CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-813

CHEMISTRY REVIEW(S)

NDA 21-813

Elestrin (Estradiol Gel), 0.06% w/w

BioSante Pharmaceuticals, Inc

Division of Reproductive and Urologic Products

Zhengfang Ge, Ph.D.

Branch III, Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA # 21-813

2. REVIEW # 1

3. REVIEW DATE: Dec 13, 2006

4. REVIEWER: Zhengfang Ge

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
CMC IQA by Dr. D. Chritner	April 13, 2006
End of phase II for IND 51,229	April 24, 2003
Letter for sponsor's CMC questions	April 3, 2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission	Feb 16, 2006
Amendment	June 13, 2006
Amendment	Oct 11, 2006
Amendment	Nov 16, 2006
Amendment	Dec 8, 2006
Amendment	Dec 13, 2006

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	BioSante Pharmaceuticals, Inc
Address:	111 Barclay Blvd, Suite 280 Lincolnshire, IL 60069
Representative:	
Telephone:	847-478-0500X100

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Elestrin
b) Non-Proprietary Name (USAN): Estradiol
c) CAS No: 50-28-2
d) Code Name/# (ONDQA only): None
e) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: This application was filed under the provisions of section 505(b)(1) of Federal Food, Drug and Cosmetic act and 21 CFR 314.50.

10. PHARMACOL. CATEGORY: Treatment of moderate-to-severe vasomotor symptoms associated with menopause.

11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: 0.06% (w/w)

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

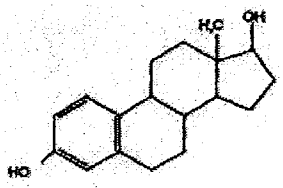
___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name:

[ ]

Molecular Formula: $C_{18}H_{24}O_2 \cdot 1/2H_2O$



$.1/2H_2O$

Molecular Weight: 281.4

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[ ]	II	[ ]	[ ]	3	Adequate	27-Jan-2006	Reviewed by B. Cai, Ph.D. for ANDA 75-182
[ ]		[ ]	[ ]	7	N/A		Complies to USP
[ ]		[ ]	[ ]	7	N/A		Complies to NF

			NF				
[ ]		[ ]	[ ]	3	Adequate	31-Jul-2002	Reviewed by M. Gautam-Basak, Ph.D. for NDA 21-470, complies to NF
[ ]	III	[ ]	[ ]	4	N/A		Sufficient information in this NDA

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Applicable		
EES	Acceptable	22-SEP-2006	
Pharm/Tox	Not Applicable		
Biopharm	See review notes for in-		

	vitro test		
LNC	Not Applicable		
Methods Validation	Not Applicable		
DMETS	Recommendation captured in Labeling review	9-Aug-2006	Laura Pincock
EA	Adequate		Section II/B of this review
Microbiology	Approval	11-Oct-2006	

The Chemistry Review for NDA 21-813

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The sponsor has provided adequate resolution for all the CMC issues found during the review. From CMC point of view, this NDA can be approved.

[ ]

1. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:
The drug substance is Estradiol with a molecular formula of $C_{18}H_{24}O_2 \cdot 1/2H_2O$ and molecular weight of 281.4. The sponsor cross referenced DMF [ ] for related CMC information. The DMF was reviewed and found adequate on 27-Jan-2006 by Dr. B. Cai. No updated information was submitted to the DMF after the review. The sponsor provided an adequate acceptance specification and Certification of Analysis for the drug substance. The manufacturing facility is inspected with an acceptable recommendation from Office of Compliance.

Drug Product:
The drug product is a topically applied estradiol gel with a concentration of 0.06% w/w. The inactive ingredients include ethanol, propylene glycol, diethylene glycol monoethyl ether, [ ], triethanolamine, purified water, and edetate disodium. All excipients are either USP or NF. The drug product is packaged in a [ ]mL metered dose pump.

The sponsor briefly summarized pharmaceutical development in this section. Because estradiol is practically insoluble in water, a mixture of solvents including [ ] [ ] is used to dissolve estradiol. Assay specifications of these

solvents are provided and acceptance criteria are adjusted based on the Agency's recommendation in order to insure the efficacy of the drug delivery. Additionally, the sponsor accepted Agency's recommendation for the specifications of impurities, physical appearance and provided adequate adjustment for the drug product specification. The final specification for the drug product is acceptable.

Brief manufacturing process and process controls are provided in this NDA. The manufacturing process contains [ ] The critical process controls and critical parameters are [ ] [ ] Batch uniformity is tested after batch reconciliation.

The sponsor provided 18 month long term stability data and 6 month accelerated stability data for drug product in the original NDA and updated the long term stability data to 24 month in an amendment. All the long term stability data are within the specifications for 24 months except assay results for DGME. Assay results for DGME are greater than[ ]% (upper limit of the specification) at 12 and 18 months. The sponsor conducted investigation for the DGME assay and revised sample handling during the test. The stability data at 24 month is within the specification with a revised sample handling of the DGME assay. Based on the long term stability data, the sponsor's proposal of 24 month expiration date is **acceptable**.

The sponsor proposed to use "transdermal estradiol gel" as established name. In order to be consistent with the previous approved estradiol drug product. The established name "estradiol gel" was conveyed to the sponsor. Some other minor modifications for the labeling were also conveyed to the sponsor. The sponsor has accepted the Agency's requests for these changes. Therefore, the labeling is now acceptable from the CMC prospective.

B. Description of How the Drug Product is Intended to be Used

The drug product will be applied once daily to the upper arm using a metered-dose pump which delivers 0.87 g of estradiol gel per actuation. The drug product is indicated for the treatment of moderate- to-severe vasomotor symptoms[ ] [ ] at / doses: 0.87 g/day, 1.7 g/day.[ ]

[ ] [ ]

C. Basis for Approvability or Not-Approval Recommendation

The CMC information for the drug substance is referenced to DMF[ ] which is found adequate previously. The review of this NDA found that the sponsor provided adequate CMC information regarding composition, manufacturing process and process controls for the drug product. The sponsor provided adequate responses for the Agency's information requests and updated drug product specifications based on the Agency's requests. The updated stability data is adequate to support 24 months of expiring date. The sponsor has accepted all the CMC modifications in the labeling. The GMP inspection of the manufacturing facilities has found that the facilities are adequate. From CMC prospective, the NDA may be approved.

[ ]

III. Administrative

A. Reviewer's Signature

In DFS

B. Endorsement Block

Chemist: Zhengfang Ge
Chemistry Branch Chief: Moo-Jhong Rhee
ProjectManager: George Lyght

C. CC Block

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/s/

Zhengfang Ge
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CHEMIST

Moo-Jhong Rhee
12/14/2006 08:58:06 AM
CHEMIST
Chief, Branch III

NDA 21-813

5S

Elestrin™ (estradiol gel)

BioSante Pharmaceuticals Inc.

PM: George Lyght

Facilities Review/Inspection

See CMC Review page 62 & 63

require the inclusion of an Environment Assessment despite qualification for a categorical exclusion.

III. List Of Deficiencies To Be Communicated

None

IV. Attachments

FDA CDER EES

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21813/000 Sponsor: BIOSANTE

Org Code : 580 111 BARCLAY BLVD

Priority : LINCOLNSHIRE, IL 60069

Stamp Date : 16-FEB-2006 Brand Name : BIO-E-GEL (ESTRADIOL TOPICAL

PDUFA Date : 16-DEC-2006 GEL 0.06%)

Action Goal : Estab. Name:

District Goal: 17-OCT-2006 Generic Name: ESTRADIOL TOPICAL GEL 0.06%

Dosage Form: (GEL)

Strength : 0.06%

FDA Contacts: G. LYGHT Project Manager 301-796-0948

Z. GE Review Chemist 301-796-1358

D. CHRISTNER Team Leader 301-796-1341

Overall Recommendation: ACCEPTABLE on 22-SEP-2006by S. FERGUSON(HFD-3 22) 301-827- 9009

WITHHOLD on 19-SEP-2006by J. D AMBROGIO(HFD -322) 301-827- 9073

Appears This Way
On Original

Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division:	Division of Reproductive and Urologic Products
NDA:	21-813
Applicant:	BioSante Pharmaceuticals, Inc
Stamp Date:	16-Feb-2006
PDUFA Date:	15-Dec-2006 (16-Aug-2006 if PRIORITY)
Trademark:	Bio-E-Gel
Established Name:	Estradiol gel
Dosage Form:	Gel
Route of Administration:	Topical
Indication:	Treatment of Vasomotor Symptoms[ ] [ ]
PAL:	Donna F. Christner, Ph.D.

	YES	NO
ONDQA Fileability:	x	☐
Comments for 74-Day Letter	x	☐

Summary and Critical Issues:

A. Summary

The drug product is a topically applied, hydroalcoholic gel containing estradiol 0.06% w/w, ethanol, propylene glycol, diethylene glycol monoethyl ether,[ ], triethanolamine, purified water, and edetate disodium. All excipients are either USP or NF. Drug product is packaged in either a Metered Dose Pump[ ] Regulatory guidance was provided in a number of meetings/correspondence with the company. The company has requested a Priority Review. If this is granted, the PDUFA date would be 16-Aug-2006. For a Standard Review, the PDUFA date would be 15-Dec-2006.

B. Critical issues for review

The sponsor has eliminated some of the requested testing upon stability. Justification has been provided, however, this should be carefully evaluated as to whether deleting these tests on stability is acceptable.

Although all methods will need to be evaluated, special attention should be paid to the validation of the in vitro release test to determine if the Acceptance Criteria have been accurately set.

Phase 3 clinical supplies were packaged in the MDP, while the Phase 2 supplies, manufactured by [ ] were packaged in[ ]. [ ] is no longer manufacturing the drug product. No drug product manufactured by DPT has been packaged in[ ]. For the[ ], it will need to be demonstrated that the product manufactured at DPT is similar to that manufactured at

[ ] by performing comparative in-vitro releasing testing as per our SUPAC-SS guidance. Since it will not be possible to have similarly aged samples in [ ], it may be possible to compare stability samples in [ ] to stability samples in the MDP to show that the drug product itself is similar. Extractable/leachable testing could also be performed on the [ ] held on stability to provide assurance that this packaging configuration is compatible with the drug product. USP testing should be performed prior to the decision on which therapeutic dose is efficacious in order to provide assurance that the [ ] is adequate prior to an action on the NDA.

Both container closure DMFs will require review.

C. Comments for 74-Day Letter

Please provide a side-by-side comparison of the manufacturing processes used at [ ] and DPT, outlining any differences. A flow chart would be acceptable.

For the [ ], it will need to be demonstrated that the product manufactured at DPT is similar to that manufactured at [ ] by performing comparative in-vitro releasing testing as per our SUPAC-SS guidance. Since it will not be possible to have similarly aged samples in [ ], it may be possible to compare stability samples in [ ] to stability samples in the MDP to show that the drug product itself is similar.

Extractable/leachable testing could be performed on the [ ] held on stability to provide assurance that this packaging configuration is compatible with the drug product. USP testing should be performed prior to the decision on which therapeutic dose is efficacious in order to provide assurance that the [ ] is adequate prior to an action on the NDA.

Color mock-ups for the carton and immediate container labels should be provide, in order to allow full review of these labels. Prototype [ ] labels should be submitted.

D. Review, Comments and Recommendation:

Clinical studies for this NDA have been performed under IND 51,229. The following CMC related meetings/reviews are captured in DFS:

- Pre-IND meeting on 15-Aug-2001. No specific CMC questions were posed, but guidance was given.
- Initial IND review dated 21-Nov-2001. Safe to proceed, but IR letter sent, including recommendations for development of in-vitro release testing.
- EOP II meeting on 24-Apr-2003. Guidance was given on sponsor questions. Additional tests were proposed for Assay of estradiol, ethanol, [ ], and propylene glycol. Additional testing was proposed for Content Uniformity over the entire contents of the Metered Dose Pump, including the last three actuations. All these tests would be included on stability.
- Letter dated 03-Sep-2003. Response to sponsor questions on Content Uniformity testing proposed during 24-Apr-2003 meeting.

The sponsor has requested a Priority Review, which would put the PDUFA date at 16-Aug-2006. For a Standard Review, the PDUFA date is 15-Dec-2006.

An overview of the application is provided in the ASSESSMENT NOTES at the end of this document. As outlined above, review of the application will include full reviews of two DMFs for the container closure system, along with a check of the API DMF to determine if any additional information has been submitted since the last review of the DMF. Analytical methods will need to be evaluated, especially the in vitro release method to determine if the acceptance criteria are adequately set. In addition, there has been a manufacturing site change during development of the drug product, so the equivalence of the drug products from both sites will need to be demonstrated. Two container closure systems will be used, and their compatibilty with the dosage form and the stability in both configurations will need to be evaluated.

The sponsor has provided adequate information to file the NDA from a CMC standpoint. Two preliminary comments are included for the 74 day letter, but the primary reviewer should evaluate the application to request any additional information deemed necessary. A single reviewer, Zhengfang Ge, has been assigned.

Although the timeline for the review will be decided upon at the Filing meeting, under the GRMP guidences, which are being closely adhered to by the clinical division, the review will need to be completed by Oct 2006 for a Standard review. If the clinical division agrees with the sponsor's request that the application warrents a Priority review (6 month clock), the review will need to be completed by June 2006.

Post-Filing Meeting Note: It has been determined that this NDA is not Priority. The PDUFA date will be 15-Dec-2006.

	13-Mar-2006
Donna F. Christner, Ph.D. Pharmaceutical Assessment Lead	Date
Moo-Jhong Rhee, Ph.D. Branch Chief	Date

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/s/

Donna Christner
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CHEMIST

IQA and Filing memo

Moo-Jhong Rhee
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CHEMIST
Chief, Branch III