



NDA 022038/S-005 and
NDA 022038/S-006

SUPPLEMENT APPROVAL

Vertical Pharmaceuticals, LLC
Attention: Sharon Suarez
Director, Regulatory
400 Crossing Blvd
Bridgewater, NJ 08807

Dear Ms. Suarez:

Please refer to your supplemental New Drug Application (sNDA) dated and received February 12, 2019, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Divigel® (estradiol gel) for topical use.

This Prior Approval supplemental new drug application provides for a new 1.25 gram dose regimen for Divigel® (estradiol gel).

We also refer to your sNDA dated and received December 20, 2018, submitted in response to our Prior Approval Supplement Request Letter dated, December 10, 2018. This sNDA provides for the following agreed upon revisions to the labeling for Divigel® (estradiol gel) for topical use (additions are noted by underline and deletions are noted by ~~strikethrough~~).

Under, HIGHLIGHTS, add:
RECENT MAJOR CHANGES

Boxed Warning

MM/YYYY

Under, FULL PRESCRIBING INFORMATION, revise as follows in BOXED WARNING (additions are underlined, and deletions have a ~~strikethrough~~):

**Under Estrogen-Alone Therapy
Cardiovascular Disorders and Probable Dementia (3rd paragraph)**

Only daily oral 0.625 mg CE was studied in the estrogen-alone substudy of the WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events and dementia to lower CE doses, other routes of administration, or other estrogen-alone products is not known. Without such data, it is not possible to definitively exclude these

risks or determine the extent of these risks for other products. Discuss with your patient the benefits and risks of estrogen-alone therapy, taking into account her individual risk profile.

~~In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.~~

Under Estrogen Plus Progestin Therapy Following Cardiovascular Disorders and Probable Dementia and Breast Cancer

Only daily oral 0.625 mg CE and 2.5 mg MPA were studied in the estrogen plus progestin substudy of the WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events, dementia and breast cancer to lower CE plus other MPA doses, other routes of administration, or other estrogen plus progestin products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products. Discuss with your patient the benefits and risks of estrogen plus progestin therapy, taking into account her individual risk profile.

~~In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins.~~

The language included in our December 10, 2018 letter added the following to Section 12.3; however, the Agency subsequently determined and you agreed that this language would be deleted and that 12.2 would be changed as follows (**additions are underlined, and deletions have a strikethrough**):

under, **SECTION 12**

(b) (4)

12.2 Pharmacodynamic

~~Currently, there are no pharmacodynamic data known for Divigel.~~ Generally, a serum estrogen concentration does not predict an individual woman's therapeutic response to Divigel nor her risk for adverse outcomes. Likewise, exposure comparisons across different estrogen products to infer efficacy or safety for the individual woman may not be valid.

Under, Patient Information

What is the most important information I should know about DRUG (an estrogen hormone)?

Under last bullet of section, revise as follows:

Only one estrogen-alone product and dose has been shown to increase your chances of getting strokes, blood clots, and dementia. Only one estrogen with progestin product and dose has been shown to increase your chances of getting heart attacks, strokes, breast cancer, blood clots, and dementia. Because other products and doses have not been studied in the same way, it is not known how the use of Divigel will affect your chances of these conditions. You and your healthcare provider should talk regularly about whether you still need treatment with Divigel.

APPROVAL & LABELING

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling with minor editorial revisions listed below and reflected in the enclosed labeling.

- In Full Prescribing Information, Boxed Warning, under Estrogen plus Progestin Therapy, Cardiovascular Disorders and Probable Dementia, first paragraph, the left justified line has been removed.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.¹ Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Patient Package Insert), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.²

The SPL will be accessible from publicly available labeling repositories.

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to carton and container labeling submitted on November 21, 2019, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved NDA 022038/S-005 and S-006.**” Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because for a menopause indication, necessary studies are impossible or highly impracticable in the pediatric population.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the Prescribing Information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.³

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.⁴ Information and Instructions for completing the form can be found at FDA.gov.⁵ For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.⁶

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.

³ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁴ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁵ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

⁶ <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kim Shiley, R.N., B.S.N., Regulatory Project Manager, at (301) 796-2117.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, M.D., M.M.Sc.
Director
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
 - Prescribing Information
 - Patient Package Insert

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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