# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**22-038s000**

# CHEMISTRY REVIEW(S)

# NDA 22-038

# Divigel ®(Estradiol Gel) 0.1%

## Upsher –Smith Laboratories, Inc.

**Maria E. Ysern, MSc.**
**Division of PreMarketing Assessment II, Branch III**

## Table of Contents

# Chemistry Review Data Sheet

1. NDA 22-038

2. REVIEW: #1

3. REVIEW DATE: May 24, 2007

4. REVIEWER: Maria E. Ysern, MSc.

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Original | May 01, 2006 |
| BC Amendment | Dec 4, 2006 |
| Amendment (response to telecom) | Feb 15, 2007 |
| Amendment (labeling) | May 24, 2007 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | Upsher-Smith Laboratories, Inc. |
| Address: | 6701 Evenstad Drive,<br>Maple Grove, MN USA 55369-6026 |
| Representative: | Tanya Carone, RAC |
| Telephone: | (763) 315-2006 |

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Divigel
b) Non-Proprietary Name (USAN): Estradiol Gel.

c) Code Name/# (ONDQA only): n/a
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: Type 5
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: FD&C ACT, 505 b(2)

10. PHARMACOL. CATEGORY: Hormone therapy for treatment of vasomotor symptoms (b) (4) associated with menopause.

11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: 0.25 mg, 0.5 mg and 1 mg per individual foil packet.

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: _X__Rx ___OTC

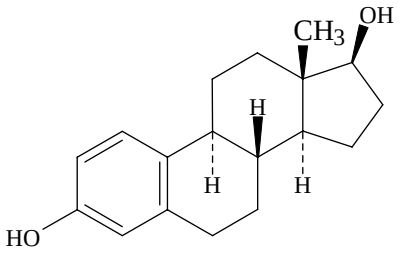
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

____X_Not a SPOTS product

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

Chemical Name: Estra-1,3,5(10)-triene-3,17-diol, (17β)
Other names: Estradiol menihydrate

Emprical Formula: $C_{18}H_{24}O_{2.}$ ½ $H_2O$
Relative Molecular mass: 281.4




- 1/2 $H_2O$

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| (b) (4) | II | | (b) (4) | 3 | Adequate | 24-Sep-2004 | Dr. Salemme |
| | II | | | 3 | Adequate | 15-Mar-2006 | Dr.Cai |
| | III | | | 4 | | | |
| | III | | | 4 | | | |

[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 |
|---|---|---|
| IND | 51,246 | Commercial IND |

18. STATUS:

**ONDQA:**

| **CONSULTS/ CMC RELATED REVIEWS** | **RECOMMENDATION** | **DATE** | **REVIEWER** |
|---|---|---|---|
| Biometrics | N/A | | |
| EES | Overall Compliance Acceptable | Dec 19, 2006 | |
| Pharm/Tox | Approval recommendation | Sep 30, 2006 | Leslie McKinney, PhD |
| Methods Validation | To be sent if needed | | |
| DEMETS | Name acceptable | May 1, 2006 | Kimberly Pedersen, RPh |
| EA | N/A | | |
| Microbiology | Recommended for approval | Sep 28, 2006 | Vinayak B. Pawar, PhD |

19. ORDER OF REVIEW (OGD Only) N/A

**The Chemistry Review for NDA 22-038**

***The Executive Summary***

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

Based on the information provided, this NDA may be approved from a CMC perspective. The Overall Compliance recommendation for the site inspections, dated 19-Dec-2006, was "Acceptable".

### B. 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 manufactured at two different sites: (b) (4), refer to DMF (b) (4), and (b) (4), refer to DMF (b) (4).
The active drug is Estradiol (USP), also called Estradiol hemihydrate.
Estradiol (USP) has an appearance of white or creamy white (b) (4) or crystalline powder. It is odorless, has a melting point of (b) (4) and its water content is NMT .
It is practically insoluble in water; (b) (4)

The two polymorphic forms are of the anhydrous material. Particle size and polymorphic form of the drug substance in this drug product are not relevant because estradiol is used in the dissolved state. The chemical characterization includes melting point, IR spectrum and optical rotation.
Synthesis impurities information as well as that for (b) (4) is provided by reference to the suppliers DMF (b) (4) for (b) (4) and DMF (b) (4) for (b) (4) and a table with the structures is provided in the NDA.
The proposed regulatory analytical methods and corresponding acceptance criteria comply with the current USP requirements for estradiol: (b) (4) melting range, specific rotation, water, chromatographic purity (related substances) and assay. In addition, specifications for individual related substances and (b) (4) are proposed and reference is given to the corresponding DMF for justification.

The estradiol is packaged in a [redacted] bag of a suitable size, sealed and placed in another [redacted] bag which is also sealed and placed in a [redacted] container of suitable size. The drug substance is stored at [redacted] in the original package at ambient temperature and humidity, consistent with the manufacturer's labeled storage conditions.

The suppliers, [redacted], give a shelf life of five years for the active ingredient when stored at room temperature, protected from light.

Batch analysis data are provided for drug substance batches used to produce the drug product batches most directly involved in the development of estradiol gel, 0.1 % for the US market.

**Drug Product:**

The drug product is a smooth, clear to opalescent alcohol based gel in which the active ingredient, estradiol, is dissolved. The excipients include: Carbomer [redacted] NF [redacted]; Triethanolamine [redacted]. Propylene Glycol USP, [redacted] Ethanol [redacted].

All of the excipients have been used extensively in topically applied drug and cosmetic products in the US and comply with USP/NF monographs.

The drug product has been commercially available outside the US since 1994.

The formulation [redacted] was shown to be bioequivalent to the original and was used in the Phase III clinical trials and is the to-be-marketed formulation.

[redacted]

The individual packets are packaged into secondary pre-printed cartons in quantities of 30 packets per carton.

The formulation is intended to release the active ingredient for absorption through the skin.

The 36 month expiry date is granted based on the stability data submitted.

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

DIVIGEL should be used daily at the dose prescribed by the physician. It should be used at the lowest dose possible and only for as long as needed.
It should be applied around the same time each day and it should be applied to clean dry and unbroken skin. The gel should be spread in a thin layer on the upper thigh in an area of 5 by 7 inches (two palm prints), not necessary to massage or rub. The entire contents of the package should be used. Alternate between the left and the right upper thigh from day to day to avoid irritation. The gel should be allowed to dry before dressing.

**C. Basis for Approvability or Not-Approval Recommendation**

The information on the manufacturing of the drug substance, Estradiol USP, has been provided by cross reference to two DMFs, (b) (4) for (b) (4) and DMF (b) (4) for (b) (4) which have been reviewed and found adequate.

The manufacturing of Divigel (Estradiol Gel,0.1%) (b) (4) The excipients are tested according to specified monographs in the current USP/NF. The packaging was deemed adequate and supported by the stability data obtained. The provided stability data justified the proposed 36-month shelf life .
The microbiology consult determined that the proposal to delete Microbial Limit testing for the Divigel®product is acceptable. The company has responded to the labeling issues and committed to the Agency ‘s requests regarding the How supplied section.
Upsher-Smith Laboratories, Inc. submitted a claim for Categorical Exclusions from the EA requirement 21 CFR 25.31 ( b ) with a calculation that the expected introduction of concentration (EIC) for Estradiol is less than 1 ppb.
Based on all the CMC information provided and an adequate cGMP status, this NDA is recommended for approval from the standpoint of CMC.

## III. Administrative

**A. Reviewer’s Signature**

**B. Endorsement Block**

Chemist / Maria Ysern
Branch Chief/ Moo-Jhong Rhee
Project Manager /George Lyght

**C. CC Block**

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

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/s/
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Maria Ysern
5/31/2007 12:54:14 PM
CHEMIST
CMC Review

Moo-Jhong Rhee
5/31/2007 04:52:23 PM
CHEMIST
Chief, Branch III