CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-038s000

PROPRIETARY NAME REVIEW(S)

MEMORANDUM	Division of Medication Errors and Technical Support Office of Surveillance and Epidemiology HFD-420; WO22, Mail Stop 4447 Center for Drug Evaluation and Research

To: Scott Monroe, MD
Acting Director, Division of Reproductive and Urologic Products
HFD-580

Through: Todd Bridges, RPh, Team Leader
Carol A. Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

From: Loretta Holmes, BSN, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

Date: June 1, 2007

Subject: **DMETS Proprietary Name and Labeling Review**
Drug: Divigel® (Estradiol Gel) 1%
NDA#: 22-038
Sponsor: Upsher-Smith Pharmaceuticals, Inc.

Review #: 2007-1231

*****NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

This memorandum is written in response to a request from the Division of Reproductive and Urologic Products (HFD-580) for a re-review of the proposed proprietary name, Divigel. Revised package insert labeling was provided for review and comment at this time.

The proposed proprietary name, Divigel, was previously reviewed by DMETS in OSE Review 06-0189, dated January 30, 2007. Two proposed proprietary names, (b) (4), were identified as having the potential to be confused with the name, Divigel. Both (b) (4) are currently INDs under review by the Agency. DMETS recommended that only the first of these applications approved be granted its desired name because Divigel and (b) (4) could not safely co-exist in the marketplace.

We learned of this review two days ago and thus, limited time was available to complete a comprehensive analysis of the proposed proprietary name. Thus, due to the high priority nature of this review, a routine analysis was not performed. The DMETS' safety evaluator was only able to conduct an expeditious search of the internet, several standard published drug product reference texts[1,2] as well

[1] MICROMEDEX Integrated Index, 2007, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

as several FDA databases[3,4] for existing drug names which sound-alike or look-alike to Divigel to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. The Saegis[6] Pharma-In-Use database was searched for drug names with potential for confusion. The proposed name was not discussed during an Expert Panel Discussion.

Since completion of our previous review, DMETS identified five additional names (Diuril, Clindagel, Torisel, Didronel, and Noxafil) as having the potential for look-alike and/or sound-alike similarities to Divigel. After initial analysis of the five names, it was determined that these names would not be reviewed further due to a lack of convincing look-alike/sound-alike similarities to Divigel in addition to differentiating product characteristics such as indication of use and strength. Additionally, the drugs Diuril, Torisel, Didronel, and Noxafil have a dosage form and route of administration that differs from those of Divigel. Therefore, we have no objection to the use of the proposed proprietary name, Divigel, provided (b) (4) are not approved.

Container labels, carton and package insert labeling for Divigel were reviewed in our previous consult. Revised package insert labeling was submitted by the sponsor, however, revised container labels and carton labeling were not. Therefore, DMETS continues to recommend the container label and carton labeling revisions communicated in OSE Review 06-0189, dated January 30, 2007. In review of the revised package insert labeling of Divigel, DMETS has focused on safety issues relating to possible medication errors. DMETS has identified the following areas of improvement which may minimize potential user error. If time allows, these recommendations should be implemented prior to approval. Otherwise, they should be considered at the time of next printing.

INSERT LABELING

(b) (4)

[redacted]

[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.
[4] Phonetic and Orthographic Computer Analysis (POCA)
[5] WWW location http://www.uspto.gov/tmdb/index html.
[6] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

In summary, DMETS continues to recommend that only one name, Divigel, (b) (4) be approved and that the first application to be approved should be granted its desired name. If Divigel is approved, the sponsors of (b) (4) should be notified that their names are no longer acceptable. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. DMETS recommends implementation of the labeling recommendations outlined above. Please copy DMETS on any correspondence to the sponsor pertaining to this issue. Additionally, the Division of Drug Marketing, Advertising, and Communications (DDMAC) finds the proposed proprietary name, Divigel, acceptable from a promotional perspective. If you have any questions or need clarification, please contact Cherye Milburn, OSE Project Manager, at 301-796-2084.

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

/s/

Todd Bridges
6/1/2007 04:55:59 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
6/1/2007 05:01:49 PM
DRUG SAFETY OFFICE REVIEWER

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; WO 22, MAIL STOP 4447)

DATE RECEIVED:	**DESIRED COMPLETION DATE:**	**OSE REVIEW #:** 06-0189
June 14, 2006	September 14, 2006	
DATE OF DOCUMENT:	**PDUFA DATE:**	
May 1, 2006	March 4, 2007	

TO: Scott Monroe, M.D.
Acting Director, Division of Reproductive and Urologic Products
HFD-580

THROUGH: Alina Mahmud, R.Ph., M.S., Team Leader
Denise Toyer, Pharm.D., Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support

FROM: Kimberly Pedersen, R.Ph., Safety Evaluator
Division of Medication Errors and Technical Support

PRODUCT NAME:	**SPONSOR: Upsher-Smith Laboratories, Inc.**
Divigel (Estradiol Gel, 1%) **NDA#: 22-038**	

RECOMMENDATIONS:

1. DMETS identified two proposed proprietary names (b) (4) that have the potential for confusion with Divigel. DMETS does not believe that Divigel (b) (4) can safely co-exist in the marketplace. Therefore, DMETS recommends that only one of these names be approved. The application that receives approval first will have rights to the name. If the approval of this application is delayed beyond 90 days from the signature date of this document, the name Divigel must be re-evaluated.

2. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review in order to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary names Divigel acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Cherye Milburn, Project Manager, at 301-796-0538.

*** Proprietary and confidential information that should not be released to the public.

Division of Medication Errors and Technical Support (DMETS)
Office of Surveillance and Epidemiology
WO 22, MAIL STOP 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME, LABEL, AND LABELING REVIEW

DATE OF REVIEW: August 23, 2006

NDA #: 22-038

NAME OF DRUG: Divigel
(Estradiol Gel) 0.1%

NDA SPONSOR: Upsher-Smith Laboratories, Inc.

*****NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

I. INTRODUCTION

This consult was written in response to a request from the Division of Reproductive and Urologic Products (HFD-580) for assessment of the proprietary name "Divigel", regarding potential name confusion with other proprietary or established drug names. Insert and carton labeling were provided for review and comment. No container labels were provided for review and comment.

PRODUCT INFORMATION

Divigel contains 0.1% estradiol as a clear, colorless gel for the treatment of moderate to severe vasomotor symptoms associated with menopause (b) (4) . Each gram of Divigel contains 1 mg of estradiol and the recommended starting dose is 0.5 mg daily. The dose may be decreased to 0.25 mg or increased to 1 mg to achieve an adequate response. Divigel is applied once daily to the skin of either the right or left upper thigh. The entire contents of a packet should be applied daily to a surface area of approximately 5 to 7 inches. To avoid irritation, the application site should be alternated on alternate days. After applying, the site should be allowed to dry and should not be washed within one hour after application. Divigel is available as single-foil packets of 0.25 mg, 0.5 mg, and 1 mg. These packets will be packaged in boxes of 30 (b) (4) .

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3,4] for existing drug names which sound-alike or look-alike to Divigel to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. The SAEGIS[6] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Divigel. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff with representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary names Divigel acceptable from a promotional perspective.

2. The Expert Panel identified six names (Erygel, Provigil, Nuvigil***, Dibenil, Ovidrel, and Renagel) as having the potential for confusion with Divigel. Independent investigation identified an additional twelve names (Disipal, Desyrel, Novafil, Danazol, Sebazole, Doxychel, Lowquel, (b) (4), and Xolegel) as having the potential for confusion with Divigel. Prescription studies found three names (b) (4) Civigel). These products along with the available dosage forms and usual dosage are listed in Table 1 (see pages 4 and 5).

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[1] MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, Missouri.
[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-06, and the electronic online version of the FDA Orange Book.
[4] Phonetic and Orthographic Computer Analysis (POCA)
[5] www location http://www.uspto.gov/tmdb/index html.
[6] Data provided by Thomson & Thomson's SAEGIS™ Online service, available at www.thomson-thomson.com

*** proprietary and confidential information that should not be released to the public

Table 1: Potential Look-Alike and Sound-Alike Names Identified for Divigel for Further Review

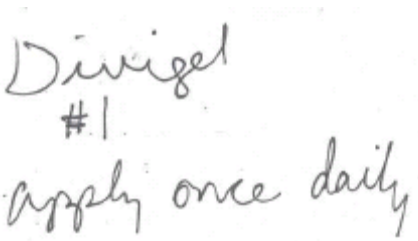
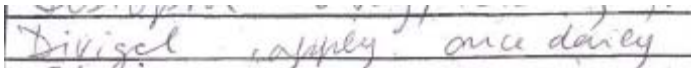
Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Divigel	Estradiol Gel, 0.1% 0.25 mg, 0.5 mg, 1 mg Boxed in 30's and 90's	0.5 mg daily	N/A
Nuvigil* (05-0091)**	Armodafinil Tablets, 50 mg, 100 mg, 150 mg, 250 mg	OSAHS or narcolepsy: 150 mg or 250 mg once daily. SWSD: 150 mg once daily 1 hour prior to shift. Dosage adjusted for severe hepatic impairment.	LA/SA
Desyrel	Trazodone HCl Tablets 50 mg, 100 mg, 150 mg, 300 mg	150 mg per day in divided doses, maximum doses 400 mg/day to 600 mg/day.	LA
			(b) (4)
Xolegel	Ketaconazole Topical Gel, 2%	Apply once daily to the affected area for 2 weeks	LA
Erygel	Erythromycin Topical Gel, 2% 30 and 60 grams	Apply as a thin film to affected area once or twice daily	SA
Provigil	Modafinil Tablets, 100 mg and 200 mg	200 mg daily.	LA
Dibenil (Discontinued)	Diphenhydramine Hydrochloride Elixir, 12.5 mg/5 mL	One to four teaspoonsful every 4 to 6 hours.	SA
Ovidrel	Choriogonadotropin Alfa Injection, 0.25 mg/0.5 mL in single-dose prefilled syringes	250 mcg subcutaneously one day following the last dose of the follicle-stimulating agent.	LA/SA
Disipal (no longer marketed in US) (European Union, Zambia, New Zealand, Isreal, Norway)	Orphenadrine HCl	Can not find information for this formulation (Hydrochloride)	LA
Novafil	Nonabsorbable monofilament surgical sutures	Use as nonabsorbable sutures in general soft tissue approximation and/or ligation, including use in cardiovascular and ophthalmic surgery, but not in microsurgery and neural tissue	LA
Danazol	Danazol Capsules, 50 mg, 100 mg, 200 mg	Endometriosis: 400 mg twice daily. Fibrocystic Breast Disease: 50 mg to 200 mg twice daily. Hereditary Angioedema: 200 mg two to three times daily.	LA
Sebazole* NDA 21-946**	Ketoconazole Gel, 2%	Apply once daily to the affected area(s).	LA
Lowquel (generics available)	Atropine Sulfate and Diphenoxylate Hydrochloride, 0.025 mg/2.5 mg	2 Tablets four times per day.	LA
			(b) (4)

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Divigel	Estradiol Gel, 0.1% 0.25 mg, 0.5 mg, 1 mg Boxed in 30's and 90's	0.5 mg daily	N/A
[redacted] (b) (4)			
Renagel	Sevelamer Hydrochloride Tablets, 400 mg and 800 mg	800 to 1600 mg, administered as one to two, 800 mg or two to four, 400 mg tablets with each meal	LA
Doxychel (discontinued, but generics and other brands available)	Doxycycline Monohydrate Oral Suspension, 25 mg/5 mL Doxycycline Hyclate Injection, 100 mg vial	Adults: 50 mg to 100 mg every 12 hours (100 mg every 12 hours for one day followed by 100 mg daily (or 50 mg twice daily). Children: 2 mg/lb twice daily.	LA
Civigel (France)	Carbomer 980, 0.2% (for dry eyes)	Could not locate	LA/SA
[redacted] (b) (4)			
Divagel (Romania)	Hexestrolum Ointment (listed in estrogen family)	Could not locate	LA/SA
*Frequently used, not all-inclusive. **LA (look-alike)/SA (sound-alike). *** Proprietary and confidential information that should not be released to the public			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Divigel with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 124 health care professionals (pharmacists, physicians, and nurses). The exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and an outpatient prescription were written, each consisting of a combination of marketed and unapproved drug products with a prescription for Divigel (see page 6). These prescriptions were optically scanned and one prescription was delivered to a random sample of participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail and sent to a random sample of participating health professionals for their interpretation and review. After receiving either written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX:  	Divigel Number 1 To apply once a day
Inpatient RX:  	

2. Results:

Three of the voice respondents interpreted the proposed name as Civigel, Vivigel, and Divagel. Civigel and Divagel are drug products marketed in other countries. (b) (4) . See Appendix A for the complete listing of interpretations from the verbal and written studies.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name, the following twenty-one names were identified as having the potential to be confused with the proposed name of Divigel: Nuvigil, Desyrel, (b) (4) Xolegel, Erygel, Provigil, Dibenil, Ovidrel, Disipal, Novafil, Danazol, Sebazole, Lowquel, (b) (4) Renagel, Doxychel, Civigel, (b) (4) and Divagel.

(b) (4)

Of the twenty-one names identified by expert panel discussions, independent review, and prescription studies, the following sixteen names will not be reviewed further due to weak orthographic similarities, weak phonetic similarities and/or lack of overlapping products

characteristics such as dosage form, strength, product specialization, lack of availability, and/or directions for use: Erygel, Provigil, Dibenil, Ovidrel, Disipal, Novafil, Renagel, Danazol, Sebazole***, Lowquel, (b) (4) Doxychel, (b) (4), and Divagel. Additionally, two of these names proposed and previously reviewed ((b)) and Sebazole***) by the Agency were considered to have the potential for confusion with the proposed name of Divigel. However, these names were not implemented by the sponsors for their drug products, thus would not result in confusion with Divigel. Moreover, (b) (4) are foreign products with limited marketing and information is not readily available in English on the world-wide web. Thus, the possibility for confusion is limited.

The remaining five names are discussed in detail below.

(b) (4)

*** Proprietary and confidential information that should not be released to the public.

(b) (4)

3. Xolegel was identified as a name with similar appearance to Divigel when scripted. Xolegel contains ketoconazole in a 2% gel for the treatment of seborrheic dermatitis in immunocompetent adults and children 12 years and older. Xolegel is to be applied once daily to the affected area for two weeks. This drug product is marketed in 15 grams tubes.

   The orthographic similarities between Xolegel and Libigel stem from the shared concluding "gel" and the potential for the leading "Xo" to resemble "Li." However, the upstroke of the "l" in Xolegel may help differentiate the name.

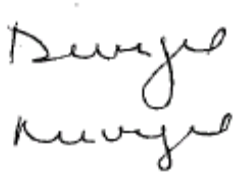
   The drug products share a similar route of administration (topical), dosage form (gel), and dosing frequency (daily). Xolegel is available in a single concentration of 2% compared to the three strengths of 0.25 mg, 0.5 mg and 1 mg. Thus, DMETS believes the potential for confusion to be minimal.

4. Nuvigil*** was identified as a name with similar appearance and sound to Divigel when scripted and spoken. Nuvigil*** contains armodafinil, which is indicated to improve wakefulness in patients with excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome

*** Proprietary and confidential information that should not be released to the public.

(OSAHS), narcolepsy, and shift work sleep disorder (SWSD). In OSAHS, Nuvigil*** is indicated as adjunct to standard treatment(s) for the underlying obstruction. The proposed dose of Nuvigil*** for OSAHS or narcolepsy is 150 mg or 250 mg once a day. The proposed dose of Nuvigil*** for SWSD is 150 mg once a day one hour prior to start of the shift period. Dose reductions are recommended for severe hepatic impairment. Nuvigil*** tablets are proposed to be provided in 60 count bottles to be stored at room temperature.

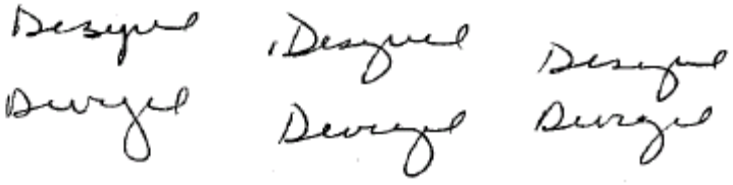
The orthographic similarities of this name pair stem from concluding "vigil" and "vigel", which appear identical on scripting. This is compounded by the potential for the leading "N" to resemble a "D." The phonetic similarities root in shared three syllable count and shared central "vig." However, the leading "Nu" of Nuvigil and "D" of Divigel should differentiate the two in speech.



The drug products share once daily dosing frequency and numerically similar strengths (0.5 mg compared to 50 mg and 0.25 mg compared to 250 mg). However, due to the placement of the decimal for 0.5 mg and 0.25 mg and the concluding zero for 50 mg and 250 mg, the strengths should be differentiated on prescription orders. The drug products differ in route of administration (oral compared to topical), dosage form (tablet compared to gel), prescription schedule (schedule IV compared to non-control status), and storage location. Due to the differing strengths, route of administration, and dosage form, DMETS believes the possibility for confusion to be minimal.

5. Desyrel was identified as a name with similar appearance to Divigel when scripted. Desyrel is indicated for the treatment of depression. This drug product is available as four tablet strengths (50 mg, 100 mg, 150 mg and 300 mg). The recommended dose is 150 mg per day, up to 400 mg to 600 mg in 2 or 3 divided doses.

   The orthographic similarities stem from leading "De" compared to "Di", which appear identical when scripted. This is compounded by the shared downstroke ("y" and "g") with similar placement and shared concluding "L."



   The products share similar numerical strengths (0.5 mg compared with 50 mg); however, the leading and concluding zeros should differentiate it upon scripting. The remaining strengths differ (0.25 mg, 1 mg compared to 100 mg, 150 mg and 300 mg). The drug products also differ in route of administration (oral compared with topical), dosage form (tablet compared to gel), indication (depression compared to estrogen replacement), and dosing frequency (two to three times daily compared to daily). Due to the differing dosing frequencies and strength, DMETS believes the possibility for confusion to be minimal.

III. COMMENTS TO THE SPONSOR

DMETS does not recommend the use of the proprietary name Divigel. In reviewing the proprietary name, the primary concerns relating to look-alike and/or sound-alike confusion with Divigel (b) (4)

(b) (4)

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/s/

Kimberly Culley-Pedersen
1/30/2007 01:03:40 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
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