable endometrial biopsy results

The thrombotic concerns arose from a high postmarketing reporting rate for thrombotic events for Yasmin. The hyperkalemia concerns were mainly theoretical, although one especially vulnerable woman with liver disease developed severe hyperkalemia during a Phase 1 trial after exposure to *a single dose of DRSP 3 mg*. The endometrial biopsy concerns arose from several large disparities between the efficacy and safety readings of the same study slides. In addition, the opinion of one of three pathologists dominated the readings when there were disparities among pathologists. The same pathologist had large disparities between his own readings of the same slides. When the FDA reviewer analyzed the results conservatively, the incidence of atypical hyperplasia of the endometrium was unacceptable.

To address the endometrial biopsy concerns, the Applicant negotiated the details of a rereading of the slides from the endometrial protection study presented in the original NDA. The rereading, presented in Study Report A17844, included 966 on-treatment biopsies for women in the following treatment groups:

1. E_2 1 mg (N=197)
2. E_2 + DRSP 0.5 mg (N=191)
3. E_2 + DRSP 1 mg (N=191)
4. E_2 + DRSP 2 mg (N=194)
5. E_2 + DRSP 3 mg (N=193).

In addition, the Applicant provided study reports for two European studies in postmenopausal women to support the endometrial biopsy data. Study Reports AR99 and AU18 provided data on

42 more subjects exposed to Angeliq (E_2 1 mg + DRSP 1 mg) and 335 subjects exposed to E_2 1 mg in combination with higher doses of DRSP (2 mg or 3 mg).

To address concerns about thrombosis and hyperkalemia, the Applicant provided new clinical data summarized in Table 9.

Table 9. Primary New Clinical Data Sources to Address Thrombosis and Hyperkalemia Concerns

Name of Study	N	Women-Years of Exposure	Treatment	Brief Description of Study	Status
EURAS	15,020	19,530	Yasmin	Prospective post-marketing surveillance in Europe	Ongoing
Phase 4 Ingenix Study	7,283	Not provided	Yasmin	Retrospective Phase 4 Study in US, postmarketing surveillance	Ongoing
Protocol 305471/ Study Report A08460	112	8	E_2 1 mg + DRSP 3 mg	RCT to study K+ in women with risk factors for hyperkalemia	Complete
Protocol 305140/ Study Report A07575	102	23	E_2 1 mg + DRSP 3 mg	RCT to study blood pressure	Complete

EURAS = European Active Surveillance Study
RCT = randomized, controlled trial
Source: created by reviewer from information in Safety Update and individual study reports

Finally, the Applicant provided an update of postmarketing spontaneous reports for Yasmin.

1.3.2 Efficacy

By prior agreement with the FDA, efficacy was shown in the original NDA submission by showing bioequivalence of the E_2 in Angeliq to an approved product, Estrace.

1.3.3 Safety

Thrombotic Risk

The most convincing data come from the European Active Surveillance Study (EURAS), which compares the incidence of thrombotic events in women using Yasmin and women using levonorgestrel-containing and other oral contraceptives. The EURAS Study supports that Yasmin users and users of levonorgestrel (LNG)-containing contraceptives have a similar incidence of death and thrombotic events.

A strength of this well-designed study is its large size. The most recent interim analysis from June 2004 provided 19,530 women-years of exposure to Yasmin, and 18,476 women-years of exposure to LNG-containing oral contraceptives. However, a problem with the EURAS Study is that it is incomplete. Nonetheless, three interim analyses of the EURAS Study have had the same conclusion: users of Yasmin and users of LNG-containing contraceptives have a similar incidence of thrombotic events.

Also, an integrated analysis of data from the Applicant's clinical trials for Yasmin and Angeliq support the EURAS findings because there have not been more women with thromboembolic events than expected in the trials. However, exposure in the clinical trials is too limited to pinpoint the incidence of a rare event, such as a venous thromboembolic event (VTE).

The high spontaneous reporting rate for death and thrombotic events in Yasmin users seen shortly following approval remains unexplained. However, because of the vagaries of spontaneous reporting, the EURAS Study, supported by clinical trials, provides a more reliable measure of VTE risk.

Nonetheless, the EURAS trial is incomplete, and relying on interim reports is not without risk. The Applicant should report the results of the completed trial to the NDA as soon as it becomes available in 2006.

Hyperkalemia Risk

The lowest approved dose of spironolactone (25 mg) has been associated with severe hyperkalemia in vulnerable patients. Spironolactone 25 mg is roughly equivalent in antimineralocorticoid potency to DRSP 3 mg. The Applicant's proposed dose is DRSP-[redacted]

Hyperkalemia has not been detected as a problem in Yasmin users since the launch of Yasmin, which contains DRSP 3 mg. While this is reassuring, it is important to point out that users of oral contraceptives are typically young, healthy women. Women seeking treatment for menopausal symptoms are older, and therefore may be more at risk for hyperkalemia because of chronic conditions or concomitant medications.

Clinically significant hyperkalemia was detected in one high risk 46-year old woman in a Phase I trial (reviewed in the original Angeliq submission). This woman took a single dose of DRSP 3 mg. She had an unusually high serum concentration of DRSP, likely related to hepatic dysfunction and concomitant medications. Otherwise, although there have been other instances of hyperkalemia, there have been no serious adverse events related to hyperkalemia in the clinical trials of Angeliq.

The present submission includes one trial that studied potassium changes in high risk women exposed to a daily dose of DRSP 3 mg (Study Report A08460). In this trial, one DRSP-exposed subject (N=112) developed serious hyperkalemia (serum potassium = 6.1 mEq/L) as predefined in the protocol, and no placebo-exposed subjects (N=118) developed serious hyperkalemia. Although the difference in the incidence of hyperkalemia between treatment groups was not statistically significant, the study was not designed to detect small differences. The report also analyzed the incidence of serum potassium greater than or equal to 5.5 mEq/L. In the DRSP/ E_2 group, 7.1% of subjects had a serum potassium $\geq$ 5.5 mEq/L on treatment, whereas in the placebo group, 2.5% of subjects had serum potassium $\geq$ 5.5 mEq/L on treatment. No subject had an adverse event related to hyperkalemia in either treatment group.

In the same study, a single subject had a serum sodium less than 130 mEq/L on treatment. She was in the DRSP/ E_2 treatment group. Another subject was hospitalized following a fall and diagnosed with dehydration eight days after completing treatment. She had a serum sodium < 130 mEq/L at her follow-up visit, three days after completing therapy. She too was in the DRSP/ E_2 treatment group. However, she was also hyperglycemic at the follow-up visit, and hyperglycemia is associated with hyponatremia.

In general, women exposed to DRSP have had small (and insignificant) mean increases in serum potassium and mean decreases in serum sodium consistent with antimineralocorticoid effect, compared with placebo groups. However, the screening process for the clinical trials excluded subjects with risk factors such as baseline electrolyte abnormalities. Even the clinical trials that studied women with risk factors for hyperkalemia carefully limited the number of risk factors and excluded women with baseline electrolyte abnormalities. In typical practice settings, women seeking treatment for hot flushes are not likely to be tested for baseline hyperkalemia, or to be denied Angeliq because of multiple risk factors for hyperkalemia. Therefore the risk of hyperkalemia may be greater than the risk seen in clinical trials.

It is unclear why a woman who simply seeks relief from menopausal symptoms should take *any* risk of electrolyte abnormalities when she has a wide choice of estrogen preparations that do not affect electrolytes. The only role of DRSP in Angeliq is to protect the endometrium from endometrial hyperplasia. As discussed in the following section, DRSP 0.5 mg provides acceptable protection of the endometrium.

To minimize the risk of electrolyte abnormalities and other adverse events, Angeliq should contain the lowest dose of DRSP that will provide endometrial protection. The Applicant did not prepare to market the DRSP 0.5 mg product because the flawed endometrial biopsy readings presented in the original NDA did not show efficacy of DRSP 0.5 mg for endometrial protection.

Endometrial Biopsy Rereading

In the rereading, on-treatment slides for all subjects from the original study were reviewed sequentially by three independent expert pathologists who were blinded to each other's diagnoses. The final diagnosis was based on the concurrence of two of three pathologists. If there was no concurrence, the most severe pathology was accepted as the final diagnosis. If polyps were detected, the final diagnosis was based on surrounding endometrial tissue. However, if a polyp was graded as cancerous, then the final diagnosis for the endometrial biopsy was carcinoma.

By all of the Applicant's analyses, every dose of DRSP tested (0.5 mg, 1 mg, 2 mg, and 3 mg) adequately protected the endometrium from hyperplasia induced by exposure to E_2 1 mg. By a more conservative FDA analysis that did not impute results for women with inadequate biopsies, all doses except the 2 mg dose protected the endometrium. The 2 mg dose of DRSP does not meet FDA criteria for protection of the endometrium because the upper bound of the confidence interval was greater than 4%. Given that lower doses of DRSP protected the endometrium, it is

likely the study was underpowered; that is, the number of informative biopsies in the DRSP 2 mg group was too small. The supportive studies from Europe suggested that the DRSP 2 mg dose was adequate for endometrial protection.

Since the lowest dose of DRSP (0.5 mg) adequately protected the endometrium from estrogen-induced hyperplasia:

- The study did not show the lowest effective dose
- The dose (——) for which the Applicant seeks approval is higher than necessary for endometrial protection.

During the review cycle, the Applicant was asked to provide justification for the ——— because the data presented supported the 0.5 mg dose. The Applicant was unable to provide valid scientific arguments for selecting the higher dose.

Safety Update

The Applicant's safety update covering the period from August 5, 2002 through December 31, 2003 did not reveal any new safety concerns.

1.3.4 Dosing Regimen and Administration

As noted above, Angeliq is a daily oral tablet containing E_2 1 mg and DRSP ——— However, the data support a daily oral tablet containing E_2 1 mg and DRSP *0.5 mg*. Moreover, the lowest effective dose of DRSP has not been determined.

1.3.5 Drug-Drug Interactions

See original medical review.

1.3.6 Special Populations

See original medical review.

10.4 Line-by-Line Labeling Review

35 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

__X__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical- 1

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/s/

Lesley-Anne Furlong
9/15/2005 10:30:31 AM
MEDICAL OFFICER

Scott Monroe
9/28/2005 08:11:35 AM
MEDICAL OFFICER
I concur with Dr. Furlong's recommendation that (0.5 mg DRSP/1 mg 17B estradiol) tablets be approved for the treatment of symptoms of moderate to severe vulvar and vaginal atrophy associated with the menopause.

Angeliq Division Director's Memorandum
(complete response to a non-approval)

For:	**NDA 21-355**
From:	**Daniel A. Shames MD** **Director,** **Division of Reproductive and Urologic Drug Products** **CDER/FDA**
NDA Submitted:	**March 19, 2004**
PDUFA Goal Date:	**September 19, 2004**
Date of Memorandum:	**September 14, 2004**
To:	**File**
Drug Name:	
Generic:	**17β Estradiol (E_2) and drospirenone (DRSP)**
Trade:	**Angeliq**
Sponsor:	
Pharmacologic categories:	**estrogen and progestin**
Dosage Form:	**Oral tablet**
Strength:	**E_2 1mg and drospirenone 1mg**
Proposed Indications:	**1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.** **2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause.**

1.0 Background and Regulatory History

Angeliq is a once daily tablet intended for menopausal women with a uterus. The proposed indications are:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.
2. Treatment of vulvar and vaginal atrophy.

Angeliq contains two hormones:

1. 17β-estradiol (E_2), an estrogen, for treatment of menopausal symptoms

2. drospirenone, a progestin, to protect the endometrium from estrogen-induced hyperplasia and cancer.

E_2 is approved and widely used for menopausal symptoms. By prior agreement with the FDA, the Sponsor supported efficacy in the original NDA submission by demonstrating bioequivalence of the E_2 in Angeliq to the approved product, Estrace.

DRSP is found in one US product, the oral contraceptive Yasmin, approved in the U.S. in May 2001. Yasmin contains DRSP 3 mg and ethinyl estradiol 0.03 mg. DRSP is unique among marketed progestins because of its antimineralocorticoid activity. DRSP 3 mg is roughly equivalent in antimineralocorticoid potency to spironolactone 25 mg.

On October 17, 2002, FDA issued a nonapproval letter for the original NDA submission of Angeliq based on concerns for thromboembolic and hyperkalemia risks as well as unreliable endometrial biopsy results. The thrombotic concerns arose from a high postmarketing reporting rate for thrombotic events for Yasmin. The hyperkalemia concerns were mainly theoretical, although one especially vulnerable woman with liver disease developed severe hyperkalemia during a Phase 1 trial after exposure to a single dose of DRSP 3 mg. The endometrial biopsy concerns arose from several large disparities between the efficacy and safety readings of the same study slides.

In the original NDA, Berlex sought approval for E_2 1 mg plus DRSP [redacted] and E_2 1 mg plus DRSP [redacted] In the complete response(CR), the Sponsor seeks approval only for the lower dose (E_2 1 mg plus DRSP [redacted]).

2.0 Data in the Complete Response

2.1 Endometrial Biopsy Concerns

To address this issue, the Sponsor agreed with the Division to submit a rereading of the slides from the endometrial protection study presented in the original NDA. The rereading, presented in Study Report A17844, included 966 on-treatment biopsies for women in the following treatment groups:

1. E_2 1 mg (N=197)
2. E_2 + DRSP 0.5 mg (N=191)
3. E_2 + DRSP 1 mg (N=191)
4. E_2 + DRSP 2 mg (N=194)
5. E_2 + DRSP 3 mg (N=193).

In addition, the Sponsor provided information from two European studies in postmenopausal women to support the endometrial biopsy data from study 17844. Study Reports AR99 and AU18 provided data on 42 more subjects exposed to Angeliq (E_2 1 mg + DRSP 1 mg) and 335 subjects exposed to E_2 1 mg in combination with higher doses of DRSP (2 mg or 3 mg).

2.2 Thrombotic and Hyperkalemia Concerns

To address the issues of thrombosis and hyperkalemia, the Sponsor provided new clinical data summarized in Table 1.

Table 1. Primary New Clinical Data Sources to Address Thrombosis and Hyperkalemia Concerns

Name of Study	N	Women-Years of Exposure	Treatment	Brief Description of Study	Status
EURAS*	15,020	19,530	Yasmin	Prospective post-marketing surveillance in Europe	Ongoing
Phase 4 Ingenix Study	7,283	Not provided	Yasmin	Retrospective Phase 4 Study in US, postmarketing surveillance	Ongoing
Protocol 305471/ Study Report A08460	112	8	E_2 1 mg + DRSP 3 mg	RCT** to study K+ in women with risk factors for hyperkalemia	Complete
Protocol 305140/ Study Report A07575	102	23	E_2 1 mg + DRSP 3 mg	RCT** to study blood pressure	Complete

*European Active Surveillance Study
**Randomized, controlled trial
Source: created by reviewer from information in Safety Update and individual study reports

Finally, the Sponsor provided an update of postmarketing spontaneous reports for Yasmin.

3.0 Data in the Complete Response

3.1 Thrombotic Risk

The strongest data regarding this issue comes from the European Active Surveillance Study (EURAS), which compares the incidence of thrombotic events in women using Yasmin and women using levonorgestrel-containing oral contraceptives. The EURAS data support the thesis that Yasmin users and users of levonorgestrel (LNG)-containing contraceptives have a similar incidence of death and thrombotic events.

EURAS is a large well-designed study. The most recent interim analysis from June 2004 provided 19,530 women-years of exposure to Yasmin, and 18,476 women-years of exposure to LNG-containing oral contraceptives. However, a potential problem with EURAS is that it is incomplete. Nonetheless, three interim analyses of EURAS have had the same conclusion that users of Yasmin and users of LNG-containing contraceptives have a similar incidence of thrombotic events.

In addition, an integrated analysis of safety data from the Sponsor's clinical trials for Yasmin and Angeliq support the EURAS findings in that there have not been more women with thromboembolic events than would be expected in the trials.

The apparently high spontaneous reporting rate for death and thrombotic events in Yasmin users seen shortly following approval, which caused the concerns expressed in the NA letter, remains unexplained. However, the Division believes that EURAS, supported by clinical trials, provides a more reliable measure of thrombotic risk than the spontaneous reporting of adverse events.

3.2 Endometrial Safety

On-treatment slides for all subjects from the original study were reviewed sequentially by three independent expert pathologists who were blinded to each other's diagnoses. The final diagnosis was based on the concurrence of two of three pathologists. If there was no concurrence, the most severe pathology was accepted as the final diagnosis. If polyps were detected, the final diagnosis was based on surrounding endometrial tissue. However, if a polyp was graded as cancerous, then the final diagnosis for the endometrial biopsy was carcinoma. By all of the Sponsor's analyses, every dose of DRSP tested (0.5 mg, 1 mg, 2 mg, and 3 mg) adequately protected the endometrium from hyperplasia induced by exposure to E_2 1 mg.

3.3 Risk of Hyperkalemia

The sponsor provided five sets of data to support the safety of Angeliq with regard to the risk of hyperkalemia.

3.31 Study A08460

Study A08460 was 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 study collected potassium safety data in women with risk factors for hyperkalemia. Subjects were postmenopausal women who were taking an angiotensin converting enzyme (ACE) inhibitor or an angiotensin receptor blocker at baseline. About one third of subjects were diabetic. Nondiabetics received a five-day course of ibuprofen. Selected subjects also underwent ACE inhibitor dose titration. Subjects were randomly assigned to receive a 28-day course of DRSP 3 mg + E_2 1 mg, or placebo. At least seven subjects failed screening because of baseline elevations in serum potassium, including one subject with baseline serum potassium of 6.2 mEq/L. The prespecified primary endpoint was the incidence of serious hyperkalemia, and hyperkalemia was defined as serum potassium greater than 6.0 mEq/L. The study was not powered for any particular incidence of hyperkalemia; instead, the size of the study was chosen to provide more potassium safety data.

Among 112 women treated with DRSP/ E_2, one subject developed serious hyperkalemia (serum potassium = 6.1 mEq/L) as predefined in the study protocol. She was a nondiabetic who received ibuprofen, and she did not suffer any adverse events related to hyperkalemia. There were no subjects among 118 in the placebo group who developed serious hyperkalemia. The report also analyzed the incidence of serum potassium greater than or equal to 5.5 mEq/L. In the DRSP/ E_2 group, 7.1% of subjects had a serum potassium $\geq$ 5.5 mEq/L on treatment, whereas in the placebo group, 2.5% (N=3) subjects had serum potassium $\geq$ 5.5 mEq/L on treatment. Overall, mean changes in sodium and potassium were small, and consistent with antimineralocorticoid effect in the DRSP group.

Primary Reviewer's Comment: "The ability of the study to detect serious potassium problems was likely compromised by excluding women with baseline electrolyte abnormalities. One DRSP-exposed subject developed serious hyperkalemia as predefined in the protocol and no placebo-exposed subjects developed serious hyperkalemia. Although the difference in the incidence of hyperkalemia between treatment groups was not statistically significant, the study was not large enough to detect small differences. No subject had an adverse event related to hyperkalemia in either treatment group."

3.32 Study A07575

Study A07575 was a multicenter, double-blind, randomized, placebo-controlled study to evaluate the effect of a continuous-combined preparation containing 1 mg estradiol and 3 mg drospirenone on blood pressure in mildly hypertensive postmenopausal women.

The study compared DRSP 3 mg/ E_2 1 mg to placebo to treat blood pressure in mildly hypertensive, postmenopausal women. There were 102 women in the DRSP/ E_2 group, and 111 women in the placebo group. The treatment phase lasted 12 weeks. Serum potassium was assessed at baseline, and at 2, 6, and 12 weeks of therapy.

The study detected no adverse events related to electrolyte abnormalities. There were small changes in serum sodium and potassium consistent with antimineralocorticoid effect in the DRSP group. The changes were neither clinically nor statistically significant.

Primary Reviewer's Comment: "The ability of the study to detect serious potassium problems was likely compromised by excluding women with baseline electrolyte abnormalities."

3.33 Interim Results of Ingenix Phase 4 Study of Yasmin:

As a Phase 4 commitment for Yasmin, the sponsor contracted with Ingenix Pharmaceutical Services to do a prospective, observational study of Yasmin users matched with users of other oral contraceptives. One of the study's goals is to address FDA concerns about the potential for electrolyte disturbances. Ingenix uses medical reimbursement claims to capture events that might be related to electrolyte disturbances (for example, death, arrhythmia, syncope, hyperkalemia). Evaluators review charts for all subjects with sentinel events. Yasmin initiators are matched with a two-fold larger group of other OC initiators each quarter for three years. After the first five quarters, there were 7,283 Yasmin users matched with 14,566 other OC users identified in the claims database.

According to the sponsor, in the first five quarters there have been no confirmed cases of hyperkalemia for Yasmin users and two confirmed cases of hyperkalemia for other OC users.

The primary reviewer examined two interim reports for the Phase 4 study, which were submitted to the Yasmin IND. Neither interim report raised safety concerns about Yasmin initiators compared with initiators of other OCs.

Primary Reviewer's Comment: " To detect hyperkalemia you must look for it, and young women of reproductive age are not routinely assessed for hyperkalemia. Nonetheless, the claims data for sentinel events have not raised any safety concerns."

3.34 Interim Report for EURAS

The study is a large postmarketing surveillance study of women on oral contraceptives (50,000 total and 15,000 Yasmin patients) that collects data through questionnaires sent to subject's homes every six months. EURAS focuses on thrombotic risks rather than risk

of hyperkalemia; however, two questions in the questionnaire may be germane to the issue of hyperkalemia. Subjects are asked if they have experienced an arrhythmia or abnormal kidney function. In addition, the study may detect deaths when investigators pursue follow-up on subjects who do not respond to the questionnaire.

The study detected no difference between Yasmin and LNG-containing OCs in the incidence of arrhythmia or abnormal kidney function.

3.35 Postmarketing Safety Data for Yasmin:

Postmarketing safety reports, including spontaneous reporting and an ongoing Phase 4 surveillance study, have not detected a problem with electrolyte imbalance in women using Yasmin. A search of the FDA's Adverse Event Reporting System (done on 14-Aug-04 using the AERS DataMart) revealed no cases of hyperkalemia and two cases of hyponatremia. One subject was hospitalized for hyponatremia about six months after starting Yasmin, but further information was not obtained. The second subject had both hyponatremia and hypokalemia, which are not consistent with the expected pattern for antimineralocorticoid excess (hyponatremia and hyperkalemia).

Non-serious foreign events are not included in the FDA's AERS system. However, the Sponsor provided the following information about hyperkalemia regarding worldwide reporting: "Fourteen spontaneous reports (all non-serious) of cases of elevated serum potassium measurement ranging from 5 to 5.6 mEq/L (where available) have been reported since its introduction into the market in November 2000 through December 31, 2003. Within this period, there were ——— women-years (wy) of use globally, resulting in a reporting rate of 0.3/100,000 wy."

Primary Reviewer's Comments: "Although it is reassuring that no clinically serious cases of hyperkalemia have been reported postmarketing in women using Yasmin for contraception, the following caveats in applying these data to Angeliq come to mind:

- In general, women using oral contraceptive users are at lower risk for hyperkalemia than women who are using hormones to treat menopausal symptoms (less likely to have kidney, liver, or heart disease, or be on concomitant medication)
- The extent of under-reporting and under-detection is unknown"

4.0 Conclusions Regarding Non Approvable Issues Addressed in Complete Response

4.1 Thrombotic Risk

I agree with the primary reviewer and team leader, that with regard to thrombotic risk, the proposed dose is safe for the proposed indication

4.2 Endometrial Biopsy Results

I agree with the primary reviewer and team leader that the concerns regarding the evaluation of the endometrial biopsies were adequately addressed in this submission.

4.3 Hyperkalemia Risk

I agree with the primary reviewer and team leader that, because that therapeutic index for the proposed dose is too narrow for the proposed indications and populations, that Angeliq is not safe for the intended use.

5.0 Lowest Effective Dose Issue

Since the lowest dose of DRSP (0.5 mg) studies adequately protected the endometrium from estrogen-induced hyperplasia, the endometrial protection study did not demonstrate the lowest effective dose of DRSP. The 1mg dose of Estradiol contained in Angeliq may not be the lowest effective dose for treatment of menopausal symptoms.

6.0 Regulatory Recommendations

The sponsor informed the agency on September 10, 2004, that it intended to pursue approval of the 0.5mg dose of drospirenone in combination with 1mg 17-β estradiol. On September 13, 2004, the sponsor informed the agency that it intended to withdraw the [redacted] strengths of drospirenone from the application. Therefore, I recommend that the amended application be considered approvable. The specific deficiencies are related to the lack of sufficient chemistry information to arrive at an approval decision regarding the 0.5mg dose of drospirenone and failure to agree upon adequate labeling.

Daniel A. Shames MD
Director, DRUDP/CDER/FDA

APPEARS THIS WAY
ON ORIGINAL

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/s/

Daniel A. Shames
9/14/04 03:27:31 PM
MEDICAL OFFICER

Angeliq™ Team Leader Review

NDA:	**21-355**
Proposed Trade name:	**Angeliq™ (Estradiol and drosperinone)**
Proposed Claim:	[redacted]
Proposed Indications:	**1. Treatment of moderate-to-severe vasomotor symptoms** **2. Treatment of vulvar and vaginal atrophy**
Dosage/Form/Route:	**1 mg 17-beta estradiol/ [redacted] drosperinone or 1 mg 17-beta estradiol/ [redacted] drosperinone oral tablets in a continuous combined regimen.**
Applicant:	**Berlex Laboratories, Inc**
Date of Submission:	**December 14, 2001**
Date of Receipt	**December 17, 2001**
Primary Clinical NDA Review Completed:	**September 12, 2002**
Date of Memorandum:	**October 17, 2002**

Background and Regulatory History

On February 12, 1997 at PreIND guidance meeting with Berlex, the Agency agree that the indications for Estrace® could be obtained for the combination product of estradiol (E_2) and drosperinone (DRSP) with successful demonstration of bioequivalence between the two drug products. IND 53,842 was opened on July-25, 1997. The Phase 3 protocol for Study A02827, the primary study supporting the endometrial protection claim for this NDA was submitted to IND 53, 842 in 1997 and the study was conducted between January 22, 1998 and April 28, 2000. In a June 14, 2000 teleconference between the Agency and the Sponsor, the Deputy Division Director of the Division of Reproductive and Urologic Drug Products, Dr. Marianne Mann confirmed with the Sponsor that bioequivalence between Estrace® and the estradiol/drosperinone combination drug product would be sufficient to gain the indications of Estrace® for the combination product. A pre-NDA meeting between the Agency and Berlex was conducted on January 24, 2001. Decisions from that meeting included the following:

- The Agency's position is that it is important to have robust trial data in the HRT population to assume that we have adequate information of the effects on potassium and creatinine clearance in this population including those with renal or hepatic impairment
- The Agency suggests a large number of patients be evaluated to include valid potassium levels to address the safety concerns in older patients
- Any patient with a serum potassium or creatinine level above the normal range should receive follow-up (EKG) testing

- In addition to the studies with ACE inhibitors, drug-drug interaction testing should be performed with drosperinone/estradiol products and NSAIDS; abnormal laboratory results such as hyperkalemia should be assessed; the results can be submitted as part of a 4-month safety update during the NDA review cycle

Yasmin, a combination oral contraceptive containing drosperinone 3 mg and ethinyl estradiol 0.03 mg was submitted in July 2000. The primary concern that arose during the review for Yasmin® was the potential for electrolyte disturbances in women treated with drosperinone, an antimineralocorticoid. Prior to approval, the Agency required that the Sponsor submit additional safety data related toYasmin's effect on serum potassium. The Sponsor submitted A0 2827 as supportive potassium safety data to NDA 21-098 for Yasmin®. Yasmin® was approved on May 11, 2001.

NDA 21-355 for Angeliq™ was received on December 17, 2001and was filed on February 17, 2002. Angeliq™ is not approved or marketed any where in the world. There are pending applications in the United States, Holland, and Australia.

Chemistry/Manufacturing/Controls (CMC)

See the CMC review by Dr. Tran for chemistry deficiencies noted in March 21, 2002 information request letters. All chemistry deficiencies were satisfactorily addressed. The Office of Compliance issued an "Acceptable" recommendation on February 4, 2002. Microbiology review was not required.

From a CMC perspective the NDA is approvable

Product Name

The tradename Angeliq™ was found to be acceptable to Office of Drug Safety on July 9, 2002

Pre-clinical Pharmacology

All pre-clinical pharmacology/toxicology is referred to approved NDA 21-098 for Yasmin®.

Angeliq™ can be approved from the standpoint of Pharmacology.

Clinical Pharmacology and Biopharmaceutics

Based on the single dose and multiple dose bioequivalence studies, supporting data from other bio-studies and the comparative dissolution data, it can be concluded that estrogens from Angeliq™ (combination E_2 + DRSP drug product) are bioequivalent to Estrace (E_2), an approved product for treatment of moderate to severe vasomotor symptoms and treatment of vulvar and vaginal atrophy. Therefore according to previous agreement with the Agency, these efficacy claims can be extrapolated to Angeliq™.

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluations II find the NDA acceptable.

Division of Scientific Investigations (DSI) Report

Four clinical sites were inspected. Two of these sites were inspected for the bioequivalence trial and two for the endometrial protection trial, A02827. The sites for the endometrial protection trial were Sarasota, Florida with principle investigator Lydia Corn, MD, and Tampa Florida with principle investigator Susan Wehle, MD. All four sites inspected were determined to be acceptable.

Clinical

Efficacy

The indications of treatment of moderate-to-severe vasomotor symptoms and treatment of vulvar and vaginal atrophy were sought based on successful demonstration of bioequivalence between Angeliq™ and Estrace® (see previous discussion under Clinical Pharmacology and Biopharmaceutics. The Agency agreed in 1997 (confirmed in 2002) that this was an acceptable approach to obtaining these indications. The current Division policy is not to grant indications to new combination estrogen/ progestin drug products containing a new molecular entity progestin based on bioequivalence to the approved estrogen-alone drug product. Yasmin®, the oral contraceptive containing ethinyl estradiol and drosperinone was approved in May 2001 prior to the submission of Angeliq™.

Endometrial Protection

Protocol A02827

Study A02827 was a randomized, double-blind, parallel group (with an estrogen only-arm), multicenter, 52 week study. The primary objective of this 13 cycle study was to evaluate the efficacy of continuous combined estradiol/drosperinone compared to continuous estradiol for protection of the endometrium against estrogen-induced hyperplasia or cancer in postmenopausal women. The analysis of bleeding patterns and the effect on frequency and severity of hot flushes and the relief of urogenital symptoms for the continuous estradiol/drosperinone combinations vs. continuous estradiol were to be compared as secondary objectives. The study was conducted at 53centers in the U.S. Enrollment criteria were consistent with those recommended for an endometrial protection study. However, subjects were not required in the study to meet the - specified criteria for hot flush frequency and severity of 7-8 per day or 60 moderate-to-severe hot flushes per week required for a vasomotor symptom study. All subjects received a complete history, general and gynecology exam (including Pap smear) at screening. Mammography and endometrial biopsies were also performed at screening. Subjects were then randomized to 1 of 5 treatment groups. Pap smear, mammography (if one year had elapsed) and endometrial biopsy were performed at the end of study visit or at early termination.

One thousand, one hundred forty-seven (1,147) subjects were randomized to the following treatment groups:

- E_2 1 mg/day + placebo – 227 subjects
- E_2.1 mg + DRSP 0.5 mg/day – 228 subjects
- E_2 1 mg + DRSP 1 mg/day – 231 subjects
- E_2 1 mg + DRSP 2 mg/day – 228 subjects
- E_2 1mg + DRSP 3 mg/day – 233

Of the 1,147 subjects randomized, a total of 5 subjects never used the study drug. A total of 845 subjects completed cycle 13 of the study. Two hundred ninety-seven (297) subjects of the 1,147 subjects randomized (26%) prematurely terminated the study. One hundred eighty nine (16.6%) subjects withdrew due to adverse events, 44 (3.9%) subjects withdrew consent, 30 (2.6%) subjects had protocol deviations, 1 (0.1%) subject withdrew for lack of efficacy and 33 (2.9%) subjects had "Other" listed as the reason for withdrawal. The discontinuation rate was highest in the E_2 + placebo arm (34%) and was similar across the E_2 + drosperinone treatment groups.

The endometrial biopsy slides were all read by [redacted] The protocol for Study A02827 specified that a safety read would be performed on end-of-study and for-cause endometrial biopsies for purposes of treating hyperplasia. The protocol further specified that any subject who develops an endometrial polyp or hyperplasia or a more serious condition would have study medications discontinued, would be given appropriate treatment and follow-up, and followed until resolution of the endometrial pathology. Per protocol, efficacy slides would be read by two pathologists. If they agreed on the diagnosis, this would be the final diagnosis. If they disagreed, a third pathologist (arbiter) would read the slide. In the event of a third pathology read, the majority diagnosis would be the final diagnosis. This approach is consistent with the FDAs current recommendations dating back to 1995 as to how endometrial biopsy slides should be read. The protocol for Study A02827, (submitted in 1997) specified that in the event that all 3 pathologist disagreed, a consensus read (involving all 3 pathologist) would occur for the determination of the final diagnosis. This is not consistent with the recommendations given to Sponsors. Recommendations dating back to 1995 call for the pathologists to be independent. To assure this independence, Sponsors have been advised (since 1998-1999) that in the event that all three pathologists disagree, a conservative approach utilizing the most severe (worst) diagnosis as the final diagnosis should be applied. Though it is not clear that this information was communicated to the IND for this protocol, the individual pathologists are aware of this from interactions on other protocols. The Division also recommends to Sponsors that it is not only the rate of hyperplasia that will be evaluated but the severity of those hyperplasias as well. In particular the reviews will be looking for the cases of atypical hyperplasias which can be difficult to distinguish from endometrial cancer. Atypical hyperplasias have the highest rate of progression to endometrioid adenocarcinomas.

The Sponsor's analysis for endometrial hyperplasia is given in Table 1

Table 1. Endometrial Hyperplasia Rates

Treatment group	Endometrial Hyperplasia Rates		
	n[b]	%	Upper bound of 95% CI[c]
E_2 1 mg/day + placebo N[a] = 155	19	12.3	17.5%
E_2.1 mg + DRSP 0.5 mg/day N[a] = 171	1	0.6%	2.7%
E_2 1 mg + DRSP 1 mg/day N[a] = 157	0	0	1.9%
E_2 1mg + DRSP 2mg/day N[a] = 161	0	0	1.8%
E_2 1mg + DRSP 3 mg/day N[a] = 162	0	0	1.8%

[a]N = evaluable subjects
[b]n = number of subjects with endometrial hyperplasia
[c]CI = Upper 95% confidence limit for a single proportion. For the E_2 0.045 mg/day group, a normal approximation was used, for the combination groups the exact method was used.

In her review of the NDA, the medical officer reviewed the safety readings for Study A02827 and discovered 9 cases of endometrial hyperplasia in the safety reads that were given benign final diagnosis in the efficacy read. Of a total of 10 hyperplasias that were read in the safety read, only 1 case was called hyperplasia in the final efficacy diagnosis. These 10 cases are listed in Table 2 (from Medical Officer Table 13).

Table 2. Safety Readings for Angeliq™ with Matching Efficacy Readings

Patient No.	Dosage DRSP (mg)	Safety Reading Biopsy Date Reader	Efficacy Readings by Reader	Exposure (months)
14022	*0.5*	*Simple hyperplasia* *8/26/98* ***Efficacy Reader 1***	*1. Inactive, atrophic* *2. Inactive, atrophic*	*13*
48006	0.5	Simple hyperplasia 8/26/98 pathologist-A, MD	1. Proliferative 2. Inactive, polyps 3. Proliferative	13
41001	*0.5*	*Atypical hyperplasia* *2/1/99* ***Efficacy Reader 1***	*1. Atypical hyperplasia* *2. Cancer* *3. Atypical hyperplasia*	*13*
52012	*0.5*	*Atypical hyperplasia* *1/28/99* ***Efficacy Reader 1***	*1. Inactive, atrophic* *2. Inactive, atrophic*	*13*
40037	1	Simple hyperplasia 9/29/99 patholgist-A	1. Inactive 2. Inactive	7
01015	2	Atypical hyperplasia 9/30/99 pathologist-A	1. Inactive 2. Inactive	13
20028	2	Atypical hyperplasia 4/26/00 pathologist-A	1. Inactive, atrophic 2. Polyps 3. Strips of benign surface and glandular epithelium 4. Consensus= Inactive, atrophic	13
24003	*2*	*Atypical hyperplasia* *8/18/98* ***Efficacy Reader 1***	*1. Menstrual/polyps* *2. Menstrual/polyps*	*7*
12007	*3*	*Simple hyperplasia* *1/28/99* ***Efficacy Reader 1***	*1. inactive/polyps* *2. polyps* *3. polyps*	*7*
02002	3	Complex hyperplasia without atypia 9/4/98 pathologist-W	1. Simple hyperplasia without atypia/polyps 2. Inactive/polyps 3. Polyps 4. Consensus = inactive/polyps	7

Nine cases of endometrial hyperplasia diagnosed in the conservative safety read have been given benign final efficacy reads. Only one case of atypical hyperplasia (Subject 41001) in the E_2.1 mg

+ DRSP 0.5 mg/day group had that diagnosis retained in the final efficacy diagnosis. Of the nine cases of endometrial hyperplasia downgraded to benign diagnoses in the efficacy read, 4 of these represent the most worrisome form of endometrial hyperplasia, atypical endometrial hyperplasia. Atypical hyperplasias have the highest rate of progression to endometrioid adenocarcinomas. Berlex was asked to explain the changes from these most worrisome diagnoses to benign diagnoses. Berlex responded that expert pathologists did the efficacy read, while non-expert pathologists performed the safety readings, and therefore the quality of the safety readings was less. However, the expert who performed as efficacy reader 1 was the same pathologist who was responsible for 4 of the 9 endometrial hyperplasias in the safety read that were changed to benign diagnoses in the efficacy reads. Of the remaining 5 endometrial hyperplasias on the safety read that became benign diagnoses in the efficacy reads, all 5 were read by _____ expert pathologists. The Division's, Board Certified Pathologist was consulted and asked to comment on the discrepancies between the safety and efficacy reads (see Consult to the NDA). His comments regarding the diagnoses for subjects 52012, 01015, 20028, (atypical hyperplasia on the safety read and inactive endometrium on the efficacy read) confirm that it is difficult to understand how these expert and experienced pathologists could achieve such discrepant diagnoses. The Division's pathologist's comments on the diagnoses for subject 24003 suggests that menstrual endometrium can sometimes look atypical but experienced gynecologic pathologists can usually distinguish menstrual endometrium from atypical hyperplasia. His comments support that although the discrepancy for subjects 14022 and 40037 are not as severely discrepant as those previously mentioned (52012, 01015, 20028 and 24003), there should not be confusion between a diagnoses of simple hyperplasia and inactive atrophic endometrium. Subject 02002 had a diagnoses of complex hyperplasia in the safety read that was read at consensus as inactive/polyp based, this reading too is concerning. Finally, the Division's pathogist's review supports that the distinction between simple hyperplastic and polyps and between simple hyperplasia and proliferative endometrium may be more subtle and thus less concerning, however, the Division has taken hyperplasia occurring in a polyp as hyperplasia.

Safety

One subject died during the course of one of the studies conducted during the drug development program for this product. This death was due to an automobile accident and was felt to be unrelated to study drug medication. Of a total of 2,156 subjects who were treated with either the combination E_2 + DRSP product or E_2 alone, 100 experienced serious adverse events. These included 8 cases of breast cancer, 1 case of ovarian cancer and 1 case of cervical cancer all occurring in the combination E_2 + DRSP groups. The breast cancer occurred in the higher DRSP groups (5 in the E_2 1mg + DRSP 2 mg/day group and 3in the E_2 1mg + DRSP 3mg/day) and were diagnosed at a mean of 15 months of therapy. In the safety database there was 1 case of myocardial infarction, 1 case of cerebral embolism, 1 case of a pulmonary embolus, 1 pulmonary artery thrombosis and 3 deep thrombophlebitis all occurring in the combination E_2 + DRSP groups. The mean duration of therapy before thrombotic events was 3 months, with a range of 1 to 24 months.

DRSP is an antimineralocorticoid that is structurally related to spironolactone. DRSP has approximately 7 times the antimineralocorticoid potency of spironolactone. FDA concerns regarding the risk for hyperkalemia led to the Sponsor's assessment of this risk in several ways. The overall database (1,727 subjects) was evaluated for women who had in-treatment potassium values > 5.5mEq/L. The percentage of hyperkalemia in subjects treated with DRSP was similar to those treated with E_2 + placebo. An assessment for potassium values > 5.5mEq/L in a subset of women on nonsteroidal anti-inflammatory drugs or ACE inhibitors also revealed that the percentage of hyperkalemia in DRSP-treated subjects (1%) was not higher than those treated with

E_2 + placebo (2%). The Medical Officer noted that there were several flaws in this method of assessment for hyperkalemia. The studies were not designed to detect potassium abnormalities. Most of the data was collected in the Phase 3 endometrial protection trial which enrolled healthy women and specifically excluded subjects with risk factors for hyperkalemia. This trial assessed potassium only after month 6 to 7 and month 12 to 13. Methodological assessments for hemolyzed specimens could have introduced bias against detecting hyperkalemia. The mean deviation from baseline was assessed in four small studies in women at risk for hyperkalemia. In three of these studies (1 assessing women on ACE inhibitors, 1 assessing women on indomethacin and 1 assessing women with renal impairment) subjects with risk factors were demonstrated to have a non-statistically or clinically significant positive change from baseline. In a fourth study of subjects with hepatic impairment, one subject developed severe hyperkalemia. This subject was a 46-year old amputee (above the knee amputation) with Type II diabetes, hypertension and mild hepatic impairment who at baseline was on furosemide 40 mg, spironolactone 100 mg, K-Dur 40 mEq, doxycycline and insulin. This subject had baseline creatinine clearance of 49mL/min. She continued all of her baseline medications into the study (including K-Dur which she was told to discontinue). She developed hyperkalemia up to 6.7 mEq/L. She was successfully treated with discontinuation of spironolactone, K-Dur and E_2 + DRSP, and the administration of Kayexalate®.

The adverse events database for combination was evaluated for adverse events (cardiovascular) that might indicate hyperkalemia. The results did not detect a trend toward increasing cardiovascular events in the DRSP-treated subjects.

Conclusion

In the determination of efficacy for the safety claim of protection of the endometrium, the Division will consider the safety reads for the determination of rate and extent of endometrial hyperplasias from Study A02827. Five cases of atypical endometrial hyperplasias are unacceptable. Further the degree of the histologic discrepancies for subjects noted to have hyperplasia (the safety endpoint) from the safety biopsy reads vs. those occurring in the efficacy reads cast doubt that any of the histology diagnoses should be relied upon for a consideration of protection of the endometrium. Evidence from the review suggests that the pathology readings were not conducted in an independent non-biased manner. Consensus reads were used to determine entrance into the study and as stated above to obtain a final diagnoses when all 3 pathologists disagreed. Based on the percentage of time that the consensus read agreed with Efficacy Reader 1 (65%) vs. Efficacy Reader 2 (32%) vs. Efficacy Reader 3 (11%), it would appear that Efficacy Reader 1 exerted an undue influence on the final diagnoses.

Two additional areas of concern for safety have arisen from the review of the combination E_2 + DRSP drug product. The first relates to the potential for hyperkalemia in the general population of postmenopausal women who would be exposed to this product. While the large Phase 3 clinical trial did not detect hyperkalemia (potassium value > 5.5mEq/L), the study was not designed with sufficient frequency of evaluation of serum potassium to make definitive decisions on the risk for hyperkalemia based on this study. There were also methodological flaws in the assessment of serum potassium levels that posed potential for bias against detection of hyperkalemia. The general population of postmenopausal women potentially exposed to this product should it be approved is expected to be a sicker population than that evaluated in the Phase 3 clinical trial in which women with risk factors were excluded. Although in general the smaller special population studies had more frequent potassium sampling, they were too small to provide reassuring data that could be applied to the general population expected to use this product. Indeed, in one of the smaller trials that evaluated individuals with hepatic impairment,

one subject became severely hyperkalemic when she was exposed to the combination E_2 + DRSP drug product in addition to other medication that put her at risk for hyperkalemia. This case illustrates the potential for problems with an older general population in which the prescriber is unlikely to evaluate baseline laboratory values before instituting estrogen/progestin therapy for treatment of menopausal symptoms. The prescriber also may not be aware of all of the medications to which his or her patient is exposed. In the case sited for a controlled clinical trial, the subject was told to discontinue one of the medications that put her at risk for hyperkalemia with the combination E_2 + DRSP drug product and she did not.

The second additional area for concern regarding the use of this combination E_2 + DRSP drug product in a general population is the potential for thrombogenic effects in this population. The Phase 3 clinical trial did not detect a greater risk. However, the clinical trial is limited in its ability to assess thrombogenic effects in a potentially sicker population. Yasmin, the oral contraceptive containing 0.03 of mg ethinyl estradiol and 3 mg of drospirenone was approved in May 2001. Since that time postmarketing reports of serious thromboemolic and other thrombotic events in Yasmin® users has raised the concern for its use in women who are younger (see Consult Dr. Scott Monroe regarding Yasmin®) and, in general, healthier than those expected to receive the E_2 + DRSP drug product for treatment of menopausal symptoms. There is insufficient data provided in this NDA to assuage the concern for this potential risk for thrombotic events in postmenopausal women.

I concur with the primary medical officer that Angeliq™ should not be approved. Efficacy has been demonstrated through bioequivalence study. The Division's reanalysis of the risk for endometrial hyperplasia demonstrates an unacceptable endometrial safety profile and, further, there is concern that the readings of the pathology slides can not be relied upon to support the endometrial safety. The data presented in the NDA does not adequately address the potential for hyperkalemia and thromboembolic events in the population of postmenopausal women who would be expected to receive this drug product. The clinical reviewing team feels that it would be difficult to conduct a clinical trial to sufficiently address safety concerns with respect to hyperkalemia and the risk for thromboembolic events and demonstrate an acceptable benefit to risk ratio for this product in postmenopausal women. Such a trial would have to be a large trial of postmenopausal subjects either on multiple medications or with co-morbidity states associated with increased risk for hyperkalemia and thromboembolic events. The endometrial safety could be addressed with conduct of a new endometrial protection clinical trial.

Shelley R. Slaughter, M.D., Ph.D.
Medical Officer Team Leader

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/s/

Shelley Slaughter
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MEDICAL OFFICER

Daniel A. Shames
10/21/02 11:56:17 AM
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NDA 21-355
Clinical Review

Drug Name:	Angeliq
Pharmacologic Category:	Estrogen and Progestin
Route of Administration:	Oral (tablets)
Dosage:	1. 1 mg drospirenone and 1 mg 17-ß estradiol 2. 3 mg drospirenone and 1 mg 17- ß estradiol
Indications:	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of vulvar and vaginal atrophy.
Applicant:	Berlex
Related NDAs:	Yasmin, NDA 21-098, approved May 11, 2001 Estrace, ANDA 84-499, approved before 1982

Date Submitted:	December 14, 2001
Date Received:	December 17, 2001
Date Review Completed:	September 12, 2002

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The Executive Summary of the Primary Clinical Review

1. Recommendations

From a clinical perspective, Angeliq is not approvable for safety reasons.

Angeliq is a once-a-day tablet, intended for women with an intact uterus. The proposed indications are:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.
2. Treatment of vulvar and vaginal atrophy.

It contains two hormones, the estrogen, estradiol (E_2), for treatment of menopausal symptoms, and the progestin, drospirenone (DRSP), for protection of the endometrium from estrogen-induced hyperplasia and cancer. The applicant requests approval of [redacted] for oral use:

[redacted]

E_2 is a widely used estrogen found in many combination estrogen plus progestin (E/P) products for menopause symptoms. On the other hand, DRSP is found in only one marketed product, the oral contraceptive Yasmin, approved in the U.S. in May 2001. DRSP is unique among marketed progestins for its potent antimineralocorticoid activity, with DRSP 3 mg roughly equivalent in antimineralocorticoid potency to spironolactone 25 mg. Because of DRSP's antimineralocorticoid properties, Yasmin's approval depended on the applicant agreeing to Phase 4 commitments to evaluate the risk of hyperkalemia.

The usual serious safety concerns for E/P products are thrombotic events and breast cancer. Estrogen is considered the cause of the increase in thrombotic events, although observational studies in recent years suggest that certain progestins may have thrombotic properties as well. Breast cancer has always been a safety concern for women using E/P products for menopause symptoms, a concern reinforced by a recent publication from the Women's Health Initiative.[1] However, the increased risk of breast cancer in the Women's Health Initiative was only significant after five years of therapy. Therefore, detection of an increased risk of breast cancer is unlikely in the typical one- to two-year clinical trials for marketing approval of E/P products.

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[1] Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA*, 2002; 288:321-333.

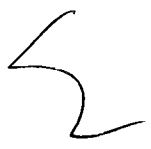
Common side effects for E/P products, such as vaginal bleeding, headaches, and breast discomfort, are usually mild and well tolerated, but can lead to discontinuations.

In this NDA, the applicant showed efficacy in treatment of menopausal symptoms by showing bioequivalence of E_2 in Angeliq to E_2 in the marketed product, Estrace. Although the data showed that DRSP protects the endometrium from E2-induced hyperplasia, evidence of bias and quality issues were detected in the pathology readings. That is, there was no evidence that DRSP 3 mg offered any benefit over DRSP 1 mg. More importantly, the safety data raised two concerns beyond those expected for E/P products used to treat menopause symptoms. The first concern was electrolyte abnormalities, particularly hyperkalemia. The second concern was the possibility that DRSP is a thrombogenic progestin, raised by postmarketing reports of thrombotic events for Yasmin.

In a Phase I study, a woman with preexisting risk factors developed severe hyperkalemia that appeared to be related to DRSP (reviewed in section 2 of Appendix). Although the risk of hyperkalemia in healthy women is probably small, the risk is not shared with other E/P products for menopause symptoms.

The other safety concern is that DRSP may be a thrombogenic progestin. Although the clinical trials for Angeliq did not detect an unusual number of thrombotic events, there have been more postmarketing reports than expected in users of Yasmin, the oral contraceptive containing DRSP. Reporting may be increased because of true increased risk, because of enhanced sensitivity to this issue, or because higher risk women are receiving Yasmin.

To address the issue of thrombotic events in Yasmin users, the European Active Study Surveillance Group launched a large prospective cohort study in 2001. Investigators expect to enroll 30,000 women by 2003, and end the study in 2006. It is prudent to await the results of this study before approving Angeliq, a product intended for women who are older than the typical Yasmin user, because older women are already at risk for life-threatening thrombotic events because of age-related cardiovascular changes.



In summary, we must set a high safety bar for a product intended to treat the discomforts of a normal stage of life. There is no shortage of therapies, and little tolerance for new risks. So far, Angeliq has shown no benefit over other E/P products to justify added risk. Therefore, the applicant must provide evidence that Angeliq offers a benefit, such as treatment of hypertension, over other therapies for menopause in order to justify the risk of hyperkalemia. In addition, the applicant must show that DRSP is not a thrombogenic progestin by showing that users of

Yasmin have no greater risk of thrombosis than users of other oral contraceptives. The large prospective cohort study described above may adequately address the thrombosis issue, or the applicant may propose additional studies. And finally, the quality issues in the endometrial biopsy readings may be addressed by a complete re-reading of the endometrial biopsy slides, by pathologists who are independent.

2. Summary of Clinical Findings

2.1 Brief Overview of Clinical Program

The three clinical trials for efficacy studied 1214 postmenopausal women, with 1142 in an endometrial protection trial, and 72 in two bioequivalence trials.

Nine clinical trials contributed to the safety database of 1893 women who took E_2 + DRSP. Most of the women (95%) were between the ages of 45 and 65.

2.2 Efficacy

The applicant showed efficacy by showing bioequivalence of E_2 in Angeliq to E_2 in the marketed product, Estrace. The FDA biopharmaceutical reviewer reviewed these two studies.

DRSP prevented E_2-induced endometrial hyperplasia. The endometrial protection trial showed one-year hyperplasia rates of less than 2% for the DRSP 1 mg, 2 mg, and 3 mg treatment groups, with the upper bound of the one-sided 95% confidence interval less than 4%. The lowest dose tested, 0.5 mg DRSP, did not meet these criteria for prevention of endometrial hyperplasia, and therefore DRSP 1 mg was the lowest dose that protected the endometrium. However, there was evidence of bias and quality issues in the pathology readings. One pathologist appeared to have undue influence in cases of disagreement among pathologists. The same pathologist had wide discrepancies in his own readings of the biopsy slides, for example, reading three slides as "hyperplasia" (including one atypical hyperplasia) for the purpose of patient care, and re-reading them as "inactive, atrophic" for the purpose of calculating hyperplasia rates.

[redacted] DRSP 3 mg showed no advantage over DRSP 1 mg in endometrial protection, bleeding profile, or any other secondary endpoints.

2.3 Safety

Except for electrolyte abnormalities and possible increased thrombotic tendencies, Angeliq had a safety profile much like other E/P regimens.

The safety database contains 1893 women who took DRSP + E_2, with 362 women exposed to DRSP 1 mg + E_2 1 mg, 641 women exposed to DRSP 3 mg + E_2 1 mg, and the remaining

women exposed to other combinations of E_2 (1 or 2 mg) and DRSP (0.5, 1, 2, 3, or 4 mg). Most women (N=1114) had 52 or more weeks of exposure. The total exposure in the safety database met ICH guidelines for drugs intended for long-term treatment of non-life-threatening conditions.[2] The probable marketing exposure will be months to years.

There was one death unrelated to study drug. A woman who took DRSP 1 mg plus E_2 1 mg for nine months died in an auto accident. She had no medical history suggesting increased risk for electrolyte abnormalities, and had normal electrolyte levels two months before the accident.

Six women had serious thromboembolic events. However, the percentage of women with serious thromboembolic events was similar to the percentage in the clinical trials of other E/P products for menopause symptoms. Concern about thromboembolic events arose from an unexpectedly high number of postmarketing reports in users of Yasmin, the oral contraceptive that contains DRSP. Concern in Europe was sufficient to launch a large prospective cohort study to evaluate thrombotic events in women using Yasmin compared with women using other oral contraceptives. Investigators expect to enroll 30,000 women in this study, which will end in 2006.

Because of FDA concerns about potential electrolyte problems, the applicant did four Phase I PK studies that exposed women with risk factors for hyperkalemia to Angeliq. The risk factors included kidney impairment, liver impairment, indomethacin intake, and ACE inhibitor intake. Altogether, these four trials exposed 65 women with risk factors for hyperkalemia to DRSP.

Among these 65 women, one woman had serious hyperkalemia related to DRSP use. This occurred in the liver impairment study. The subject was a 46-year-old woman with moderate liver impairment, who was included in the study despite having three exclusion criteria.[3] After a single dose of Angeliq (E_2 1 mg plus DRSP 3 mg), she developed persistent, severe hyperkalemia that required hospitalization and Kayexalate treatment. Her case is discussed further in the Appendix, below. This woman illustrated not only the potential for severe hyperkalemia following DRSP exposure, but also the danger of medication errors. A second woman was removed from the indomethacin study on Day 1, after a drop in creatinine clearance following indomethacin intake, and before any exposure to DRSP. What might have happened had she not been getting daily labs will never be known. However, close scrutiny of daily labs is not feasible in actual practice.

Trial exclusions decreased the likelihood of detecting electrolyte abnormalities. Overall, the trials studied healthy postmenopausal women, with the exception of the four small safety trials mentioned above. In addition, in all trials women had to have normal baseline labs to be included. As it is not the standard of care to evaluate electrolytes, liver function, and kidney function before starting E/P products, we can expect some women with these problems to be

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[2] http://www.fda.gov/cder/guidance/iche1a.pdf. Guideline for Industry. The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions.

[3] Among her exclusion criteria were insulin dependent diabetes, evidence of renal compromise at baseline, and possible vascular disease as shown by the amputated extremity, although the case report form does not give a reason for the amputation.

inadvertently exposed to Angeliq in actual practice. How this would impact the risk of hyperkalemia is not known.

Breast cancer may be increased in women using E/P products for menopause,[1] although it is possible that the increase seen in the early years of E/P therapy represents earlier diagnosis, as appears to be the case with oral contraceptives.[4] The eight breast cancers detected in the safety data for Angeliq were not excessive compared to the expected incidence of breast cancer for postmenopausal women, but the mean duration of therapy, 53.8 weeks, was short for detecting breast cancer. In addition, the Angeliq trials excluded women with baseline abnormal mammograms or a history of breast cancer, so comparing Angeliq-exposed subjects to historical controls that include all postmenopausal women is problematic.

There were no clinically significant changes in weight, blood pressure, lipids, liver function tests, or complete blood counts. In one small study there was a slight decrease in glucose tolerance in women using ethinyl estradiol (EE) plus DRSP 3 mg (a 10% increase in the $AUC_{0\text{-}3hr}$ for glucose at 6 months, compared to baseline). This is consistent with the known effects of progestins on glucose tolerance.

The most frequent adverse events (AEs) resulting in discontinuation, in order of most to least frequent, were vaginal bleeding, breast pain, headache, and depression, which are all expected for this class of drugs. The following table shows AEs occurring in more than 5% of women.

Adverse Events in More than 5% of Subjects

Adverse Event	All DRSP groups n (%)	E_2 1 mg n (%)
Breast pain	369 (19.5)	35 (13.3)
Vaginal hemorrhage	205 (10.8)	44 (16.7)
Headache	181 (9.6)	29 (11.0)
URI	153 (8.1)	40 (15.2)
Abdominal pain	147 (7.8)	31 (11.8)
Flu syndrome	138 (7.3)	15 (5.7)
Back pain	121 (6.4)	15 (5.7)
Infection	115 (6.1)	3 (1.1)
Pain in extremity	98 (5.2)	16 (6.1)

Limited data did not show significant drug-drug interactions (simvastatin and omeprazole interaction studies).

2.4 Dosing

[4] Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53,297 women with breast cancer and 100,239 women without breast cancer from 54 epidemiological studies. *The Lancet*, 1996;347:1713-1727.

The dose of E_2 in Angeliq is the same as the lowest dose of E_2 recommended for the same indications in the approved product, Estrace. The applicant did not do any dose ranging since efficacy was shown by bioequivalence, as previously agreed between the applicant and the FDA.

The doses of DRSP [redacted], 1 mg and 3 mg, were both effective at protecting the endometrium against endometrial hyperplasia, while a lower dose, 0.5 mg, was not. The applicant did not show an advantage of DRSP 3 mg over DRSP 1 mg.

An unresolved dosing issue is that the effect of DRSP alone on hot flushes was never studied. Some progestins are effective in treatment hot flushes[5,6] and DRSP may have activity as well. If so, it may be possible to reduce the E_2 dose or eliminate E_2 altogether. There might be adverse consequences to this approach, such as adverse effects on bone or lipids, but without the data, we do not know. Nonetheless, the applicant's approach, using an estrogen for efficacy and a progestin for endometrial safety, is a recognized standard for treatment of menopause symptoms.

2.5 Drug-Drug Interactions

E_2 and DRSP do not affect each other's pharmacokinetics. DRSP does not appear to induce or inhibit the cytochrome P450 enzymes 2C29 and 3A4. Estradiol drug-drug interactions were not studied in this submission. Based on what is known about the related drug, ethinyl estradiol, estradiol concentrations may vary 20-30% in the presence of hepatic enzyme inducers and inhibitors. This should not compromise safety.

2.6. Special Populations

Racial differences were not detected in the data, but the safety database was largely Caucasian (94%). There were no pharmacokinetic studies of racial differences. All ten DRSP-exposed women with endometrial hyperplasia in the endometrial protection trial were Caucasian, but so were most of the women in the trial (92%).

Too few women over 65 were studied to know if there were age-related issues in efficacy or safety. However, the limited data did not suggest a different safety profile in older women. In the endometrial protection trial, the average age of ten DRSP-exposed women who developed endometrial hyperplasia was 58 years old, not much different from the average age of trial participants, which was 56 years old.

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[5] Lobo RA, McCormick W, Singer F, Roy S. Depo-medroxyprogesterone acetate compared with conjugated estrogens for the treatment of postmenopausal women. Obstet Gynecol. 1984 Jan;63(1):1-5

[6] Loprinzi CL, Michalak JC, Quella SK, O'Fallon JR, Hatfield AK, Nelimark RA, Dose AM, Fischer T, Johnson C, Klatt NE, et al. Megestrol acetate for the prevention of hot flashes N Engl J Med 1994 Aug 11;331(6):347-52

Women with moderate liver or kidney disease have greater exposure to DRSP than women with normal liver and kidney function. DRSP exposure in women with moderate liver impairment, measured by AUC, is about twice the exposure in women with normal liver function. DRSP serum concentrations were 37% greater at steady state in women with moderate renal impairment compared with women with normal renal function.

The applicant did not study children and requested a pediatric waiver. Since the proposed indications apply to postmenopausal women, a pediatric waiver is recommended.