



NDA 202880/S-003

**SUPPLEMENT APPROVAL**

Zogenix Inc.  
5858 Horton Street  
Suite 455  
Emeryville, CA 94608

Attention: Edward F. Smith III, PhD, MBA, RAC  
Vice President, Regulatory Affairs

Dear Dr. Smith:

Please refer to your Supplemental New Drug Application (sNDA) dated and received September 30, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zohydro ER (hydrocodone bitartrate) extended-release capsules, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50 mg.

We acknowledge receipt of your amendments dated November 11 and 19, 2014, and January 5, 12, 23, and 30, 2015.

This "Prior Approval" supplemental new drug application proposes the following changes: (1) addition of excipients, polyethylene oxide (PEO) and povidone, to the drug product formulation; (2) revisions to the **DRUG ABUSE AND DEPENDENCE** section, of the package insert to address safety concerns related to new excipients; (3) revisions to **HOW SUPPLIED/STORAGE AND HANDLING** section of the package insert to reflect changes to packaging presentation introducing 60-count bottles to replace 100-count bottles; and (4) revised container labeling for the 60-count bottles.

**APPROVAL & LABELING**

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

**WAIVER OF HIGHLIGHTS SECTION**

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

## **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 <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide), with the addition of any labeling changes in pending “Changes Being Effectuated” (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 titled “SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes 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 MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, 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 IMMEDIATE CONTAINER LABELS**

Submit final printed carton and immediate container labels that are identical to the enclosed immediate container labels and immediate-container labels submitted on January 5, 2015, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 202880/S-003.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

## **POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

This new formulation of Zohydro ER (hydrocodone bitartrate) contains a specific polyethylene oxide (PEO) [REDACTED] <sup>(b) (4)</sup>. In such settings, our ability to extrapolate safety across the class of PEO products is limited due to lack of information regarding the low molecular weight impurities in these products.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to:

- Identify an unexpected risk of serious adverse outcome of renal failure due to chronic exposure to the low molecular weight impurities in the PEO components of Zohydro ER (hydrocodone bitartrate); and
- Identify an unexpected risk of serious embryo-fetal developmental and/or post-natal developmental adverse events due to chronic exposure to the excipients in Zohydro ER (hydrocodone bitartrate).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 2866-1 Analyze the polyethylene oxide (PEO) product employed in Zohydro ER (hydrocodone bitartrate) for low molecular weight impurities. Identify and quantitate the impurities. Submit a toxicological risk assessment for the exposure to the impurities taking into consideration the maximum theoretical daily dose of Zohydro ER (hydrocodone bitartrate).

The timetable you submitted on January 23, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: 01/2016

- 2866-2 Conduct an embryo-fetal development study in the rat model to assess the potential impact of polyethylene oxide (PEO) on development. The study must be designed to adequately qualify the safety of the low molecular weight PEO components (impurities/degradants) in the PEO used to manufacture Zohydro ER (hydrocodone bitartrate) when the product is consumed up to the maximum theoretical daily dose of Zohydro ER (hydrocodone bitartrate).

The timetable you submitted on January 23, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 05/2016  
Study Completion: 11/2016  
Final Report Submission: 05/2017

2866-3 Conduct an embryo-fetal development study in the rabbit model to assess the potential impact of polyethylene oxide (PEO) on development. The study must be designed to adequately qualify the safety of the low molecular weight PEO components (impurities/degradants) in the PEO used to manufacture Zohydro ER (hydrocodone bitartrate) when the product is consumed up to the maximum theoretical daily dose of Zohydro ER (hydrocodone bitartrate).

The timetable you submitted on January 23, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 06/2016  
Study Completion: 03/2017  
Final Report Submission: 09/2017

2866-4 Conduct a pre- and post-natal development study in the rat model to assess the potential impact of polyethylene oxide (PEO) on development. The study must be designed to adequately qualify the safety of the low molecular weight PEO components (impurities/degradants) in the PEO used to manufacture Zohydro ER (hydrocodone bitartrate) when the product is consumed up to the maximum theoretical daily dose of Zohydro ER (hydrocodone bitartrate).

The timetable you submitted on January 23, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 07/2016  
Study Completion: 05/2017  
Final Report Submission: 11/2017

Submit the protocols to your IND 065111, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”**, **“Required Postmarketing Final Report Under 505(o)”**, **“Required Postmarketing Correspondence Under 505(o)”**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to

report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

### **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 package insert(s) to:

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

You must submit final promotional materials and package insert(s), 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 <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

### **EXPIRY DATING PERIOD**

A 24-month expiry dating period is granted for Zohydro ER, all dosage strengths in 60 count HPDE bottles, when stored at 20° to 25°C (68° to 77°F) with excursions permitted from 15° to 30°C (59° to 86°F).

### **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 Dominic Chiapperino, PhD, Senior Regulatory Health Project Manager, at (301) 796-1183.

Sincerely,

*{See appended electronic signature page}*

Sharon Hertz, MD  
Acting Director  
Division of Anesthesia, Analgesia, and  
Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURES:

Content of Labeling  
Carton and Container Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SHARON H HERTZ  
01/30/2015