[redacted] FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-813

SUMMARY REVIEW

DIVISION OF REPRODUCTIVE AND UROLOGIC PRODUCTS (DRUP)

DIVISION DIRECTOR MEMORANDUM

NDA	NDA 21-813 (and by cross-reference to NDA[ ])
Type of Application	Original
Applicant	BioSante Pharmaceuticals, Inc Lincolnshire, IL 60069
Proprietary Drug Name	Elestrin ™
Established Drug Name	Estradiol gel
Drug Class	Estrogen
Indications (Proposed)	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause [ ]
Route of administration	Transdermal
Dosage Form	Gel
Dosing Regimen	Once daily application of 0.87, 1.7[ ] gel/day, containing 0.52, 1.02[ ] mg estradiol/dose, and delivering systemically [ ] [ ] mg estradiol/24 hrs, respectively
CDER Receipt Date	February 16, 2006
PDUFA Goal Date	December 16, 2006
Date of Memorandum	December 15, 2006
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 both the 0.87 g (0.52 mg estradiol)/day and 1.7 g (1.02 mg estradiol)/day dose of estradiol gel be approved for the indication of treatment of moderate to severe vasomotor symptoms (VMS) associated with the menopause.[ ]

[ ]
[ ]
[ ]
[ ]

1.2 Basis for Recommendation regarding Approvability

Indication of VMS. The Applicant has demonstrated in a single adequate and well-controlled clinical trial that both the 0.87 g (0.52 mg estradiol)/day and 1.7 g (1.02 mg estradiol)/day dose of estradiol gel is safe and effective for the treatment of moderate to severe VMS associated with the menopause. [ ]

[ ]

[ ]

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

Elestrin ™ (estradiol gel) is a transdermal formulation composed of 0.06% estradiol in a hydroalcoholic gel. The inactive ingredients include ethanol, propylene glycol, diethylene glycol, monoethyl ether, carbomer[ ], triethanolamine, purified water, and edetate disodium. All excipients are either USP or NF. The drug product is packaged in a[ ] mL metered dose pump and is to be applied once daily to the upper arm. The metered dose pump delivers 0.87 g of estradiol gel, containing 0.52 mg estradiol, per actuation.

Numerous estrogen alone and estrogen plus progestin drug products are currently approved 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), Climara-Pro® (estradiol plus levonorgestrel); and

- Vaginal ring: Femring® (estradiol acetate).

3. OVERVIEW OF CLINICAL PROGRAM

The primary source of efficacy data submitted in support of the VMS [ ] indications was a single, 12-week, placebo-controlled, Phase 3 clinical trial (Study EST005). Study EST004, a Phase 2 dose-ranging study was conducted prior to primary Phase 3 Study EST005. Study EST004 was only 4-weeks duration and was considered supportive of the proposed indication of VMS.

Study EST005 was a parallel-group, placebo-controlled, randomized study designed to detect a statistically and clinically meaningful difference between the estradiol gel dose groups and placebo. The protocol called for randomizing 127 subjects per group equally to the following treatment groups: 0.87 g gel/day, 1.7 g gel/day, 2.6 g gel/day and placebo; only 69 subjects, however, were randomized in the 2.6 g gel/day dose group because the Applicant expected that the effect size for the higher dose would be sufficiently large that a lesser number of subjects would provide adequate power.

The primary sources of safety data were Phase 3 Study EST005 and Phase 2 Study EST004. A total of 645 treated subjects were represented in these two studies (484 subjects in Study EST005 and 161 subjects in Study EST004). Adverse event data was pooled across Studies EST005 and EST004 for (a) the 2.5 g/day estradiol gel treatment group in Study EST004 and the 2.6 g/day estradiol gel treatment group in Study EST005 and (b) for the placebo treatment groups in these two studies. Adverse event data were presented by dose group across all additional doses in both studies (0.625 g/day estradiol gel and 1.25 g/day estradiol gel in Study EST004 and 0.87 g/day estradiol gel and 1.7 g/day estradiol gel in Study EST005).

Division Director's Comments

- *The Division of Reproductive and Urologic Products (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 indications treatment of moderate to severe VMS* [ ]
- *The data provided in NDA 21-813 are adequate to support the safety and efficacy of the VMS indication* [ ]

[ ]

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 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" recommends that one or more 12-week, randomized, double-blind, placebo-controlled clinical trials be conducted that evaluate the following four 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.

For study inclusion, subjects should have a minimum of 7 to 8 moderate to severe hot flushes per day at baseline, or 50 to 60 moderate to severe hot flushes per week at baseline. 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 two moderate to severe hot flushes above placebo at Week 4 through Week 12.

4.1.2 Efficacy Findings (VMS Indication)

The daily moderate to severe hot flush frequency was calculated as the total number of moderate to severe hot flushes recorded in the subject's daily diary during the seven days immediately preceding and including the weekly study date, divided by the number of those seven days with completed diary entries. Severity was calculated as the sum of the average daily hot flush severity rating divided by the number of hot flushes on those seven days with diary entry completed. 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 analysis for mean number of moderate to severe hot flushes and the change from baseline during treatment is shown in Table 1.

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

Week	Hot Flush Frequency and Mean Change [a]			
	0.87 g/day (N = 136)	1.7 g/day (N = 142)	2.6 g/day (N = 69)	Placebo (N = 137)
Baseline[b]				
Mean Number (±SD)	13.30 ± 4.6	13.10 ± 6.5	12.87 ± 6.5	13.47 ± 4.5
Week 4				
Mean Number	6.55	4.87	3.69	7.91
Mean Change	-6.5	-8.00	-9.32	-5.14
p-value vs. placebo [c]	ns	<0.0001	<0.0001	
Week 5				
Mean Number	5.50	4.03	3.19	7.83
Mean Change	-7.47	-8.81	-9.83	-5.14
p-value vs. placebo [c]	<0.001	<0.0001	<0.0001	
Week 12				
Mean Number	4.00	2.50	2.05	7.30
Mean Change	-8.50	-10.02	-10.66	-5.35
p-value vs. placebo [c]	<0.0001	<0.0001	<0.0001	<0.0001

a Difference from baseline to each week based on LS mean derived from the ANCOVA model with factors for baseline, treatment site, and treatment by baseline interaction.

b Unadjusted means and standard deviation. Baseline based on the first 14 days of the screening period.

c Dunnett's adjustments for multiple dose comparisons.

Source: Adapted from Table 1, clinical Team Leader Review, Dec. 13, 2006.

Division Director's Comments

- *The two highest doses of estradiol gel, 1.7 g/day and 2.6 g/day, demonstrated both statistically significant (p<.001) and clinically meaningful reductions in the mean daily number of moderate to severe hot flushes at Week 4 and maintained these reductions through Week 12 compared to placebo.*
- *Estradiol gel 0.87 g/day, however, demonstrated only a marginally significant (p=.0511) reduction at Week 4. At Week 5, however, this dose of estradiol gel also demonstrated a statistically significant (p<.001) and clinically meaningful reduction in the mean daily number of moderate to severe hot flushes that was maintained through Week 12.*

The outcome of the primary efficacy analyses for the mean daily severity of moderate to severe hot flushes and the change from baseline during treatment is shown in Table 2.

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

Week	Hot Flush Severity and Mean Change[a,b]			
	0.87 g/day (N = 136)	1.7 g/day (N = 142)	2.6 g/day (N = 69)	Placebo (N = 137)
Baseline[c]				
Mean Severity (±SD)	2.42±0.32	2.4±0.27	2.41±0.32	2.41±0.32
Week 4				
Mean Severity	1.93	1.70	1.45	2.12
Mean Change	-0.45	-0.67	-0.96	-0.24
p-value vs. placebo[d]	ns	<0.0001	<0.0001	
Week 5				
Mean Severity	1.85	1.59	1.34	2.12
Mean Change	-0.50	-0.77	-1.05	-0.22
p-value vs. placebo[d]	<0.01	<0.0001	<0.0001	
Week 12				
Mean Severity	1.52	1.15	0.86	2.05
Mean Change	-0.77	-1.17	-1.51	-0.26
p-value vs. placebo[c]	<0.0001	<0.0001	<0.0001	<0.0001

a Difference from baseline to each week based on LS mean derived from the ANCOVA model with factors for baseline, treatment site, and treatment by baseline interaction.
b Severity score 1=mild; 2=moderate; 3=severe.
c Unadjusted means and standard deviation. Baseline based on the first 14 days of the screening period.
d Dunnett's adjustment for multiple dose comparisons.
Source: Adapted from Table 2, clinical Team Leader Review, Dec. 13, 2006.

Division Director's Comment

- *The two highest doses of estradiol gel, 1.7 g/day and 2.6 g/day, demonstrated statistically significant (p<.001) reductions in the mean daily severity of moderate to severe hot flushes at Week 4 and maintained these reductions through Week 12 compared to placebo.*
- *Estradiol gel 0.87 g/day, did not demonstrated a significant reduction in the mean daily severity of moderate to severe hot flushes at Week 4. At Week 5, however, this dose of estradiol gel also demonstrated a statistically significant (p<0.01) reduction in the mean daily severity of moderate to severe hot flushes that was maintained through Week 12.*
- *Although treatment with the 0.87g/day dose of estradiol gel did not achieve a statistically significant greater effect than treatment with placebo until Week 5, in terms of reduction in the frequency and severity of hot flushes, this dose of 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 slightly longer length of time possibly required to achieve clinical effectiveness with this lower dose of estradiol gel.*

4.2.1 Primary Assessments and Endpoints

For the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause, the Agency's 2003 draft clinical evaluation guidance document recommends the following three co-primary endpoints:

- Mean change from baseline to Week 12 in the vaginal cytology (percentages of superficial and parabasal cells). For study inclusion, subjects should have no greater than 5% superficial cells on a vaginal smear at baseline. The primary efficacy analysis should show a statistically significant increase in superficial cells and a statistically significant decrease in parabasal cells.
- Mean change from baseline to Week 12 in vaginal pH. For study inclusion, subjects should have a vaginal pH > 5.0 at baseline. The primary efficacy analysis should show a statistically significant lowering of vaginal pH.
- Mean change from baseline to Week 12 in the moderate to severe self-assessed symptom of VVA identified by the subject as being the most bothersome to her. For study inclusion, subjects should self-identify the one most bothersome moderate to severe vulvar and vaginal atrophy symptom. The primary efficacy analysis should show a statistically significant improvement in the moderate to severe symptom identified by the subject as most bothersome. The recommended subject self-assessed symptoms of vulvar and vaginal atrophy include:
  - Vaginal dryness (categorized as none, mild, moderate or severe)
  - Vaginal and/or vulvar irritation/itching (categorized as none, mild, moderate, or severe)
  - Dysuria (categorized as none, mild, moderate, or severe)
  - Vaginal pain associated with sexual activity (categorized as none, mild, moderate, or severe)
  - Vaginal bleeding associated with sexual activity (categorized as none, mild, moderate, or severe)

  Symptoms were assigned values of 1, 2, or 3 for severities of mild, moderate, and severe, respectively, for purpose of analyses.

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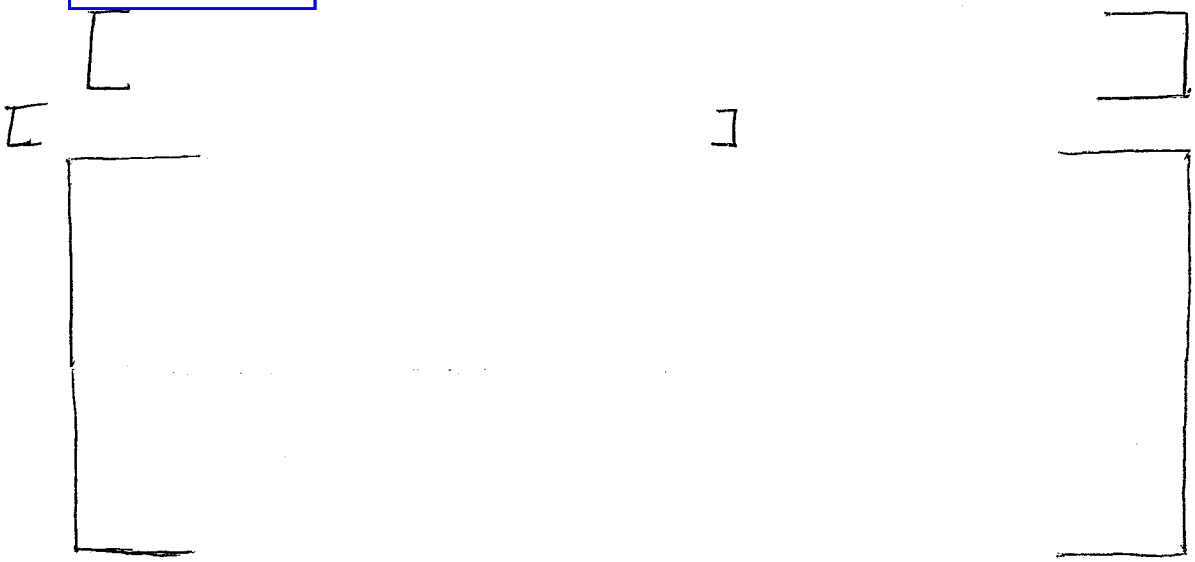
Division Director Memorandum (12/15/06)



5. SAFETY FINDINGS

5.1 Deaths and Other Serious Adverse Events

There were no deaths in the clinical trial.

A total of three subjects experienced a serious adverse event (SAE) among the 484 treated subjects in Study EST005. One SAE occurred during the single-blind placebo lead-in period. The remaining two SAEs occurred during the 12-week double-blind treatment period. Subject 261 (2.6 g/day estradiol gel treatment group, 54 years of age) experienced a worsening of a cervical cyst noted at study entry and an increase in endometrial thickness at end-of-study (4 mm at screening at baseline, 6 mm at end-of-study). She required hospitalization approximately three months after the last dose of study medication and underwent a transabdominal hysterectomy and bilateral salpingoophorectomy. The event was considered possibly related to study drug. Subject 106 (1.7 g/day estradiol gel treatment group, 50 years of age) experienced a severe staphylococcal infection in her left thumb at a site of previous surgery which required hospitalization. Medication was discontinued. The event was not considered related to study drug.

5.2 Endometrial Changes and Endometrial Hyperplasia

Endometrial hyperplasia with and without atypia, while not unexpected with unopposed estrogen therapy, is infrequently observed in 12-week clinical trials of unopposed estrogen therapy. No subject in the 0.87 g/day estradiol gel treatment group was diagnosed with endometrial hyperplasia. One subject in the 1.7 g/day estradiol gel treatment group was diagnosed with complex hyperplasia with atypia based on an endometrial biopsy at 90 days of study participation. This subject subsequently received a fractional dilatation and curettage with findings of: "endometrial curettings and polyps; benign endometrial polyps with focal hyperplasia, simple and complex, without atypia". Complex atypical hyperplasia is a concerning pathological diagnosis. However, it would be difficult to determine that the endometrial safety profile was unacceptable based on a single case. In contrast, the reported rate of 11.1% endometrial hyperplasia in the 2.6 g/day estradiol gel treatment group (5 of 45 subjects) exceeds

the endometrial hyperplasia rate observed in other controlled 12-week clinical trials of unopposed estrogen therapy and is of concern.

Division Director's Comment

- [redacted]

5.3 All Adverse Events

Per the Integrated Summary of Safety, the reproductive disorders class was observed to be most affected by treatment with estradiol gel; the incidence of adverse events in this class overall and individually (breast tenderness, metrorrhagia, vaginal discharge, endometrial hyperplasia, nipple pain) increased in a time and dose-dependent manner. There was a higher incidence of overall treatment-emergent adverse events (TEAEs) of this class in the estradiol gel all doses group than in the all placebo group and the difference was statistically significant (110 subjects [23.6%] versus 15 subjects [8.4%], respectively).

Division Director's Comment

- *The types and percentages of subjects reporting these TEAEs are to be expected during treatment with estrogens and are similar to those reported during clinical trials for other approved estrogen products.*

5.4 Overall Assessment of Safety Findings

Both the 0.87 g/day and the 1.7 g/day dosing regimens of estradiol gel were well tolerated. More subjects in the 1.7 g/day estradiol gel treatment group, however, discontinued (6.3%, nine of 142 subjects) than in the 0.87 g/day estradiol gel treatment group (2.9%, four of 136 subjects). In addition, more subjects in the 1.7 g/day estradiol gel treatment group discontinued due to adverse events (3.5%, five of 142 subjects) than in the 0.87 g/day estradiol gel treatment group (0.7%, 1 of 136 subjects).

Division Director's Comments

- *The above rates of discontinuation due to adverse events are not unexpected and pose no safety concerns for the 0.87 g/day and the 1.7 g/day estradiol gel dosage strengths.*
- *Overall, the safety data presented in the submission shows that the overall safety profiles of the 0.87 g/day estradiol gel dose and the 1.7 g/day estradiol gel dose are acceptable for the proposed indications.*
- [redacted]

6. OTHER DISCIPLINES

There are no unresolved toxicology, CMC (chemistry, manufacturing, or control), or clinical pharmacology issues. The proposed trade name Elestrin (estradiol gel) was acceptable to both the Division of Medication Errors and Technical Support (DMETS) and DDMAC.

7. LABELING

Final revised labeling submitted by the Applicant on December 14, 2006 is acceptable.

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/s/

Scott Monroe
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MEDICAL OFFICER