

NDA 021732/S-025

## SUPPLEMENT APPROVAL

Endo Operations Limited  
Attention: Julie Davis Sims  
Director, Regulatory Affairs  
1400 Atwater Drive  
Malvern, PA 19355

Dear Julie Sims:

Please refer to your supplemental new drug application (sNDA) dated and received July 10, 2025, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vantas (histrelin acetate).

We also refer to our letter dated June 12, 2025, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we have determined should be included in the labeling for GnRH agonist products. This information pertains to the risk of severe cutaneous adverse reactions (SCAR).

This supplemental new drug application provides for revisions to the labeling for Vantas. The agreed upon changes to the language included in our June 12, 2025, letter are as follows (additions are noted by underline and deletion are noted by ~~striketrough~~).

### 5.6 Severe Cutaneous Adverse Reactions

VANTAS can cause severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP). SCARs, including SJS/TEN, DRESS, and AGEP, occurred in patients receiving VANTAS or other GnRH agonists; including cases with visceral involvement and/or requiring skin grafts.

Monitor patients for the development of SCARs.

If a SCAR is suspected, interrupt VANTAS until the etiology of the reaction has been determined. Consultation with a dermatologist is recommended. If a SCAR is confirmed, or for other grade 4 skin reactions, permanently discontinue VANTAS.

## 6.2 Postmarketing Experience

*Skin Reactions: erythema multiforme, bullous dermatitis, dermatitis exfoliative, DRESS, SJS/TEN, and AGEP.*

## 17. PATIENT COUNSELING INFORMATION

### Severe Cutaneous Adverse Reactions

Inform patients and/or caregivers that severe cutaneous adverse reactions (SCARs), including ~~Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP)~~, which may be life threatening or fatal, may occur during treatment with VANTAS. Advise patients and/or caregivers to contact their healthcare provider or seek medical attention right away if they experience signs or symptoms of SCARs, e.g., a prodrome of fever, flu-like symptoms, mucosal lesions, progressive skin rash, or lymphadenopathy [see *Warnings and Precautions (5.6)*].

In addition, corresponding changes were made to the Patient Package Insert.

### **APPROVAL & LABELING**

We have completed our review of this application, as amended. It is 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.

- Updated the Recent Major Changes revised date
- Updated the Revised Dates
- Added vertical line to section 5.6

### **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.<sup>1</sup> 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.

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

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*.<sup>2</sup>

The SPL will be accessible from publicly available labeling repositories.

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).

### **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.

Because none of these criteria apply to your supplemental application, you are exempt from this requirement.

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.<sup>3</sup>

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.<sup>4</sup> Information and Instructions for completing the form can be found at FDA.gov.<sup>5</sup>

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<sup>2</sup> 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>.

<sup>3</sup> For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

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

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

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-related information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related 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).

### **PATENT LISTING REQUIREMENTS**

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

### **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, contact Meredith Hillig, M.S., Safety Regulatory Project Manager, at 301-796-1218, or via email at [Meredith.Hillig@fda.hhs.gov](mailto:Meredith.Hillig@fda.hhs.gov)

Sincerely,

*{See appended electronic signature page}*

Oladimeji Akinboro, MD, MPH  
Associate Director for Safety  
Office of Oncologic Diseases  
Office of New Drugs  
Center for Drug Evaluation and Research

### **ENCLOSURES:**

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

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**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.**  
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/s/  
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