CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202515Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, M.D.
Subject	Deputy Division Director Summary Review
NDA/BLA #/Supplement #	202-515/000
Applicant Name	Hospira, Inc.
Date of Submission	January 14, 2011
PDUFA Goal Date	November 14, 2011
Proprietary Name / Established (USAN) Name	Morphine Sulfate Injection USP
Dosage Forms / Strength	2 mg/mL, 4 mg/mL, 8 mg/mL, 10 mg/mL, 15 mg/mL, (b) (4)
Proposed Indication(s)	1. Management of pain not responsive to non-narcotic analgesics
Action/Recommended Action:	Approval of the Carpuject and iSecure Syringe products

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Timothy Jiang, M.D., Ellen Fields, M.D., M.P.H.
Statistical Review	N/A
Pharmacology Toxicology Review	Elizabeth Bolan, Ph.D., Dan Mellon, Ph.D.
CMC Review/OBP Review	Ying Wang, Ph.D., Prasad Peri, Ph.D.
Microbiology Review	Bryan S. Riley, Ph.D., Stephen E. Langille, Ph.D.
Clinical Pharmacology Review	N/A
Division of Drug Marketing, Advertising and Communications	Mathilda Fienkeng, Pharm.D., Lisa Hubbard Pharm.D.
CSS Review	Alicja Lerner, M.D., Ph.D., Michael Klein, Ph.D.
Office of Medication Error Prevention and Risk Management	Richard A. Abate, R.Ph., M.S., Lubna Merchant, M.S., Pharm.D.
Biopharmaceutics Review	Minerva Hughes, Ph.D., Angelica Dorantes, Ph.D.

Signatory Authority Review Template

1. Introduction

The applicant has not conducted any new clinical or nonclinical studies and is relying on the Agency's prior findings of safety and efficacy for Duramorph (Baxter, NDA 18565) to support this 505(b)(2) application. The applicant originally sought (b) (4) intravenous (IV) (b) (4) The IV route of administration is adequately supported through reference to NDA 18565. There are (b) (4) concentrations, 2 mg/mL, 4 mg/mL, 8 mg/mL, 10 mg/mL, 15 mg/mL, (b) (4) and several packaging configurations under this NDA. Carpuject and iSecure syringes are single-use pre-filled syringes, (b) (4)

2. Background

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 to support continued marketing of these products. The current application is for a product that has been marketed, although previously unapproved.

Morphine was isolated from opium as early as 1806. Opiate receptors were first identified in the early 1970's followed by the discovery of the first endogenous opiate-like substance, enkephalin. The existence of mu, delta and kappa sub-types of opiate receptors was also confirmed in the 1970's. Morphine, along with most of the clinically used opioids, is relatively selective for the mu receptor and it is through the mu receptor that it exerts its clinical effects.

For parenteral morphine sulfate products, such as the subject of this NDA, there is clear evidence of efficacy and safety based 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. As a parenteral solution, pharmacokinetic studies can be waived based on an appropriately supported biowaiver request. A biowaiver request has been made for (b) (4) IV routes of administration, however, as described below, (b) (4)

3. CMC/Device

Drug Substance
The drug substance is manufactured in [redacted] and all information is referenced in DMF [redacted]. Specifications that are provided in the NDA for the drug substance mostly follow the USP monograph. Additional specifications for related substances meet ICH Q3A guidance.

Drug Product
The drug product, Morphine Sulfate Injection USP, is a sterile aqueous solution. There are [redacted] configurations of the container closure system and [redacted] concentrations of the drug product in this application. The Carpuject and iSecure syringes are intended for single use intravenous [redacted] administration and are available in 2 mg/mL, 4 mg/mL, 8 mg/mL, 10 mg/mL, and 15 mg/mL concentrations. [redacted]

The drug product contains edetate disodium [redacted]. There are no preservatives, per se, [redacted]

The drug product specifications are in accordance with the USP monograph with additional acceptance criteria for related substances. As described in the Pharmacology/Toxicology section, the drug substance and drug product impurity/degradant [redacted] and the drug product degradants [redacted] all exceeded ICH Q3A/B(R2) qualification thresholds. The Applicant was asked to tighten their drug substance acceptance specification for [redacted] from NMT [redacted] to NMT 0.15% to be in accordance with ICH Q3A(R2) thresholds for qualification and agreed to do so along with additional qualification studies for the impurities in the drug product as described below.

[redacted]

[redacted]

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Stability testing supports an expiry of twenty-four (24) months for all presentations of the drug product when stored at controlled room temperature (20 – 25°C; 68 – 77°F).

A microbiology review was performed for this sterile parenteral solution. The drug product is (b) (4) filled. According to Dr. Riley's review, the applicant has proposed (b) (4) that are not supported by microbiological data, and as such, pose serious risk to the patient if the (b) (4) can support microbial proliferation. (b) (4) [redacted]"

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

4. Nonclinical Pharmacology/Toxicology

As noted by Dr. Bolan, the pharmacology and toxicology of morphine have been well characterized and no studies with morphine were submitted by the Applicant or required to support this NDA. A literature review by Dr. Bolan was conducted in order to update the nonclinical sections of the product label, specifically reproductive and developmental toxicology and genetic toxicology.

All excipients in the drug product are below levels found in drugs previously approved for parenteral use and are considered acceptable for NDA 202515. There are no concerns with extractables or leachables from the syringe plunger and vial stopper materials for this product.

The drug substance and drug product impurity/degradant, (b) (4) and the drug product degradants, (b) (4), all exceed ICH Q3A/B(R2) qualification thresholds. The Applicant submitted a literature-based justification to support the safety of the increased specifications that was not acceptable. The Applicant was asked to tighten their drug substance acceptance specification for (b) (4) from NMT (b) (4) to NMT 0.15% to be in accordance with the specification in the morphine sulfate drug substance DMF (DMF (b) (4)) which meets ICH Q3A(R2) thresholds for qualification and agreed to do so.

For the drug product, the qualification required includes a minimal genetic toxicology screen (two *in vitro* genetic toxicology studies) with (b) (4), tested up to the limit dose for the assay along with repeat-dose toxicology studies of 90 days duration with (b) (4). The applicant has committed to conducting these studies as a post marketing requirements (PMR). Data from an Ames Test and an *in vitro* chromosomal aberration assay were submitted in the application and

demonstrated that [redacted] is not genotoxic and can be considered qualified for genotoxic potential.

As noted by Dr. Bolan, the reason these studies are suitable to be completed post marketing is that the drug product is already a currently marketed product and these drug product degradants have been previously reported as morphine drug product degradants in the literature.

Dr. Bolan reviewed a brief summary of the study design for the 13-week toxicology study submitted by the applicant and found that the study design appears to be acceptable for a repeat-dose toxicology study to qualify the three impurities. She noted that combining the three impurities is an acceptable approach, however, if toxicity is observed, it will not be possible to determine which individual impurity is responsible for the observed toxicity. The proposed dose levels of 1x human equivalent dose (HED) and 3x HED are acceptable provided the HED is based on a maximum daily dose of 722 mg/day of morphine.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology and toxicology issues not adequately addressed by the PMR that preclude approval.

The PMR consists of the following studies:

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

2. Conduct an in vitro genetic toxicology study to detect point mutations with the isolated drug product impurity [redacted], tested up to the limit dose for the assay.

3. Conduct an in vitro genetic toxicology study to detect chromosome aberrations with the isolated drug product impurity [redacted], tested up to the limit dose for the assay.

4. Conduct an in vitro genetic toxicology study to detect chromosome aberrations with the isolated drug product impurity [redacted], tested up to the limit dose for the assay.

5. Conduct a 3-month repeat-dose toxicology study in a single species with the following drug product impurities: [redacted].

5. Clinical Pharmacology/Biopharmaceutics

There were no pharmacokinetic studies submitted in support of this application. The applicant requested a waiver of the CFR's requirement to provide data from in vivo bioavailability or bioequivalence studies to support the approval of Morphine Sulfate Injection on the basis that the product is an injectable solution and its bioavailability is self-evident, as per 21 CFR §320.22 (Criteria for waiver of evidence of in vivo bioavailability or bioequivalence).

In support of the requested biowaiver for Morphine Sulfate Injection, the applicant provided a formulation comparison table with composition data for approved products and literature references for bioavailability and pharmacokinetic performance. After review of the information provided, Dr. Hughes concurred with the request for a waiver for the intravenous route (b) (4)

(b) (4)

I concur with the conclusions reached by the biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval of the morphine sulfate for the intravenous route of administration. (b) (4)

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

No new clinical efficacy studies were performed in support of this application. The Applicant has relied on the Agency's previous findings of efficacy and safety for the reference drugs Duramorph (NDA 018565) by Baxter Healthcare, and Morphine Sulfate Duramorph (NDA 018565) by Baxter Healthcare, (b) (4) The applicant has also submitted 59 published articles that included randomized controlled trials of morphine (55 for acute pain, and four for chronic pain) which have been reviewed. Dr. Jiang has reviewed the submitted literature and found that the information available is supportive of the efficacy of morphine sulfate in treating a variety of painful conditions, such as post-surgical, acute, and chronic pain.

8. Clinical Safety

There were no safety data submitted in support of this NDA. Safety for the intravenous use of Morphine Sulfate is based on reliance of the Agency's prior findings for Duramorph.

9. Advisory Committee Meeting

As a parenteral solution of morphine sulfate with no novel issues, an advisory committee meeting was not held for this NDA.

10. Pediatrics

This NDA did not trigger the requirements of PREA, as parenteral morphine sulfate does not represent a change in active ingredient, dosage form, route of administration, indication of dosing regimen relative to parenteral morphine sulfate products already approved. The applicant did propose language for pediatric patients and submitted literature to support this language. The referenced product, Duramorph, has no information for pediatric use and the package insert has the following language: "Adequate studies, to establish the safety and effectiveness of spinal morphine in pediatric patients, have not been performed, and usage in this population is not recommended." (b) (4)

(b) (4)

11. Other Relevant Regulatory Issues

Financial Disclosure
There were no clinical studies conducted in support of this application.

Facility Inspections
Two manufacturing sites were submitted in the Site Establishment Information. The (b) (4) site was identified as responsible for drug substance testing, excipient testing, component testing, manufacture of drug product in Carpuject syringes and iSecure syringes, in-process control testing, release testing of drug product, packaging and labeling of the drug product, alternate stability testing site for the registration and commercial batches, and alternate stability samples storage site for the commercial batches. (b) (4)

The same Establishment Evaluation Request Detail Report in EES has an Acceptable recommendation for the (b) (4) site.

Controlled Substances Staff
The review by Dr. Lerner notes that morphine sulfate is listed under Schedule II of the Controlled Substances Act. Dr. Lerner initially made the following recommendations:

1. As a Schedule II drug under the CSA, all Schedule II narcotic regulations and procedures regarding manufacture, distribution, dispensing, storage, recordkeeping, and disposal of morphine sulfate injections should be in place and strictly followed.
2. Although this drug is primarily intended for use in the hospital setting, because of the current public health problem of prescription drug abuse, we request the sponsor submit the following additional information to FDA as periodic reports every 6 months for the first 2 years of marketing and then annually for the next 5 years:
    a. Compile and analyze all postmarketing cases that relate to abuse, misuse, diversion and overdose of the product.
    b. All sales to patients that occur outside of the hospital setting.

However, in a later addendum, she noted that her recommendation on reports to the Agency was intended to comply with the standard reporting requirements for an approved NDA (21 CFR 314.80 and 314.81), and does not relate to the criteria for PMR/PMC (Section 130 of FDAMA 1997).

12. Labeling

Carton and Container Labeling
Mr. Abate of the Division of Medication Error Prevention and Analysis conducted a review of the proposed container labels and carton and insert labeling for areas of vulnerabilities that could lead to medication errors. A number of suggestions were sent to the applicant and incorporated into the container and carton labels. The term (b) (4) was removed from the display panel of the labels to avoid errors with the use of these products for intrathecal or epidural delivery. Although preservative free, the formulation contains edetate disodium and cannot be used for intrathecal or epidural delivery of morphine. While initially, medications errors were noted for the Morphine Carpuject based on the green needle cover which is common to more than one Carpuject product, additional investigation found that the errors were old and FDA has not received reports of wrong drug medication errors recently. Therefore, the change in color was not required and FDA will continue to monitor for reports of similar errors in the future. If such errors are noted, changes will be requested to address confusion between products.

Package Insert
The package insert was submitted in Physician Labeling Rule format. Major changes to the package insert included (b) (4) Most sections of the package insert were updated. Changes recommended by Dr. Fienkeng of DDMAC were incorporated into the package insert. The changes proposed by FDA were agreed to by the applicant.

There is no patient labeling for this product.

There is no proposed proprietary name.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval of the Carpuject syringe and iSecure syringe products.

- Risk Benefit Assessment

The data submitted in support of this NDA are adequate to approve Morphine Sulfate, USP for the management of pain not responsive to non-narcotic analgesics for the intravenous route of administration in adults for the Carpuject syringe and iSecure syringe products. (b) (4)

(b) (4)

- Recommendation for Postmarketing Risk Management Activities

None

- Recommendation for other Postmarketing Study Requirements

As discussed in the Pharmacology and Toxicology section, the reason the studies described below are suitable to be completed post marketing is that the drug product is already a currently marketed product and these drug product degradants have been previously reported as morphine drug product degradants in the literature. The following PMRs have been communicated to the applicant who has agreed to conduct the studies:

1. Conduct an in vitro genetic toxicology study to detect point mutations with the isolated drug product impurity (b) (4), tested up to the limit dose for the assay.

2. Conduct an in vitro genetic toxicology study to detect point mutations with the isolated drug product impurity (b) (4), tested up to the limit dose for the assay.

3. Conduct an in vitro genetic toxicology study to detect chromosome aberrations with the isolated drug product impurity (b) (4), tested up to the limit dose for the assay.

4. Conduct an in vitro genetic toxicology study to detect chromosome aberrations with the isolated drug product impurity (b) (4), tested up to the limit dose for the assay.

5. Conduct a 3-month repeat-dose toxicology study in a single species with the following drug product impurities: (b) (4).

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/s/

SHARON H HERTZ
11/14/2011