CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-038s000

OTHER REVIEW(S)

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

DATE: May 4, 2007

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

VIA: George Lyght, R.Ph., Regulatory Health Project Manager
Division of Reproductive and Urologic Products

FROM: Sharon R. Mills, B.S.N., R.N., C.C.R.P.
Patient Product Information Specialist
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THROUGH: Toni Piazza-Hepp, Pharm.D., Deputy Director
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SUBJECT: DSRCS Review of Patient Labeling (PPI) for Divigel (estradiol Gel, 0.1%), NDA 22-038.

Background and Summary

Upsher-Smith Laboratories, Inc. submitted NDA 22-038 for Divigel (Estradiol Gel, 0.1%) on May 1, 2006, which includes patient labeling. The review division received a major amendment to the NDA on February 12, 2007 and notified the sponsor that the user fee goal date would be extended 3 months to June 4, 2007, since the major amendment is within 3 months of the original goal date. DSRCS has been consulted to review the patient labeling (PPI) for this NDA.

See the attached Patient Package Insert (PPI) for our recommended revisions to the proposed PPI submitted for Divigel (estradiol gel, 0.1), NDA 22-038. The purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications. We have reviewed the PPI to ensure that it is consistent with the "*Guidance for Industry Revision 4*: *Noncontraceptive Estrogen Drug Products*

for the Treatment of Vasomotor Symptoms-Recommended Prescribing Information for Health Care Providers and Patient Labeling."

The PPI revisions are based on the proposed Professional Information (PI) submitted on May 1, 2006 and then revised by the sponsor and submitted on April 6, 20087. Patient information should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the PPI.

Comments and Recommendations

1. A PPI is required for Divigel. The sponsor should follow the "*Guidance for Industry Revision 4*: *Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms-Recommended Prescribing Information for Health Care Providers and Patient Labeling"* in developing and modifying this PPI. The "Patient Instructions for Use" should be appended to the PPI.
2. The draft PPI submitted by the sponsor has a Flesch Kinkaid grade level of 7.6, and a Flesch Reading Ease score of 63.0. To enhance comprehension, patient materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level). The reading scores as submitted by the sponsor are acceptable. We have simplified the wording where possible, made it consistent with the Professional Information (PI) and removed unnecessary information. These recommended changes are consistent with current research to improve risk communication to a broad range of audiences including those with lower literacy levels.
3. In several places, we have noted where information is in the PPI and is not in the PI. The sponsor will need to add language to the PI as noted, or the information must be deleted from the PPI. The PPI must be consistent with the PI. An example of this is in the section, "What should I do if I get Divigel in my eyes?" The *Dosage and Administration* section of the PI states that "Contact of the gel with eyes should be avoided." Whereas, the PPI tells patients, "If you get Divigel in your eyes, flush your eyes right away with lukewarm tap water."
4. Figure numbers and reference to the figures have been added to the "Patient Instructions for Use" to make them easier for patient comprehension. A figure should be added to better illustrate to patients what the area of coverage should look like.

Comments to the review division are ***bolded, underlined and italicized*** in the attached document. We are providing to the review division a marked-up and clean copy of the revised PPI. We recommend using the clean copy as the working document.

Please let us know if you have any questions.

22 Page(s) of Draft Labeling have been Withheld in Full following this page as B4 (CCI/TS)

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

/s/

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5/4/2007 03:51:08 PM
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