CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202880Orig1s003

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, MD
Subject	Division Director Summary Review
NDA/Supplement #	202880/S-003
Applicant Name	Zogenix, Inc
Date of Submission	September 30, 2014
PDUFA Goal Date	January 30, 2015
Proprietary Name / Established (USAN) Name	Zohydro ER/ hydrocodone bitartrate
Dosage Forms / Strength	Extended-release capsule, 10, 15, 20, 30, 40 and 50 mg
Proposed Indication	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
Action/Recommended Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Pharmacology Toxicology Review	Elizabeth Bolan, PhD, R. Daniel Mellon, PhD
CMC Review OBP Review	Arthur Shaw, PhD, Assadollah Noory, PhD, John Duan, PhD
Division of Pediatric and Maternal Health	Carol H. Kasten, MD, Tamara Johnson, MD, MS, Lynne P. Yao, MD
OSE DMEPA	James Schlick, RPh, MBA, Vicky Borders-Hemphill, PharmD

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication ErrorsPrevention
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OPDP=Office of Prescription Drug Promotion
DCDP=Division of Consumer Drug Promotion
OMP=Office of Medical Policy Initiatives
DMPP=Division of Medical Policy Programs

Signatory Authority Review Template

1. Introduction

This application is a prior approval CMC supplement for a new formulation of Zohydro ER. The new formulation contains the same immediate-release and extended-release beads containing hydrocodone as the original formulation and has (b) (4) a high molecular weight polyethylene oxide and Povidone (b) (4) The addition (b) (4) is intended to provide (b) (4) .

2. Background

The approval of Zohydro ER on October 25, 2013 was met with a tremendous amount of confusion, misunderstanding, and misinformation.[1] Zohydro ER was the first extended-release hydrocodone product indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. It was approved in 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50 mg strengths for twice daily dosing, the same as for the current formulation. There was also much criticism that Zohydro ER was not an abuse-deterrent formulation. (b) (4)

During the development of this formulation, the Applicant has changed (b) (4) from the first version (b) (4), and based on a pilot study, reports that exposure to an aqueous environment results in the formation of a gelatinous mass. (b) (4)

3. CMC/Device

There was (b) (4). Information describing the pharmaceutical development of new drug product was submitted by reference to DMF (b) (4). Dr. Shaw reviewed DMF (b) (4) and found it to be acceptable. There was no need for additional facilities inspections for the manufacturing sites.

The Applicant requested a biowaiver for in vivo bioavailability studies. Dr. Noory notes in his review that the two excipients added [redacted], that there is an existing IVIVC established for the approved Zohydro ER formulation, and that there is dose proportionality from the 10 mg up to the 50 mg strength. Dr. Noory concluded that the predicted bioavailability of the new product following the application of the level A IVIVC has been adequately documented. He noted that the predicted percent difference of in vivo exposure (AUC and Cmax) for the new formulation compared to the approved formulation, based on the IVIVC and the observed data for the approved product, ranges from -7.76 to 3.79, which is within bioequivalence limits. An in vitro alcohol interaction study evaluated the potential for dose dumping, and demonstrated similar in vitro dissolution behavior in the presence of alcohol for the new and approved formulations. Dr. Noory found that the proposed labeling is adequate to address this risk.

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance, and with the conclusions reached by the biopharmaceutics reviewer regarding the acceptability of the biowaiver request. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

The following is from the review by Dr. Bolan:

> Several of the excipients in the IR and ER HC-containing beads common to the Zohydro and ZX004 formulations (sugar spheres, [redacted], silicon dioxide and talc)are [redacted] in the ZX004 formulation. [redacted] do not present a toxicologic concern for this product because the amounts are still below acceptable levels when the product is used at the maximum theoretical daily dose (MTDD) of HC of 3 g.
>
> Two excipients, PEO and Povidone [redacted] are unique to the ZX004 formulation. The Povidone [redacted] has an ADI as determined by the World Health Organization that is [redacted] than the levels in ZX004 when the product is used at the MTDD of HC. It is therefore considered acceptable. The levels of the PEO used in this drug product [redacted]. To support the safety of the levels of the PEO in this product, the Applicant references DMF [redacted] for the drug product formulation which references DMF [redacted] to support the safety of the PEO. Drug Master File [redacted] has been found to be inadequate because of the lack of adequate characterization of low molecular weight entities in the PEO polymer. These low molecular weight entities could include [redacted] and specifications for these impurities in the excipient master file may be required. However, because of the longstanding history of use of PEO in many products which reference DMF [redacted] this deficiency will not be an approval issue for Supplement 003 for NDA 202880. The levels of PEO in ZX004 when used at the MTDD of HC are considered acceptable from a pharmacology/toxicology perspective

for this NDA. Pharmacology toxicology recommends that the Applicant conduct several studies as post-marketing requirements (PMR) to fully characterize the toxicity of the PEO.

The drug product impurity and degradant specifications for the new formulation are the same as the original formulation. The specifications are acceptable from a pharmacology/toxicology perspective.

Additionally, the Applicant has submitted labeling changes to Section 13.1 which included the description of negative results of an in vivo comet assay with HC in the mutagenicity section. This study was submitted as a post-marketing requirement by Zogenix and has been reviewed. The study was found to be valid and negative and revised wording will be included in the label.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that postmarketing studies are required to fully characterize the toxicity of the PEO in this formulation. These are the same postmarketing requirements for PEO that were approved for another recently approved product, Hysingla ER. There are no outstanding pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology

There was no new clinical pharmacology information submitted in support of this application.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

There was no new clinical efficacy information submitted in support of this application.

8. Safety

There was no new clinical safety information submitted in support of this application.

9. Labeling

The package insert was updated to reflect a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and to create a new subsection for information with regard to females and males of reproductive potential no substantive changes, according to the recently (December 4, 2014) announced publication of the "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling," also known as the Pregnancy and Lactation Labeling Rule (PLLR). The recommended changes to labeling sections 8.1 Pregnancy, 8.2 Lactation, 17.1 Information for Patients and Caregivers, and to the Medication Guide have been agreed to by the applicant.

The container label has the addition of a new formulation flag intended to be in place for six months. The container label also reflects the change from 100-count to 60-count bottles, with new NDC numbers.

10. Decision/Action/Risk Benefit Assessment

- Regulatory Action -Approval
- Risk Benefit Assessment

[redacted] (b) (4)

There are no reasons, however, to expect any difference in the clinical efficacy or safety profile, and the formulation changes were found acceptable. Therefore, the product can be expected to be as safe and effective as the original formulation.

The issue for further comment is the presence of [redacted] (b) (4) As noted by Dr. Bolan, this amount [redacted] (b) (4), once dosing reaches high levels. For products with identified maximum daily doses, it is easy to determine the dose for conducting toxicological risk assessments for the active substance, excipients, and any impurities or degradants. However, unlike most other drugs, most mu agonist opioids have no technical ceiling for dosing, and due to the physiological phenomenon of tolerance, some patients require high doses over time. Therefore, a maximum "theoretical" daily dose (MTDD) has been established for the purpose determining dosing for toxicological risk assessment. Out of an abundance of caution, a MTDD of 3 grams has been selected for hydrocodone. There is little expectation that patients will reach that level of dosing except, perhaps, in certain extreme situations. When applying a MTDD of 3 grams to this formulation of Zohydro ER, the amount of polyethylene oxide [redacted] (b) (4). Again, out of an abundance of caution, the postmarketing requirements described below have been implemented. These postmarketing study requests are not novel. The same requirements accompanied the recent approval of another extended-release opioid analgesic containing an amount of PEO [redacted] (b) (4)

- Recommendation for Postmarketing Risk Management Activities

Zohydro ER will remain in the Extended-Release and Long-Acting Opioid Analgesic REMS, and all prior postmarketing study commitments remain.

- Recommendation for other Postmarketing Study Commitments

The polyethylene oxide used in this formulation is in FDA-approved drug products, but the daily dose of the excipient in this product based on the maximum theoretical daily dose is [redacted] (b) (4) the requirement to submit a toxicological risk assessment for the exposure to the possible low molecular weight impurities that may occur, taking into consideration the maximum theoretical daily dose for a single entity, extended-release hydrocodone analgesic product. Given the long history of use of the excipient and the likelihood that most individuals will not reach the maximum theoretical daily dose, more definitive characterization of these impurities was considered acceptable to be completed post marketing by requiring the following studies:

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).

This study will be conducted 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).

This study will be conducted 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).

This study will be conducted 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).

This study will be conducted according to the following schedule:

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

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[i] Incorrect statements about Zohydro ER included that the strengths were higher than any other opioid. Based on available information about relative oral potency, hydrocodone is approximately similar in potency to oxycodone, 1.5 to 2-fold as potent as morphine, about one third as potent as oxymorphone, and one third to one quarter as potent as hydromorphone. This information is presented in the following table. The highest existing strengths of extended-release oxycodone on the market is 80 mg, of extended-release morphine is 200 mg, of extended-release oxymorphone is 40 mg, and of extended-release hydromorphone is 32 mg. So not only is the 50 mg dose of Zohydro ER not higher than products already on the market at the time of its approval, it was somewhat lower than for other opioids, based on these relative potency values.

Table Comparison of Doses for ER Opioids

Opioid	Approximately comparable oral doses	Doses comparable to 120 mg hydrocodone	Maximum marketed ER product strength	Dosing Interval
Morphine	60 mg	180 mg (240 mg)*	200 mg	Q8, BID, QD
Hydrocodone Hysingla ER **Zohydro ER**	45 mg (30 mg)*		 120 mg 50 mg	 QD BID
Oxycodone	45 mg (30 mg)*	120 mg	80 mg	BID
Oxymorphone	10 mg	25 mg (40 mg)*	40 mg	BID
Hydromorphone	12 mg	32 mg (48 mg)*	32 mg	QD

*Estimates of relative oral potency differ. Relative to morphine, oxycodone and hydromorphone may be 1.5- to 2-fold stronger. Figures in parentheses represent the values for the 2-fold estimate.

Relative to approved hydrocodone products, currently available combination products with hydrocodone have as much as 10 mg per dosage unit, but unlike Zohydro ER which is dosed every 12 hours, hydrocodone combination products are labeled for dosing as often as every 4 hours resulting in a substantially larger number of pills being dispensed.

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/s/

SHARON H HERTZ
01/30/2015