CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-038s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-038 SUPPL # HFD # 580

Trade Name Divigel

Generic Name (estradiol gel) 0.1%

Applicant Name Upsher-Smith Laboratories Inc.

Approval Date, If Known June 4, 2007

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-371 Estrasorb

NDA# 21-166 Estrogel

NDA# 21-813 Elestrin

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study P04-001

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study P04-001

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 51,246	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: George Lyght
Title: Regulatory Health Project Manager
Date: 05-17-07

Name of Office/Division Director signing form: Scott Monroe, M.D.
Title: Acting Director.

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Scott Monroe

6/4/2007 07:34:26 PM

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE:	January 11, 2007
TO:	George Lyght, Regulatory Project Manager Audrey Gassman, M.D., Medical Officer Division of Reproductive and Urologic Drug Products
THROUGH:	Constance Lewin, M.D., M.P.H. Chief, Good Clinical Practice Branch I (GCPB1, HFD-46) Division of Scientific Investigations (DSI)
FROM:	Roy Blay, Ph.D. Reviewer, GCPB1, DSI, HFD-46
SUBJECT:	Evaluation of Clinical Inspections
NDA:	22-038
APPLICANT:	Upsher-Smith Laboratories, Inc.
DRUG:	Divigel (estradiol gel, 0.1% 0.25mg, 0.5mg, and 1mg)
THERAPEUTIC CLASSIFICATION:	Standard
INDICATION:	Treatment of vasomotor symptoms (b) (4) associated with menopause.
CONSULTATION REQUEST DATE:	September 6, 2006
DIVISION ACTION GOAL DATE:	January 15, 2007
PDUFA DATE:	March 2, 2007

I. BACKGROUND

The indication for the investigational drug Divigel (estradiol gel, 0.1% 0.25mg, 0.5mg, and 1mg) is for the treatment of vasomotor symptoms (b) (4) associated with menopause. It is not a new molecular entity. The primary efficacy

endpoint addressed was the reduction in the number/severity of vasomotor symptoms in treated subjects as compared with their respective non-treatment baseline periods.

The following sites were selected for inspection because they were among the largest enrollers. All sites conducted the same protocol (P04-001) entitled, "Placebo-Controlled, Randomized, Double-Blind, Multicenter Study, to Demonstrate the Efficacy of 12 Weeks of Treatment with USL-221 on Moderate to Severe Vasomotor Symptoms and Vulval/Vaginal Atrophy in Postmenopausal Patients".

II. RESULTS (by site):

Name	City, Country	Protocol	Insp. Date	EIR Received Date	Final Classification
Richard Hedrick, Jr ,M.D.	Winston-Salem, NC	P04-001	3-9 Nov 2006	27 Dec 06	NAI
William Koltun, M.D.	San Diego, CA	P04-001	17-26 Oct 2006	7 Nov 06	VAI
Ronald Hazen,, M.D.	Saginaw, MI	P04-001	11-24 Oct 2006	27 Nov 06	NAI

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations. Data unreliable.

Protocol # P04-001

1. Site # 023
   Richard Hedrick, Jr, MD
   Hawthorn OB/GYN Assoc, PA
   1806 South Hawthorne Road
   Winston-Salem, NC 27103

   a. Sixty-seven subjects were screened for this study and 39 subjects were evaluable. The records of 16 subjects were audited. The audit included, but was not limited to, review of the primary efficacy endpoint (reduction in moderate to severe vasomotor symptoms), inclusion/exclusion criteria, reporting of adverse events, informed consent, and drug accountability.

   b. There were no limitations to the inspection.

   c. The inspection did not reveal any regulatory violations in the conduct of this study.

   d. The data appear acceptable in support of the relevant indication.

2. Site #029
   William Koltun, M.D.
   Medical Center for Clinical Research
   9040 Friars Road Suite 540
   San Diego, CA 92108

   a. Forty-seven subjects were screened and 33 subjects were evaluable. The records for all 33 evaluable subjects were audited. Records reviewed included, but were not limited to, source diaries, CRFs, adverse event reporting, and drug accountability records.

   b. There were no limitations to the inspection.

   c. The inspection revealed deviations from the investigational plan including the randomization of subject 2908 without a qualifying mammogram, the dispensation of a new diary to subject 2947 without collecting and reviewing the prior diary; inadequate records in that subject 2944 had an adverse event of breast tenderness whose relationship to treatment was deleted without explanation; and a lack of reporting adverse events possibly caused by drug treatment in that subject 2491 experienced irritation (redness) at the application site that was not reported in the CRF.

   d. The data appear acceptable in support of the relevant indication.

3. Site 058
   Ronald Hazen, M.D.
   Synergy Medical Education Alliance
   1000 Houghton
   Saginaw, MI 48602

   a. Twenty-six subjects were screened and 18 subjects were evaluable. The records for seven subjects were audited in detail. The audit included, but was not limited to, review of data integrity, reporting of adverse events, informed consent, and drug accountability.

   b. There were no limitations to the inspection.

   c. The inspection did not reveal any regulatory violations in the conduct of this study.

   d. The data appear acceptable in support of the relevant indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The inspections of Drs. Hedrick, Koltun, and Hazen did not identify any regulatory violations that would adversely impact data acceptability. Overall, the data appear acceptable in support of the respective indication.

{See appended electronic signature page}

Roy Blay, Ph.D.
Reviewer, Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

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

/s/

Roy Blay
1/12/2007 03:57:42 PM
CSO

Constance Lewin
1/12/2007 04:14:22 PM
MEDICAL OFFICER

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-038 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Divigel
Established Name: estradiol gel
Strengths: 0.1%

Applicant: Upsher-Smith Laboratories, Inc.
Agent for Applicant (if applicable):

Date of Application: May 1, 2006
Date of Receipt: May 4, 2006
Date clock started after UN:
Date of Filing Meeting: June 13, 2006
Filing Date: July 3, 2006
Action Goal Date (optional): User Fee Goal Date: June 4, 2007

Indication(s) requested: 1. Treatment of moderate to severe vasomotor symptoms associated with menopause, (b) (4) .

Type of Original NDA: (b)(1) ☑ (b)(2) ☐
AND (if applicable)
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☑ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 5
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☑ NO ☐

User Fee Status: Paid ☑ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application.*

Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☑ NO ☐
  If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☑

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
  YES ☐ NO ☑

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☑
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☑

- Does the submission contain an accurate comprehensive index? YES ☑ NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES ☑ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☑ NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES ☑
   This application is: All electronic ☐ Combined paper + eNDA ☑ This application is in: NDA format ☐ CTD format ☐
   Combined NDA and CTD formats ☐

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☑ NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format? SPL, Labeling, Safety information, Clinical Studies.- All labeling (SPL format and Microsoft Word version), Safety information, Case Report Forms (CRF) and Study Reports.

Additional comments: Paper submission included discipline summaries, Integrated summary of safety (ISS), Integrated summary of efficacy (ISE) and benefit-risk analysis for the product, signed forms and certificates.

3. This application is an eCTD NDA. YES ☐
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES ☑ NO ☐
- Exclusivity requested? YES, ☑ 3 Years NO ☐
NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*
- Correctly worded Debarment Certification included with authorized signature? YES ☑[NO ☐
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*
- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
YES ☑ NO ☐
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☐ NO ☐
- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☑

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☑ NO ☐
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*
- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☑ NO ☐
☐
- PDUFA and Action Goal dates correct in tracking system? YES ☑ NO ☐
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 51,246
- Are the trade, established/proper, and applicant names correct in COMIS? YES ☑ NO ☐
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☑
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) Clinical/ 2-23-05 & CMC/ 6-22-05 NO ☐
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) 04-02-04 NO ☐
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☑ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☐ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☑ NO ☐

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☑ NO ☐
  ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☐ YES ☑ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☑ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☑ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☑

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☑

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☑

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☑ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☑ NO ☐

- If a parenteral product, consulted to Microbiology Team? YES ☐ NO ☐
  Not a parenteral product, but a micro. Consult was done. YES ☑

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 13, 2006

NDA #: 22-038

DRUG NAMES: Divigel (estradiol gel) 0.1%

APPLICANT: Upsher-Smith Laboratories, Inc.

BACKGROUND: The Sponsor submitted the application Divigel (estradiol gel) as a NDA with the requested indications of: (1) Treatment of moderate-to-severe vasomotor symptoms associated with menopause (b) (4)

The NDA is for an estrogen gel to be applied once daily to the skin. It is packaged in single dose sachets of 0.5 mg, 1.0 mg and 1.5 mg doses. Similar approved products are Estrasorb and Estrogel. Divigel was originally developed by Orion Pharma and was approved in Finland in 1994. The sponsor is using a new formulation.

(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Shelley R. Slaughter, M.D., Ph.D, Bruce Patsner, M.D., Sandra Suarez, Ph.D., Ameeta Parekh, Ph.D., Donna Christner, Ph.D., Shahla Farr, Ph.D., Mahboob Sobhan, Ph.D., Leslie McKinney, Ph.D., Lynnda Reid, Ph.D., Margaret Kober, R.Ph., M.P.A., George Lyght, R.Ph.

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization	Reviewer
Medical:	Bruce Patsner, M.D., Audrey Gassman, M.D.
Secondary Medical:	Shelley R. Slaughter, M.D.,Ph.D.
Statistical:	Shahla Farr, Ph.D., Mahboob Sobhan, Ph.D., Ling Chen, Ph.D.
Pharmacology:	Leslie McKinney, Ph.D., Lynnda Reid, Ph.D.
Statistical Pharmacology:	
Chemistry:	Donna Christner, Ph.D., Maria Ysern, Ph.D.
Environmental Assessment (if needed):	
Biopharmaceutical:	Sandra Suarez, Ph.D., Ameeta Parekh, Ph.D. Myong-Jin Kim, Pharm.D.
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	

DSI: Roy Blay, Ph.D.
OPS:
Regulatory Project Management: George Lyght, R.Ph.,
Margaret Kober, R.Ph., M.P.A.

Other Consults: DMETS
DSRCS
DDMAC

Per reviewers, are all parts in English or English translation? YES ☑ NO ☐
If no, explain:

CLINICAL FILE ☑ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☑ NO ☐
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO ☑

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A ☑ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☑ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☑ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☑ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? ☐ NO ☑
  YES

PHARMACOLOGY/TOX N/A ☐ FILE ☑ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☑

CHEMISTRY FILE ☑ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☑ NO ☐
- Sterile product? YES ☐ NO ☑
  If yes, was microbiology consulted for validation of sterilization?
  YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments: Combined paper + eNDA

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☑ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

☐ No filing issues have been identified.

☑ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1.☑ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3.☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. ☑ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5.☑ Convey document filing issues/no filing issues to applicant by Day 74.

George Lyght, R.Ph.
Regulatory Project Manager

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

/s/

George Lyght
5/16/2007 12:56:10 PM
CSO

George Lyght
5/16/2007 01:01:39 PM
CSO