CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-813

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-813**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**2/21/06**
PRODUCT:	**Bio-E-Gel (estradiol gel)**
INTENDED CLINICAL POPULATION:	**Treatment of moderate-to-severe vasomotor symptoms associated with menopause**
SPONSOR:	**BioSante Pharmaceuticals, Inc. Licolnshire, Illinois**
DOCUMENTS REVIEWED:	**Vol. 1, 2, 3 and 12**
REVIEW DIVISION:	**Division of Reproductive and Urological Drug Products (HFD-580)**
PHARM/TOX REVIEWER:	**Krishan L. Raheja, D.V.M., Ph.D.**
PHARM/TOX SUPERVISOR:	**Lynnda Reid, Ph.D.**
DIVISION DIRECTOR:	**Dan Shames, M.D.**
PROJECT MANAGER:	**George Lyght**

Date of review submission to Division File System (DFS): 8-9-06

TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: The pharmacology, pharmacokinetics, and toxicology of transdermally and orally administered estradiol have been extensively investigated previously under various submissions. Also extensive published literature is available to establish the safe use of estradiol. The safety of the excipient, [ ], is provided under [ ] DMF [ ] and has been approved under NDA 21-794 for ACZONE (5% Dapsone gel [ ]) for the topical treatment of acne vulgaris. Based on the information on pharmacology/toxicology submitted, Pharmacology recommends approval of NDA-21-813 for Bio-E-Gel for the treatment of moderate-to-severe vasomotor symptoms associated with menopause.

B. Recommendation for nonclinical studies: None.

C. Recommendations on labeling: Labeling will be per class labeling in accord with FDA labeling guidance issued by CDER as Guidance for Industry: noncontraceptive estrogen drug products for the treatment of vasomotor symptoms and vulvar and vaginal atrophy symptoms- recommended prescribing information for health care providers and patient labeling, revision 4. Rockville (MD): United States Department of Health and Human Services, Food and Drug Administration; 2005 Nov (Draft)

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings: In vitro skin permeability studies were conducted using human cadaver skin and guinea pig skin mounted in Franz Vertical Diffusion Cells. It was demonstrated that there were no significant differences between Bio-E-Gel and Oestrogel (Rontagel, marketed in Europe) regarding cumulative amount of permeated estradiol at any time point throughout the 24 hours of study drug application using human cadaver skin. In the dose-proportionality study using guinea pig skin, the in-vitro flux rate of estradiol was shown to be dose-related. The flux rate for the Bio-E-Gel containing [ ] was greater than Bio-E-Gel without [ ] which in turn was greater than Rontagel, a comparator marketed in Europe, which does not contain [ ]. Bio-E-Gel had no apparent toxicity in the primary skin irritation study in rabbits. No other nonclinical studies were conducted by the sponsor. However, subchronic toxicology, genotoxicology and reproductive toxicology studies provided in DMF [ ] along with all ICH recommended toxicology studies including oral and transdermal carcinogenicity studies reviewed under NDA 21-794 adequately establish the safety of the excipient, [ ].

B. Pharmacologic activity: Estrogens serve many functions in the body. They stimulate oocyte maturation and endometrial growth, decrease bone resorption, initiate the development of secondary sex characters, maintain reproductive organs and glands, and affect the activity of the CNS. At menopause, the decrease in estrogen concentration is accompanied by vascular instability (hot flashes and night sweats) and an increased rate of bone loss.

C. Nonclinical safety issues relevant to clinical use: None. Estrogns are used as component of combined oral contraceptives and for hormone therapy (HT) in postmenopausal women. As HT, estradiol has been approved as an oral drug (Estrace), as transdermal patches (Alora, Climara, Esclim, Estraderm, FemPatch, and Vivelle), and as vaginal cream (Estrace vaginal cream). The excipient, transcutol is a component of the approved product ACZONE (5% dapsone) Topical Gel, containing [ ], for the treatment of acne vulgaris under NDA 21-794.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-813
Review number: 1
Sequence number/date/type of submission: 000/2-16-06/original submission
Information to sponsor: Yes ( ) No (*)
Sponsor and/or agent: BioSante Pharmaceuticals, Inc. Lincolnshire, Illinois
Manufacturer for drug substance: [redacted]

Reviewer name: Krishan L. Raheja, D.V. M., Ph.D.
Division name: DRUDP
HFD #: 580
Review completion date: 8-9-06

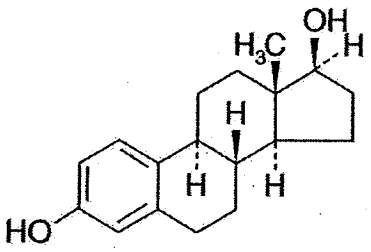
Drug:

Trade name: Bio-E-Gel
Generic name: Transdermal Estradiol gel
Code name: none given
Chemical name: 1. Estra-1,3,5(10)-triene-3,17-diol, (17B)
2. Estra-1,3,5(10)-triene-3,17B-diol
CAS registry number: 50-28-2
Molecular formula/molecular weight: $C_{18}H_{24}O_2.1/2\ H_2O/281.4$

Excipient:

Trade name: [redacted]
Generic name: Diethylene glycol monoethyl ether (DEGEE)

Structure:



Estradiol

Relevant INDs/NDAs/DMFs: IND 51,229; [redacted] DMF [redacted] for drug substance. [redacted] Corporation DMF [redacted] for [redacted]

Drug class: Estradiol (Estrogen), [redacted]

Intended clinical population: For the treatment of moderate to severe vasomotor symptoms [redacted]

Clinical formulation: Gel. Bio-E-Gel is a topical estradiol formulation. It is completely homogeneous, transparent and non-staining hydroalcoholic gel containing 17-B estradiol 0.06% in formulation composed of an acrylic polymer (carbomer). Bio-E-Gel is supplied in a Metered Dose Pump (MDP) [redacted] and as a unit dose [redacted] containing 0.625, 1.25 and 2.5 g gel intended to be applied topically once a day. The gel composition is given in table 1 below:

Table 1

Component[a]	Grade	Function	Quantity/g	% w/w
Estradiol	USP/EP	Active	0.006 g	0.06%
Ethanol, [redacted]	USP			
Propylene glycol	USP			
Diethylene glycol monoethyl ether [redacted]	NF			
Carbomer 940 [redacted]	NF			
Triethanolamine [redacted]	NF			
Purified water	USP			
Edetate disodium	USP			

[a]= [redacted]

Route of administration: Transdermal

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 21-813 are owned by BioSante Pharmaceutical Inc. or are data for which BioSante Pharmaceutical Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 21-813 that BioSante Pharmaceuticals Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that BioSante Pharmaceuticals, Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 21-813.

Studies reviewed within this submission:

1. An in vitro human skin permeation and skin layer distribution study (EP103) comparing Bio-E-Gel and Rontagel, a comparator product marketed in Europe
2. An in vitro skin permeation time- and dose-proportionality study (EP86/99) using guinea pig skin
3. A rabbit skin irritation study(10084) with topical application of Bio-E-Gel

Studies not reviewed within this submission: Nonclinical studies to support the safety of [ ] were submitted and reviewed under DMF [ ].

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary: Estrogens are a group of hormones that play an important role in normal sexual and reproductive development of women. Of the active estrogens i.e., 17-B estradiol, estrone and estriol, estradiol is the most potent. Estrogens serve many functions in the body. They stimulate oocyte maturation and endometrial growth, decrease bone resorption, initiate the development of secondary sex characters, maintain reproductive organs and affect the activity of the CNS. At menopause, the decrease in estrogen concentration is accompanied by vascular instability (hot flashes and night sweats) and increase rate of bone loss. No pharmacology studies were conducted with the Bio-E-Gel transdermal estradiol product.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: At the molecular level, the mechanism of estrogen action is via transcriptional activation of a limited set of genes. Following diffusion across cell membrane, estrogens bind to and activate nuclear receptors. The activated estrogen receptor binds to specific DNA sequences, or hormone-response elements, that enhances the transcription of adjacent genes and in turn lead to observed biological effects at the tissue level. Two estrogen receptors, ERα and ERβ have been identified. Estrogen receptors have been identified in estrogen responsive tissues (reproductive tract, breast, hypothalamus, liver, and bone in women).

Drug activity related to proposed indication: The objective of the estrogen therapy is to restore estradiol concentrations so that they approximate the premanopausal state with estradiol: estrone ratio of equal or greater than 1, which is difficult to attain with oral estrogens due to pre-systemic metabolism to estrone. Topical formulations provide estrogen serum concentrations that are not subject to first-pass hepatic metabolism and provide better estradiol: estrone ratios. Circulating estrogens modulate the pituitary secretion of gonadotropins, LH and FSH through a negative feedback mechanism. Estrogens reduce the elevated levels of these hormones seen in postmenopausal women.

2.6.2.3 Secondary pharmacodynamics : None conducted.

2.6.2.4 Safety pharmacology: No safety pharmacology studies were conducted with Bio-E-Gel. All referred to estrogen approved products.

2.6.2.5 Pharmacodynamic drug interactions: No drug interaction studies were conducted with Bio-E-Gel. However according to FDA labeling guidance it was stated that "In vitro and in vivo studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4, such as St. John's wort preparations (Hypericum perforatum), Phenobarbital, carbamazepine, and rifampin, may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in uterine bleeding profile. Inhibitors of CYP3A4, such as erythromycin, clarithromycin, ketoconazole, ritonavir, and grapefruit juice, may increase plasma concentrations of estrogens and may result in side effects".

2.6.3 PHARMACOLOGY TABULATED SUMMARY

None provided

2.6.3 PHARMACOKINETICS/TOXICOKINETICS

No in vivo nonclinical pharmacokinetic studies of the Bio-E-Gel product were conducted.

Two in vitro single dose absorption and pharmacokinetics studies were conducted with Bio-E-Gel. These skin permeability and dose-proportionality studies were conducted using human cadaver skin and guinea pig skin.

In the first study with human cadaver skin, approximately 6 mg of gel/cm^2 or a comparator, Oestrogel (Rontagel) were loaded over the skin, which was maintained at 37C. The cumulative amount of in vitro flux of estradiol (ng/cm^2) is shown in table 2 below:

Table 2

Time	Oestrogel	Bio-E-Gel
O	9	0
9	9.4	14.9
16.5	39.0	59.4
24	51.3	78.2

Values are mean of 6 observations

It was stated that although there was no significant differences between treatments regarding cumulative amount of permeated estradiol at any time point throughout the 24 hours of study drug application, the permeation rate for bio-E-Gel was higher compared to Oestrogel (4.22 +/- 1.48 ng/h.cm^2 vs 2.79 +/- 1.12 ng/h.cm^2).
Examination of the skin layers did not indicate any differences between treatments regarding permeation into the stratum corneum, epidermis, or dermis.

In the dose-proportionality study, Bio-E-Gel doses of 25 mg, 50 mg or 75 mg were loaded over the skin. The in vitro flux rate of estradiol across guinea pig skin was 0.12 +/- 0.01, 0.37 +/- 0.04 and 0.53 +/- 0.08 ug/h.cm^2 for the 25, 50 and 75 mg doses, respectively. Results thus showed that dose-related linear increase was noted with 2 high doses.

PK in humans
Plasma estradiol PK parameters after repeated administration of Bio-E-Gel were summarized as given in table 3 below:

Table 3

Parameter	Bio-E-Gel 2.5 mg/day	Oestrogel 2.5 mg/day
AUC (pg.h/ml)	1924.4 +/- 1124.7	1797.9 +/-926.4
C_{max} (pg/ml)	119.9 +/- 99.5	114.1 +/- 76.7
T_{max} (h)	7.5 +/- 10.2	21.0 +/- 8.5
C_{ss} (pg/ml)	107.3 +/- 66.4	85.0 +/- 52.4
Daily dose delivered (ug)	108.3 +/- 63.3	101.2 +/- 52.3

Values are mean +/- SD for 8 observations.

Skin stripping results on day 8 prior to dosing after skin was cleaned showed that approximately 10 fold less estradiol was recovered than that recovered 6 hr after dosing. The total amount of estradiol recovered 6 hours after Bio-E-Gel dosing was less than 5 ug whereas for Oestrogel it was 8 ug.

2.6.4 PHARMACOKINETICS TABULATED SUMMARY

None provided.

2.6.6 TOXICOLOGY:

Study title: Primary skin irritation study in rabbits.
This study was reviewed under IND 51,229 SS# 000 dated 11-7-01

Key study findings: Bio-E-Gel had no apparent toxicity

Study no: Protocol No. 326
Volume #, and page #: 3 of 4, page 1516
Conducting laboratory and location: [redacted]
Date of study initiation: 12-20-2000
GLP compliance: yes
QA report: yes ( ) no (*)
Drug, lot #, radiolabel, and % purity: Lot 001004
Formulation/vehicle: Bio-E-Gel quantitative composition is given in table 4 below:

Table 4

Components	(%w/w)
Active ingredient Estradiol	0.06
Excipients [redacted] Propylene glycol USP [redacted] Triethanolamine USP Purified water USP	[redacted]

Note: The formulation shown in the table was used in the preclinical studies. However, the intended commercial formulation of Bio-E-Gel contains [redacted]

Methods (unique aspects):
Dosing: dermal application
Species/strain: New Zealand albino rabbits
#/sex/group or time point (main study): 3/s
Satellite groups used for toxicokinetics or recovery: none
Age: not given
Weight: not given
Doses in administered units: 0.5 ml of Bio-E-Gel to a 6 mm^2 shaved patch
Route, form, volume, and infusion rate: transdermal-dorsal and trunk area. Area covered with gauze for 4 hours and scored according to Draize at 1, 24, 48 and 72 hours after patch removal

Observations and times:
Clinical signs: skin irritation recorded

Results:
Mortality: none
Clinical signs: no apparent skin irritation or toxicity. Draize score zero at all time point observations

Summary of individual study findings:

Toxicology summary: The formulation was considered to be non-irritating in the rabbit skin irritation test.

Toxicology conclusions: Bio-E-Gel was not irritating to skin on single application for 4 hours.

No genetic toxicology, carcinogenicity or reproductive and developmental toxicology studies were conducted with Bio-E-Gel.

2.6.6.1 Overall toxicology summary

The safety of estradiol is supported by reference to previous findings of safety for similar products and published literature citations. Toxicology information in Bio-E-Gel labeling will be per class labeling as provided in FDA draft labeling guidance for non-contraceptive estrogen drug products.

2.6.7 TOXICOLOGY TABULATED SUMMARY

None submitted

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Based on the safety profile of estradiol in several approved products and the toxicology information available for excipient [redacted] Pharmacology concludes that the proposed Bio-E-Gel formulation is reasonably safe for the proposed use.

Recommendations: Pharmacology recommends approval of Bio-E-Gel for the treatment of moderate-to-severe vasomotor symptoms associated with menopause.

Suggested labeling: Labeling will be per estrogens class labeling as provided in FDA draft labeling guidance for non-contraceptive estrogen drug products.

APPENDIX/ATTACHMENTS None

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/s/

Krishan L. Raheja
8/9/2006 11:21:27 AM
PHARMACOLOGIST

Lynnda Reid
8/9/2006 01:35:02 PM
PHARMACOLOGIST

Memo to the file

Date: 12-11-06

NDA #: 21-813

Date of submission: 2-16-06

Sponsor: BioSante Pharmaceuticals, Inc. Lincolnshire, Illinois

Drug Product: Elestrin (transdermal estradiol gel)

Indication: HRT

Subject: Labeling

Reviewer: Krishan L. Raheja, D.V.M., Ph.D.

Through P/T Supervisor: Lynnda Reid, Ph.D.

Regulatory action: The final label submitted by the sponsor on 1-25-06 is acceptable from the Pharmacology/Toxicology perspective.

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/s/

Krishan L. Raheja
12/11/2006 12:18:20 PM
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