CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200403Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, M.D.
Subject	Deputy Division Director Summary Review
NDA/BLA #	200-403/000
Applicant Name	Hospira, Inc.
Date of Submission	October 7, 2011 (Class 1 Resubmission in response to 2/25/11 TA action)
PDUFA Goal Date	December 7, 2011
Proprietary Name / Established (USAN) Name	Hydromorphone Hydrochloride Injection/ Hydromorphone Hydrochloride Injection
Dosage Forms / Strength	Solution, 1 mg/mL, 2 mg/mL, 4 mg/mL
Proposed Indication(s)	1. For the management of pain in patients where an opioid analgesic is appropriate or the management of pain in patients where an opioid analgesic is appropriate.
Action/Recommended Action	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	N/A
Statistical Review	N/A
Pharmacology Toxicology Review	Belinda Hayes, Ph.D., Dan Mellon, Ph.D.
CMC Review	Xiaobin Shen, Ph.D., Danae Christodoulou, Ph.D., Prasad Peri, Ph.D.
Biopharmaceutics Review	Angelica Dorantes, Ph.D., Patrick Marroum, Ph.D.
Microbiology Review	Denise Miller, Steve Langille, Ph.D., James McVey
Clinical Pharmacology Review	Wei Qiu, Ph.D., Suresh Doddapaneni, Ph.D., Yun Xu, PhD
DDMAC	Mathilda Fienkeng
DSI	
CDTL Review	N/A
OSE/DMEPA	Zachary Oleszczuk, Pharm.D., Carol Holquist, R.Ph.
CSS Review	JianPing Gong, M.D., Ph.D., Michael Klein, Ph.D.
Project Management	Lisa Basham, M.S., Parinda Jani

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Errors Prevention
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

Numerous unapproved narcotic analgesics are currently marketed, many under the mistaken belief that, as very old products, it was not necessary for applications to be submitted for review under the Drug Efficacy Study Implementation in support of the continued marketing of these products. The current application is for injectable hydromorphone hydrochloride via intravenous, subcutaneous and intramuscular routes. The application was filed under the 505(b)(2) regulations referencing Dilaudid (NDA 19-034, Purdue Pharma). The primary difference between the products represented in this application and the referenced drug is the many configurations included in the current application: ampule, vial, Carpuject cartridge and iSecure cartridge.

The initial action for this application submitted under the 505(b)(2) regulations referencing the Agency's prior findings of efficacy and safety for Dilaudid (NDA 19-034) was a tentative approval because of a late-listed patent for the referenced drug, Dilaudid (patent number 6589960), that does not expire until November 9, 2020. Because this patent was timely filed, and Hospira was sued by Purdue for patent infringement, this application was under a 30-month stay of approval.

In support of this class 1 resubmission requesting full approval of this 505(b)(2) application, the applicant submitted an amendment describing the dismissal of litigation between the applicant and Purdue Pharma who holds the NDA for the referenced drug, Dilaudid.

2. Background

For immediate-release hydromorphone products, such as the subject of this NDA, there is clear evidence of efficacy and safety based on the Agency's prior findings from other products. Therefore, the focus of this type of 505(b)(2) application is the chemistry, manufacturing and controls information, and the individual product's pharmacokinetic characteristics and how these relate to the product referenced in the NDA. The applicant requested and was granted a biowaiver in lieu of a relative bioavailability study, which is common for parenteral solutions. In this product, there was originally a drug-related concern based on the presence of an (b) (4) impurity with a structural alert for mutagenicity, (b) (4). As noted in the pharmacology/toxicology review, there are two impurities in the drug substance that contain this structural moiety; however, the levels of these impurities have been reduced to acceptable levels.

3. CMC/Device

In an amendment to the NDA, reviewed during this cycle, the applicant submitted the chemical characterization and toxicological evaluation of [redacted] which has a proposed acceptance criterion of NMT [redacted]. [redacted] is a [redacted] impurity formed [redacted]. It was hypothesized to [redacted] The applicant reduced the acceptance criteria of [redacted] to NMT [redacted]. This complies with ICH Q3A. Therefore, there is no longer any need for any postmarketing commitments

Updated stability data supports a claimed expiry of 24 months.

From the first cycle review:

Drug Substance

Hydromorphone hydrochloride drug substance [redacted] Support for the drug substance is via reference to DMF [redacted] manufactured by [redacted] DMF [redacted] was last reviewed in October 2007 and was deemed adequate. There has been no change to the DMF that affects its quality since that review.

Drug Product

The drug product is a clear, colorless to nearly colorless sterile aqueous solution packaged in USP [redacted] glass ampules, vials, and cartridges, in 1 mg/mL, 2 mg/mL, and 4 mg/mL concentrations. The pH range is 3.5 – 5.5. None of the excipients - [redacted] sodium lactate, lactic acid, sodium chloride, [redacted] and [redacted] sodium hydroxide – are novel. The 10 packaging configurations are presented in the following table from Dr. Shen's review. The drug product is manufactured by Hospira Worldwide Inc, in McPherson, KS.

Table Packaging Configurations

Packaging Configuration	Strength (mg/mL)	Fill Volume (mL)	Package Type	Package Capacity (mL)
1	1	1	Ampule	1
2	2	1	Ampule	1
3	4	1	Ampule	1
4	2	1	Vial	2
5	1	1	Carpuject Cartridge	2.5
6	2	1	Carpuject Cartridge	2.5
7	4	1	Carpuject Cartridge	2.5
8	1	1	iSecure Cartridge	1.5
9	2	1	iSecure	1.5

			Cartridge	
10	1	0.5	iSecure Cartridge	1.5

The materials making up various configuration stoppers, caps and plungers meet USP requirements and are suitable for pharmaceutical use. No leachables were found emanating from the various configuration stoppers, caps and plungers into the solutions based on data from 18-month real time stability studies.

The drug product specifications and acceptance criteria were found to be acceptable and the product was found to meet these criteria. (b) (4) total impurities were observed to gradually increase, and increased faster at accelerated conditions and at higher concentrations, but were well within the proposed acceptance criteria. The proposed expiry of 24 months was adequately supported by 12 months of long-term and six months of accelerated stability data. The product was found to be photo labile and a corresponding light protection statement is included on the label.

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections received an overall "Acceptable" cGMP recommendation from the Office of Compliance on May 25, 2010. Stability testing supports an expiry of 24 months. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

In the current submission, the applicant tightened the specification of (b) (4) to meet ICH Q3A (R2) safety qualification threshold and the manufacturer of the drug substance conducted a the quantitative structure-activity relationship (QSAR) analysis of (b) (4) Results from this analysis provided the following characterization of (b) (4)

(b) (4)

As a result of this work, the following postmarketing commitments identified in the original action letter are no longer required:

1. Conduct an in vitro genetic toxicology study to detect point mutations with the isolated drug substance impurity identified as "[redacted] tested up to the limit dose for the assay.

2. Conduct an in vitro genetic toxicology study to detect chromosome aberrations with the isolated drug substance impurity identified as "[redacted] tested up to the limit dose for the assay.

3. Conduct a 3-month repeat-dose toxicology study in a single species with the isolated drug substance impurity identified as "[redacted]

From the first cycle review:

No pharmacology or toxicology studies were submitted in support of this NDA. The Applicant is relying on the Agency's previous finding of safety for Dilaudid (NDA 19-034) and information from the literature.

Impurities and degradants that are [redacted] and have structural alerts for mutagenicity. [redacted] obtained from the DMF supplier. The Agency has determined that a specification of NMT [redacted] for [redacted] in high potency opiates such as hydromorphone, however, [redacted] this specification to NMT [redacted]

[redacted] was identified as [redacted] impurity and degradation product in hydromorphone drug substance. The applicant agreed to [redacted] consistent with ICH Q3A (R2).

[redacted] have been identified as [redacted] impurities in the hydromorphone drug substance. They are [redacted]. The applicant has revised the specification for [redacted] to NMT [redacted] (NMT [redacted] which is acceptable based on a proposed maximum daily dose of [redacted] for hydromorphone, and [redacted] to [redacted] to meet ICH Q3A (R2).

[redacted] has been identified as [redacted] impurity in the hydromorphone drug substance. The Applicant has hypothesized that it is [redacted], but the identity of [redacted] has not been fully elucidated. The [redacted] manufacturer, [redacted] specification to NMT [redacted] as per ICHQ3A (R2). As a result, safety qualification must be provided. However, as this DMF was previously deemed acceptable to support an approved generic drug product, this may be addressed in the post-marketing period.

[redacted] has been identified as [redacted] impurity in the hydromorphone drug [redacted] data from Toxicology Data Network indicates that [redacted] is a potential carcinogen in rodents. In contrast, existing genetic toxicology data on [redacted] suggests that [redacted] is not genotoxic based on the Ames test, in vivo mouse micronucleus assay and in vivo mouse lymphoma cell test. The existing rodent carcinogenicity data report suggest a NOEL for oral carcinogenicity at ~90 mg/m^2 in the rat and ~105 mg/m^2 in the mouse (female) based on body surface area providing a significant safety margin exists of more than 128,000-fold for tumor development. Therefore, the proposed specification of NMT [redacted] mcg/day is acceptable.

The specifications proposed by the Applicant for the drug product impurities are adequate according to ICH Q3B (R2).

As noted by Dr. Hayes, the applicant has not adequately responded to the Agency request to either tighten the specification of the drug substance (b) (4) or provide adequate safety qualification. The applicant must provide definitive identification of the impurity structure (b) (4) NMT (b) (4) or provide adequate safety qualification consisting of a minimal genetic toxicology screen (one in vitro assay for mutagenicity, one in vitro assay for DNA damage) and a repeat-dose toxicology study of three months duration to support the proposed specification of NMT (b) (4) As this (b) (4) DMF has been previously deemed adequate by the FDA for an approved generic drug, this concern may be addressed via a post-marketing requirement.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

From the first review cycle:

No new clinical pharmacology studies were conducted with the proposed products. As summarized by Dr. Qiu, the pharmacokinetic characteristics of hydromorphone have already been studied. Hydromorphone is approximately 8-19% bound to plasma proteins. It is extensively metabolized via glucuronidation in the liver, with greater than 95% of the dose metabolized to hydromorphone-3-glucuronide. Only a small amount of hydromorphone dose is excreted unchanged in the urine. The terminal elimination half-life of hydromorphone after an intravenous dose is about 2.3 hours.

Dosing adjustments are necessary for patients with moderate hepatic impairment due to an increase in exposure by approximately 4-fold. There is no data for patients with severe hepatic impairment and, therefore, no specific dosing recommendations can be made. Similarly for patients with moderate and severe renal impairment, dosing must also be adjusted due to an increase in exposure by approximately 2-fold and 4-fold, respectively.

The applicant requested a BA/BE waiver in place of conducting the studies. Dr. Dorantes from the ONDQA-Biopharmaceutics group evaluated the information supporting the biowaiver request and concluded that the applicant's request was acceptable and the biowaiver for the proposed hydromorphone hydrochloride Injection product was granted.

I concur with the conclusions reached by the clinical pharmacology reviewer and the biopharmaceutics reviewer that there are no outstanding clinical pharmacology or biopharmaceutics issues that preclude approval.

6. Quality Microbiology

From the first review cycle.

The drug substance (b) (4) The manufacture of the drug product includes (b) (4) The container closure integrity was found to be acceptable for each packaging configuration. The following additional information is standard practice to obtain post-approval".

Post-Approval Stability Protocol and Stability Commitment

Hospira commits to place the first three commercial batches on stability and tested according to the stability protocol. Thereafter, at least 1 commercial batch of each configuration will placed on stability annually.

- Container Closure Integrity – is demonstrated by sterility testing at 0, 12, and 24 month time points for the long term storage conditions. The sterility testing is per USP <71>.

- Endotoxin –testing follows USP <85> with a specification of NMT (b) (4) EU/mg. The samples are tested at the 0 and 24 month time points under the long term storage conditions.

I concur with the conclusions reached by the quality microbiology reviewer that there are no outstanding microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

No new clinical studies were submitted for review.

8. Safety

No new clinical studies were submitted for review.

9. Advisory Committee Meeting

This application was not taken to an advisory committee as the drug product is not novel, the drug substance is similar to an approved product for the application to rely on prior findings of efficacy and safety, and there are no unique or unanswered issues.

10. Pediatrics

No pediatric studies are required as this application does not represent a new drug product, new route of administration, new indication or new dosage form.

11. Other Relevant Regulatory Issues

The applicant has submitted this application under the 505(b)(2) regulations referencing the Agency's prior findings of efficacy and safety for Dilaudid (NDA 19-034). Although a product that has been on the market since 1984, there is a late-listed patent for Dilaudid (patent number 6589960) that does not expire until November 9, 2020. Because this patent was timely filed, and Hospira was sued by Purdue for patent infringement, this application was under a 30-month stay of approval. Therefore, only a TA action could be taken.

In support of this class 1 resubmission requesting full approval of this 505(b)(2) application, the applicant submitted an amendment in which they acknowledged that the referenced drug, Dilaudid of Purdue Pharmaceutical Products, is subject to a period of patent protection under U.S. Patent No. 6,589,960. The applicant further acknowledged that NDA 200403 was filed with a Paragraph IV certification and provided a copy of the litigation notice filed by the patent owner to the Agency. The litigation between the parties has been dismissed with prejudice pursuant to a stipulation filed with the Court. In other words, the applicant was sued by Purdue on October 8, 2010. The patent infringement suit was dismissed by a US district court (Illinois) on 6/27/11 and, as a result, the application is cleared for approval.

From the first review cycle:

> The Controlled Substances Staff was consulted and had the following comments:
> There are no preclinical and clinical abuse potential studies in the NDA submission. The Sponsor is not seeking any claims or labeling statements regarding abuse deterrence or abuse resistance of the formulation.
>
> Hydromorphone is a CII substance under Controlled Substances Act (CSA) and is historically associated with high levels of abuse. Therefore, CSS reminds the Sponsor to store and handle the product consistently with regulations for Schedule II narcotic drugs by storing in a securely locked, substantially constructed cabinet or enclosure with limited access to prevent theft or diversion into illegal channels of distribution.

12. Labeling

Several proprietary names were proposed last cycle that were rejected. A new proposed proprietary name, "(b) (4) was proposed, but found (b) (4) and so was rejected by DMEPA. The labeling review from DMEPA had the following comments:

> Our evaluation found the 2 mg/mL Carpuject container label is similar to the 1 mg/mL Carpuject container label. This similarity has lead to a selection error that resulted in an overdose. Additionally, the 2 mg/mL Carpuject label for hydromorphone has also been confused with the container label for Hospira's lorazepam 2 mg/mL Carpuject syringe. As such, the labels need to be revised prior to approval. We have provided recommendations for the container labels to help minimize confusion of these products and to revise the labels and labeling to include required information on the labels and labeling in Section 5.1.

The comments were submitted to the applicant and adequate changes were made.

Labeling comments from DDMAC were incorporated into the package insert.

The applicant had proposed dosing every (b) (4) as needed as was present in the package insert for Dilaudid. However, during the review of this application, the Dilaudid package insert was amended to dosing every 2 to 3 hours as needed. As a result, the change was incorporated into the package insert for this application.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Approval

- Risk Benefit Assessment

The safety and efficacy of hydromorphone hydrochloride can be expected to be comparable to Dilaudid. The updated package insert and improvements to the carton and container labels will provide clearer information for prescribers and reduce the risk for medication errors. Legal issues preventing reference to the Agency's prior findings of efficacy and safety for Dilaudid, NDA 19-034, have been resolved.

- Recommendation for Postmarketing Risk Management Activities

None.

- Recommendation for other Postmarketing Study Commitments

None

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/s/

SHARON H HERTZ
12/01/2011