CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-038s000

SUMMARY REVIEW

DIVISION OF REPRODUCTIVE AND UROLOGIC PRODUCTS (DRUP)
DIVISION DIRECTOR MEMORANDUM

NDA	NDA 22-038 (b) (4)
Type of Application	Original
Applicant	Upsher-Smith Laboratories, Inc Maple Grove, MN 55369
Proprietary Drug Name	Divigel
Established Drug Name	(Estradiol gel) 0.1%
Drug Class	Estrogen
Indications (Proposed)	1. Treatment of moderate to severe vasomotor symptoms associated with menopause (b) (4)
Route of administration	Transdermal
Dosage Form	Gel
Dosing Regimen	Once daily application of 0.25 g, 0.5 g, or 1.0 g of estradiol gel/day containing 0.25 mg, 0.5 mg, and 1.0 mg estradiol/dose, respectively
CDER Receipt Date	May 4, 2006
PDUFA Goal Date	June 4, 2007 (with 3-month extension)
Date of Memorandum	June 4, 2007
Division Director	Scott E. Monroe, MD Acting Division Director, DRUP

1. RECOMMENDATIONS

1.1 Recommendation regarding Approvability

- I concur with the primary Medical Reviewer and the clinical Team Leader that Divigel (0.25 g gel [0.25 mg estradiol]/day, 0.5 g gel [0.5 mg estradiol]/day, and 1.0 g gel [1.0 mg estradiol]/day) be approved for the indication of treatment of moderate to severe vasomotor symptoms (VMS) associated with the menopause. For the 0.25 g dose, labeling will indicate that a statistically significant greater reduction in vasomotor symptoms, compared to that of placebo, was delayed until Treatment Week 7.

(b) (4)

1.2 Basis for Recommendation regarding Approvability

Indication of VMS. The Applicant has demonstrated in a single, adequate and well-controlled, multicenter Phase 3 clinical trial (Study P04-001) that both the 0.5 g estradiol gel (0.5 mg estradiol) and the 1.0 g estradiol gel (1.0 mg estradiol) daily doses were fully effective for the treatment of moderate to severe VMS associated with the menopause by Treatment Week 4. The assessment of fully effective is based on the recommendations of the Agency's 2003 draft Guidance for Industry entitled "Estrogen and Estrogen/Progestin Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation" (hereafter referred to as the draft HT Clinical Trial Guidance). The 0.25 g estradiol gel (0.25 mg estradiol) daily dose was not fully effective until Treatment Week 7. The safety profiles for all doses of (1) estradiol gel 0.1% (Divigel) in principal Study P04-001 and supportive Phase 1 studies conducted by the Applicant and (2) estradiol gel 0.1% in studies previously conducted by another company (Orion, Finland) were acceptable for an estrogen drug product for the treatment of VMS associated with the menopause.

(b) (4)

1.3 Recommendation on Risk Management Steps and/or Phase 4 Studies

1.3.1 Recommendation on Risk Management Steps

No postmarketing risk management steps, other than appropriate labeling that clearly delineates the potential risks of estrogen therapy, are required or requested.

1.3.2 Phase 4 Studies

No Phase 4 clinical study commitments are required or requested.

2. BACKGROUND

2.1 Estradiol Gel 0.1% and Other Estrogen Products

Divigel ([estradiol gel] 0.1%) is a transdermal formulation composed of 0.1% 17ß-estradiol in a clear to opalescent alcohol based gel. The excipients include carbomer (a viscosity building agent), triethanolamine (a neutralizing agent for carbomer), propylene glycol (a solvent), ethanol (a solvent), and water. All of the excipients have been used extensively in topically applied drug and cosmetic products in the US. The drug product is packaged in single-dose foil-laminate packets.

According to the primary Medical Reviewer, estradiol gel 0.1% was originally developed by Orion (Turku, Finland) and first approved in Finland in 1994. (b) (4)

Numerous estrogen alone and estrogen plus progestin drug products are currently approved in the U.S. for the treatment of moderate to severe vasomotor symptoms and/or moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. These include:

- Oral tablets: Premarin (conjugated estrogens), Estrace (estradiol), Femtrace (estradiol acetate), Prempro/Premphase (conjugated estrogens plus medroxyprogesterone acetate), Prefest (estradiol plus norgestimate), and Activella (estradiol plus norethindrone acetate);
- Transdermal systems: Alora (estradiol), Climara (estradiol), Estraderm (estradiol), Vivelle (estradiol), Vivelle-Dot (estradiol), and Climara-Pro (estradiol plus levonorgestrel);
- Other Topical transdermal products: Estrasorb (estradiol hemihydrate emulsion), Estrogel (estradiol gel), and Elestrin (estradiol gel);
- Vaginal ring: Femring® (estradiol acetate).

(b) (4)

2.2 Significant Review Issues

Subject Diaries. A significant portion of the review of this Application was devoted to assessing the integrity of the subject diary documents that were used to collect the primary efficacy data (i.e., frequency and severity of daily hot flushes). During the review of a limited number of photocopies of subject diaries, the primary Medical Reviewer noted items in some of diaries that were of concern to her. These concerns included (1) alterations of dates in what appeared to be different handwriting, (2) "duplicate" entries for a given day, (3) differences in the time of gel application on a given study visit date recorded on one page of the diary from that for the same gel application date recorded on a different diary page, and (4) absence of subject numbers on each "page" of the dairy. These observations prompted the primary Medical and Statistical Reviewers to request photocopies of additional diaries on 2 occasions. Certified photocopies of subject diaries from 130 of 488 subjects in the primary Phase 3 study (Study P04-001) were eventually reviewed. The primary Medical Reviewer made the following statement in the Executive Summary of her review:

> *"Though this reviewer does not concur with the changes made to the statistical analysis plan and many irregularities in the information collected on these diaries were noted, this reviewer has concluded after thorough review and consideration of additional information provided by the Sponsor that the extent of the irregularities did not substantially affect the*

outcome of the comparison of the drug product to placebo and there was not appearance of an intent to alter the source documentation."

In regard to this issue, the clinical Team Leader made the following statement in the Executive Summary of her review:

"After complete review of 130 out of 488 source diary copies, it was determined that despite the discovery of numerous discrepancies, the vast majority of the discrepancies did not affect the actual efficacy data. Fifteen (11.5%) of the 130 source diary copies [15 out of 488 mITT data population (3.1%)] had discrepancies in the efficacy data. Three of these had changes to the post-treatment efficacy information with an additional 12 having some manipulation of the baseline efficacy information. A sensitivity analyses eliminating these 3% of the mITT population was similar to the analysis including the discrepant data. Of course, in the absence of review of the entire data set one can not say with absolute certainty that a greater percentage of problems would have been uncovered. However, the clinical and statistical team determined that there was no obvious evidence of an attempt at fraud and the random sampling suggested effect on the actual vasomotor symptom data was limited."

In regard to this issue, the primary Statistical Reviewer made the following statement regarding the subject diaries in her review:

"Additional data alterations, mostly changes in dates and crossed out numbers, were noted in these additional source diaries, but it appeared the integrity of the efficacy data was not compromised to affect the efficacy conclusions."

The primary Medical Reviewer describes in detail in her review the diary-related problems that were noted.

Division Director's Comments

- *I concur with the primary Medical Reviewer, primary Statistical Reviewer, and the clinical Team Leader that the issues noted during the review of certified photocopies of subject diaries did not compromise the integrity of the primary efficacy data to an extent that would potentially compromise the primary efficacy conclusions.*
- *Based on my independent limited review of selected diaries, I did not find the items of concern to be outside of the range of findings that are to be expected with subject-completed diaries. I do concur with the reviewers that better diary design and/or instruction of site coordinators might have resulted in fewer items of concern.*
- *Some of the items of concern (e.g., lack of subject identifiers on each "page") should not have been concerns because the monthly subject diary consisted of a single, folded sheet of paper that did not warrant a patient identifier on each "weekly-fold."*
- *To obtain an independent assessment of the quality of the data recorded in the subject diaries, I asked the Division of Scientific Investigation (DSI) to specifically comment on this matter. Dr. Roy Blay of DSI provided the following statement:*

  "Per your request, I have re-evaluated the Establishment Inspection Reports (EIRs) as they relate to the status of the diaries and contacted, as needed, the FDA investigators who conducted these inspections for any additional insights/impressions they might have to share regarding their review of the diaries. Neither my review of

the EIRs nor my conversations with the FDA investigators revealed any significant deficiencies with the diaries."

- *Full review by the Division of Reproductive and Urologic Products (DRUP) of all Patient Reported Outcome (PRO) instruments (e.g., subject diaries) prior to their use and the replacement of paper diaries with electronic diaries in future studies would likely avoid many of the problems observed in Study P04-001.*

Revisions to the Statistical Analysis Plan. A statistical analysis plan (SAP) that detailed the planned analyses of the primary Phase 3 study (Study P04-001) was finalized on September 1, 2005 by the Sponsor and submitted to DRUP. The SAP was subsequently revised and amended on November 21, 2005 ***prior to*** unblinding and data lock. The revised SAP, however, was not sent to the Division for review. The revised SAP (1) established data handling rules for duplicate and blank diary entries, (2) further defined missing diary data in the baseline and post-baseline periods, (3) clarified the application of the LOCF approach, (4) further defined the analysis for pooled center interaction, (5) (b) (4), and (6) redefined the analysis of covariance (ANCOVA) model used for the efficacy analysis.

Division Director's Comments

- *Both the primary Medical and Statistical Reviewers did not agree with some of the items in the amended SAP. The statistical reviewer, however, concluded that the procedures described in the amended SAP did not have a material effect on the efficacy conclusions.*
- *I do not believe that failure to submit the amended SAP to the Division is of significant concern. The SAP was amended prior to unblinding of the data. Any "unacceptable" procedures described in the amended SAP could be "undone" by asking the Applicant to modify an unacceptable data handing assumption or data analysis.*

3. OVERVIEW OF CLINICAL PROGRAM

The primary source of efficacy data submitted in support of the VMS (b) (4) was Study P04-001. This was a randomized, parallel, placebo-controlled, double-blind, multicenter Phase 3 study in postmenopausal women with moderate to severe vasomotor symptoms. Subjects received treatment with Divigel (Estradiol gel, 0.1%) or placebo for 12 weeks. The study was conducted at 48 sites in the U.S. and Canada. Prior to randomization, subjects completed the symptom diary for at least 12 days, which provided baseline data for the efficacy analyses. Four hundred ninety five (495) healthy postmenopausal women who met the eligibility criteria during the screening evaluations were randomized in a 1:1:1:1 manner to one of 4 treatment groups: 1.0 mg estradiol (1.0 g of estradiol gel, 0.1%), 0.5 mg estradiol (0.5 g of estradiol gel, 0.1%), 0.25 mg estradiol (0.25 g of estradiol gel, 0.1%), or placebo gel. All subjects applied the study drug topically to the thigh once daily, alternating between the left and right thigh daily, for 12 weeks. For evaluation of vasomotor symptoms, subjects were to maintain a daily diary of hot flush frequency and severity. Severity was scored as mild, moderate, or severe.

The safety database was composed of Phase 3 Study P04-001, three Phase 1 studies conducted by the Applicant, and 4 non-U.S. studies previously conducted by Orion that used the original formulation of estradiol gel 0.1%.

Division Director's Comments

- *DRUP has generally accepted data from a single adequate and well-controlled clinical trial as potentially adequate to support the safety and effectiveness of an estrogen drug product for the indication (b) (4) of treatment of moderate to severe VMS (b) (4)*
- *The data submitted in NDA 22-038 are adequate to support the safety (in conjunction with supportive safety data submitted by the Applicant) and efficacy of the VMS indication (b) (4)*

4. EFFICACY

4.1 Indication of Treatment of Vasomotor Symptoms (VMS)

4.1.1 Primary Efficacy Assessments and Endpoints

For the treatment of moderate to severe VMS associated with the menopause, the draft HT Clinical Trial Guidance recommends that one or more 12-week, randomized, double-blind, placebo-controlled clinical trials be conducted that evaluate the following 4 co-primary endpoints:

- Mean change in frequency of moderate to severe vasomotor symptoms from baseline to Week 4.
- Mean change in frequency of moderate to severe vasomotor symptoms from baseline to Week 12.
- Mean change in severity of moderate to severe vasomotor symptoms from baseline to Week 4.
- Mean change in severity of moderate to severe vasomotor symptoms from baseline to Week 12.

The primary efficacy analysis should show a statistically significant reduction in hot flush frequency and severity within 4 weeks of initiation of treatment that is maintained throughout 12 weeks of treatment compared to placebo. The primary efficacy analysis also should show a clinically significant reduction in frequency defined in the draft Guidance as a reduction of at least 2 moderate to severe hot flushes above placebo at Week 4 through Week 12.

4.1.2 Efficacy Findings (VMS Indication)

The modified intent-to-treat population (mITT) consisted of 488 subjects (96.8% of those randomized). The initial planned analysis was an Analysis of Covariance (ANCOVA) model. All vasomotor analyses were performed using the LOCF method of imputation of missing diary data. A step-down sequential approach was used to analyze the 3 active treatment groups (1.0 g, 0.5 g, and 0.25 g of estradiol gel, respectively). During the initial analyses, the data were determined to be non-normally distributed using the Wilkes-Shapiro test; consequently, a van Elteren's test (an extension of the Wilcoxon rank sum test) was used to analyze the primary

efficacy co-endpoints and results were expressed in terms of median values instead of mean values.

The outcome of the primary efficacy analysis for median number of moderate to severe hot flushes and the change from baseline during treatment is shown in Table 1.

Table 1 Median Daily Number of Moderate to Severe Hot Flushes and Change from Baseline during Treatment (modified Intent-to-Treat Population with LOCF)

Week	Median Hot Flush Frequency and Median Change form Baseline			
	0.25 mg/day (N = 121)	0.5 mg/day (N = 119)	1.0 mg/day (N = 124)	Placebo (N = 124)
Baseline				
Median Number	9.72	9.24	9.64	9.32
Week 4				
Median Number	4.86	3.71	1.93	5.64
Median Change	-5.0	-5.73	-7.20	-3.63
p-value vs. placebo*	0.132	0.011	<0.001	
Week 5				
Median Number	3.86	3.43	1.36	5.57
Median Change	-5.71	-6.63	-7.34	-4.05
p-value vs. placebo*	<0.01	<0.01	<0.001	
Week 6				
Median Number	3.86	2.86	1.14	5.66
Median Change	-5.71	-6.79	-7.61	-4.06
p-value vs. placebo*	<0.001	<0.001	<0.001	
Week 7				
Median Number	3.29	2.29	1.02	5.36
Median Change	-6.62	-7.14	-7.71	-4.37
p-value vs. placebo*	<0.001	<0.001	<0.001	
Week 12				
Median Number	3.00	1.57	0.43	4.93
Median Change	-6.88	-7.29	-8.35	-4.48
p-value vs. placebo*	<0.001	<0.001	<0.001	

* The van Elteren's test stratified by pooled center was used to evaluate treatment comparisons between each active dose and placebo.

Source: Adapted from Table 1, clinical Team Leader Review, June 3, 2007 and Table 8, primary Statistical Review, May 30, 2007.

Division Director's Comments

- *The two highest doses of estradiol gel, 0.5 mg estradiol/day and 1.0 mg estradiol/day, demonstrated both statistically significant ($p = 0.011$ and $p<0.001$, respectively) and clinically meaningful reductions in the median daily number of moderate to severe hot flushes at Week 4 and maintained these reductions through Week 12 compared to placebo.*

- *The lowest dose of estradiol gel, 0.25 mg estradiol/day, however, did not demonstrate a statistically significant and clinically significant reduction in the median daily number of moderate to severe hot flushes until Week 5.*

For the severity calculation, hot flushes were assigned weighting factors of 3, 2, and 1 for severe, moderate, and mild flushes, respectively. The outcome of the primary efficacy analyses for the median daily severity of moderate to severe hot flushes and the change from baseline during treatment is shown in Table 2.

Table 2 Median Daily Severity of Moderate to Severe Hot Flushes and Change from Baseline during Treatment (modified Intent-to-Treat Population with LOCF)

Week	Median Hot Flush Severity and Median Change from Baseline			
	0.25 mg/day (N = 121)	0.5 mg/day (N = 119)	1.0 mg/day (N = 124)	Placebo (N = 124)
Baseline				
Median Severity	2.52	2.51	2.52	2.54
Week 4				
Median Severity	2.39	2.27	2.02	2.45
Median Change	-0.07	-0.18	-0.47	-0.04
p-value vs. placebo*	0.283	<0.001	<0.001	
Week 5				
Median Severity	2.31	2.26	1.78	2.44
Median Change	-0.16	-0.29	-0.67	-0.04
p-value vs. placebo*	<0.05	<0.001	<0.001	
Week 6				
Median Severity	2.31	2.14	1.71	2.45
Median Change	-0.13	-0.39	-0.76	-0.05
p-value vs. placebo*	NS	<0.001	<0.001	
Week 7				
Median Severity	2.25	2.00	1.38	2.43
Median Change	-0.24	-0.46	-1.06	-0.06
p-value vs. placebo*	<0.001	<0.001	<0.001	
Week 12				
Median Severity	2.11	2.00	0.86	2.42
Median Change	-0.33	-0.56	-1.69	-0.13
p-value vs. placebo*	0.021	0.002	<0.001	

* The van Elteren's test stratified by pooled center was used to evaluate treatment comparisons between each active dose and placebo.

Source: Adapted from Table 2, clinical Team Leader Review, June 3, 2007 and Table 9, primary Statistical Review, May 30, 2007.

Division Director's Comment

- *The two highest doses of estradiol gel, 0.5 mg estradiol/day and 1.0 mg estradiol/day, demonstrated statistically significant (p<0.001) reductions in the median daily severity of moderate to severe hot flushes at Week 4 and maintained these reductions through Week 12 compared to placebo.*

- *The lowest dose of estradiol gel, 0.25 mg estradiol/day, however, did not demonstrate a statistically significant reduction in the median daily severity of moderate to severe hot flushes that was maintained until Treatment Week 7.*
- *Although treatment with the 0.25 mg/day dose of estradiol did not achieve a statistically significant, persistently greater effect than treatment with placebo, in terms of a reduction in <u>both</u> the frequency and severity of hot flushes, until Week 7, this dose of estradiol gel should be approved. A significant number of women are likely to derive clinical benefit from this lower dose of estradiol gel. Labeling will reflect the longer length of time possibly required to achieve clinical effectiveness with this lower dose of estradiol gel.*

(b) (4)

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5. SAFETY FINDINGS

5.1 Safety Database

The safety cohort of Study P04-001 consisted of 495 subjects who received at least one dose of study medication. In addition, safety data from 3 Phase 1 studies (P04-003 [21 subjects], P04-002 [54 subjects], and P04-005 [16 subjects] as well as 4 non-US studies conducted by the original Sponsor (Orion) with a different formulation (Study 63806 [60 subjects],

Study 63808 [401 subjects], Study 63811 [40 subjects], and Study 638019 [216 subjects]) were included in the integrated summary of safety (ISS).

5.2 Deaths and Other Serious Adverse Events

There were no deaths in primary Phase 3 Study P04-001 or any of the 3 Phase 1 studies conducted by the Applicant. In the 4 studies conducted by Orion, there was a single death from an acute myocardial infarction that occurred after 10 months of treatment with study drug. No further information on this subject was available.

In the studies conducted by the Applicant, there were 4 serious adverse events: 3 in Study P04-001 and one in Study P04-005. These events were (1) a pulmonary embolus in a women status post-cholecystectomy for symptomatic gall stones who was receiving 0.5 mg estradiol/day; (2) chest pain without a clear etiology in a women receiving 1.0 mg estradiol/day; (3) chest pain that was subsequently diagnosed as secondary to gastritis; and (4) chest pain after 3 doses of 1.0 mg estradiol.

5.3 All Adverse Events

In Study P04-001, treatment-emergent adverse events were reported in 56.2% (278 of 495 subjects). There was a trend for an increasing incidence of patients with treatment-related adverse events with increasing dose (12.0%, 18.9%, 21.1%, and 34.4% of patients in the placebo and 0.25 mg, 0.5 mg, and 1.0 mg estradiol treatment groups, respectively). Ten of the 495 subjects (2%) discontinued because of an adverse event. These events were migraine, meningioma, vertigo/disorientation, thickened endometrium, arthralgia/sciatica, vaginal hemorrhage, non-cardiac chest pain, and postoperative pulmonary embolism (each in one subject) as well depression (reported in 2 subjects). The adverse events were mostly (8 of the 10) clustered in the 1 mg estradiol/day dose group. Adverse events that were reported by ≥ 5% of patients in any estradiol gel treatment group are shown in Table 6.

Table 6 Number (%) of Subjects with Common Adverse Events in Study P04-001 *

	Estradiol gel			Placebo
SYSTEM ORGAN CLASS Preferred Term	0.25 mg/day N=122 n (%)	0.5 mg/day N=123 n (%)	1.0 mg/day N=125 n (%)	N=125 n (%)
INFECTIONS & INFESTATIONS				
Nasopharyngitis	7 (5.7)	5 (4.1)	6 (4.8)	5 (4.0)
Upper Respiratory Tract Infection	7 (5.7)	3 (2.4)	2 (1.6)	2 (1.6)
Vaginal mycosis	1 (0.8)	3 (2.4)	8 (6.4)	4 (3.2)
REPRODUCTIVE SYSTEM & BREAST DISORDERS				
Breast Tenderness	3 (2.5)	7 (5.7)	11 (8.8)	2 (1.6)
Metrorrhagia	5 (4.1)	7 (5.7)	12 (9.6)	2 (1.6)

* Adverse events reported by ≥5% of patients in any estradiol gel treatment group.
Source: Modified from approved Package Insert.

5.4 Endometrial Changes and Endometrial Hyperplasia

As stated by the clinical Team Leader in her review: "One of the most concerning adverse events most commonly associated with use of unopposed estrogens in women with a uterus is endometrial hyperplasia. The Draft HT Clinical Trial Guidance recommends that for 12 week

trials for VMS (b) (4), subjects with a uterus receive an endometrial biopsy at baseline and at end-of-study. Unfortunately, the Sponsor received mixed messages from the Agency regarding the Clinical Trial Guidance recommendations for baseline and end-of-study endometrial biopsy and did not follow these recommendations for this study." Although 210 subjects (90% of those with a uterus) had an endometrial biopsy at baseline, only 49 subjects had an endometrial biopsy at the end of the study. Among theses 49 end-of-treatment biopsies, there were no cases of hyperplasia. There was a single case of disordered proliferative endometrium.

To further evaluate endometrial safety, the primary Medical Reviewer also reviewed the endometrial biopsy findings from Study 63808. Study 63808 was an open-label study of 401 menopausal subjects who used estradiol gel 0.1% (doses ranging from 0.5 mg to 1.5 mg estradiol) combined with 10 mg of medroxyprogesterone acetate for 12 days every month or for 12 days every third month. In the assessment of the group of subjects treated with estradiol gel, 0.1% combined with progestin for 12 days every month, there was no evidence of hyperplasia. Only one case of hyperplasia was seen (a subject in the group receiving the progestin every third month).

Division Director's Comment

- *The clinical Team Leader stated the following in her review: "Taken in total the histology data for Divigel alone or estradiol gel, 0.1% in combination with progestin yields no signal for concern for endometrial safety." I concur with her assessment.*

5.5 Overall Assessment of Safety Findings

Division Director's Comments

- *The overall safety profile for Divigel (0.25 mg estradiol, 0.5 mg estradiol, and 1.0 mg estradiol) is acceptable for an estrogen drug product for the treatment of VMS.*
- *As with all estrogen drug products, labeling should include the findings of the WHI study and all other class warnings and precautions.*

6. OTHER DISCIPLINES

There are no unresolved toxicology, CMC (chemistry, manufacturing, or control), or clinical pharmacology issues. The proposed trade name Divigel was acceptable to the Division of Medication Errors and Technical Support (DMETS) as long as neither of two other drugs in clinical development with proposed proprietary names of (b) (4), respectively, were approved prior to the approval of Divigel. Neither of these latter drugs is approved as of the date of this action for Divigel.

7. LABELING

Final revised labeling submitted by the Applicant on June 4, 2007 is acceptable.

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/s/

Scott Monroe
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MEDICAL OFFICER