CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204223Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, M.D.
Subject	Division Director Summary Review
NDA #	204-223
Applicant Name	Becton, Dickinson, and Co.
Date of Submission	May 2, 2013
PDUFA Goal Date	November 2, 2013
Proprietary Name / Established (USAN) Name	Morphine Sulfate for Injection
Dosage Forms / Strength	Solution for injection, 2 mg/mL, 4 mg/mL, 5 mg/mL, 8 mg/mL and 10 mg/mL.
Proposed Indication(s)	Management of pain not responsive to non-narcotic analgesics
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	
CMC Review	Julia Pinto, Ph.D., Prasad Peri, Ph.D.
OBP Review	Elsbeth Chikhale, Ph.D., John Duan, Ph.D.
Pharmacology Toxicology Review	N/A
Clinical Pharmacology Review	N/A
Medical Officer Review	N/A
Statistical Review	N/A
Product Quality Microbiology Review	Steven P. Donald, M.S., Bryan Riley, Ph.D.
OC, OMPQ, DGMPA, NDMAB	Vibhakar Shah, Ph.D., Tara Gooen,
OSE/DMEPA	Vicky Borders-Hemphill, Pharm.D., Jamie Wilkins Parker, Pharm.D.
OPDP/DCDP	

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
NDMAB = New Drug Manufacturing Assessment Branch/DGMPA = Division of Good Manufacturing Practice Assessment
OMPQ =Office of Manufacturing and Product Quality/ OC =Office of Compliance

1. Introduction

This is a resubmission of this 505(b)(2) application for Morphine Sulfate Injection USP, 2 mg/mL, 4 mg/mL, 5 mg/mL, 8 mg/mL and 10 mg/mL, in prefilled syringes containing 1 mL following an initial complete response action on March 31, 2013. The Applicant plans to rely on the Agency's prior findings of efficacy and safety for Hospira Morphine Sulfate Injection 2 mg/mL, 4 mg/mL, 8 mg/mL, 10 mg/mL and 15 mg/mL (NDA 202515), approved Nov 14, 2011 and Meridian Medical Technology Morphine Sulfate Injection 15 mg/mL (NDA 19999) approved on July 12, 1990.

The applicant seeks both intravenous (IV) and intramuscular (IM) routes of administration and has submitted a biowaiver request for the IV route of administration, a relative bioavailability study using the highest strength and biowaiver for the lower strengths for the IM route of administration. This application will focus on the outstanding deficiency from the first review cycle, stemming from a 483 issued for the drug product manufacturer due to failure of oxygen scavenger canisters placed in the drug product packaging. The following deficiency was conveyed to the Applicant in the complete response letter issued March 31, 2013:

> During a recent inspection of the BECTON, DICKINSON & Co, manufacturing facility, located in Wilson, NC, for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

2. Background

The following background is from my first cycle memo and describes the support for the proposed IM route of administration:

> Morphine is a mu agonist opioid analgesic. Morphine is listed under schedule II of the Controlled Substances Act as it is known to have a high potential for abuse and abuse of morphine may lead to addiction. Parenteral morphine has been in use in the management of pain for over 100 years. The product under review in this application is very similar to the referenced approved products with minor differences from the Hospira's product and a difference in volume, concentration and volume from the Meridian product. The initial dose chosen for parenteral morphine is based on a number of factors including, but not limited to, patient age, health status, and size of the patient, nature of the pain, extent of recent use of opioids, and past responses to opioid analgesics. Subsequent doses are based on the response to the first dose with regard to efficacy and adverse events. For the purpose of IV use, this formulation does not differ from the referenced product in any way that can be expected to affect efficacy or safety, and pharmacokinetic studies have been waived based on a biowaiver request reviewed by the biopharmaceutics reviewer. There are more factors than can influence the exposure to morphine following IM administration than IV administration, such as concentration, volume, and needle length. Therefore, for the

IM route of administration a relative bioavailability study was required as the concentration and volume of the product under review differ from the referenced product. Bioequivalence is not a requirement for the IM route of administration to be acceptable for several reasons, as long as the exposure is not unexpected in a way that would question safety or efficacy. First, medical staffs are unlikely to expect that the product under review will perform the same as the Meridian autoinjector. The Meridian autoinjector is not in general use in hospitals but, rather, is used most commonly in settings such as the military. Next, dose selection is based primarily on the factors previously described. Last, as described in the clinical pharmacology review, the overall exposure is similar, even though Cmax is less for the new product, compared to the Meridian autoinjector.

3. CMC/Device

As noted by Dr. Pinto in her first cycle review:

The drug substance is Morphine Sulfate, USP. The Chemistry, Manufacturing, and Control (CMC) information for this API is referenced to DMF (b) (4), held by (b) (4). The DMF was reviewed and recommended as satisfactory by A. Shaw, Rev #3 March 28 2011 and Rev #4, NAI, May 2012. The API will be stored and shipped in (b) (4) and has a retest period of (b) (4) months.

The drug product, Morphine Sulfate Injection USP is a clear and colorless solution for injection formulated in a single-dose prefilled syringe in concentrations of 2mg/ml, 4mg/ml, 5mg/ml, 8mg/ml and 10 mg/ml. The manufacturing process consists of (b) (4) The drug product is formulated as a solution in water comprising morphine sulfate, USP as the drug substance, and inactive ingredients that include sodium chloride, citric acid (b) (4), edatate disodium and calcium chloride (b) (4). The RLD for this drug product is Hospira's Morphine Sulfate, USP Injection wherein the same excipients are used with the exception of sodium citrate (b) (4) and calcium chloride (b) (4).

The syringe system is comprised of a transparent type 1 glass barrel assembled with a plastic luer lock adapter (LLA), a plastic rigid elastomeric tip cap (PRTC) an elastomeric plunger stopper and a plastic plunger rod. Morphine sulfate is formulated in a single dose pre-filled syringe in concentrations of 2mg/ml, 4mg/ml, 5mg/ml, 8mg/ml and 10 mg/ml. The manufacturing process and the syringe fill have been reviewed by Microbiology Reviewer (Donald Stevens, MS) as satisfactory. The DP is made by Becton-Dickinson at their Wilson, NC facility. The Office of Compliance has recommended a withhold status and issued a 483 for this facility. An overall recommendation is pending.

> The recommended storage temperature is 25° C (77° F) with excursions permitted from 15° to 30°C (59°-86°F) and an expiry of 24 months is supported.
>
> Sufficient CMC information, to assure the identity, strength, purity, and quality of the drug product, is provided in this NDA submission.

The request for a biowaiver was reviewed during the first review cycle by Dr. Chikhale, the following is from her first cycle review:

> A waiver from the CFR's requirement to provide data from an *in vivo* bioequivalence study for the IV route of administration (for all strengths) is granted based on the formulation comparison of the proposed drug product and Hospira's morphine sulfate injection (the IV reference product). A waiver from the CFR's requirement to provide data from an *in vivo* bioequivalence study for the lower strengths (2 mg/mL, 4 mg/mL, 5 mg/mL, and 8 mg/mL) using the IM route of administration is also granted, based on the formulation comparison of these lower strengths and the 10 mg/mL strength. From the Biopharmaceutics perspective, NDA 204223 for Morphine Sulfate Injection (2 mg/mL, 4 mg/mL, 5 mg/mL, 8 mg/mL, and 10 mg/mL) is recommended for APPROVAL.

A product quality microbiology assessment was conducted during the first cycle review by Mr. Donald who noted that, "the compounded drug substance is sterile (b) (4) filled into presterilized syringes and fitted with sterile tip caps and sterile plunger stoppers. Filled and sealed syringes are (b) (4) packaged." No product quality microbiology deficiencies were identified.

In Dr. Pinto's current review, she notes:

> The CMC NDA review (February 21, 2013) by ONDQA found that sufficient CMC information is provided, to assure the identity, strength, purity, and quality of the drug product. However, a 483 was issued for the drug product manufacturer, Becton Dickinson in Wilson NC, by the Office of Compliance (OC), in November 2012. The firm did not satisfactorily respond to all the issues identified by OC. The outstanding deficiency is in regard to the function of the StabilOx oxygen canisters placed in the packaging of the drug product, to limit the amount of exposure to oxygen. Upon inspection 9% of the canisters were found to "fail" in that, an increase in residual oxygen was observed after packaging. Therefore, OC requested that the firm investigate the failure, and provide validated quality control methods to assure adequate functioning of the canisters. A detailed overview of the 483 is referenced to a review by Vibhakar Shah, Ph.D. (March 28, 2013). OC issued an overall recommendation of Withhold and therefore this NDA was recommended as a complete response, due to the pending resolution of the "withhold" recommendation by OC.
>
> On May 2, 2013, Becton Dickinson filed a resubmission of this NDA, stating that their facilities were ready for re-inspection. The issues discussed above and on the 483 were thought to have been resolved by OC, and in May 2013, the Becton Dickinson facilities

were recommended as adequate. This recommendation was the object of Memo 2 for this NDA by J. Pinto. Later, in June 2013, OC informed the OND PM, that an overall acceptable recommendation had been prematurely made in EES and the status in EES was changed from an overall acceptable to pending. As of September 2013, the BD facilities were re-inspected and the Inspector (Thomas LaReese) has found all the issues listed on the 483 have been resolved. OC has provided an overall acceptable recommendation for all facilities related to this NDA. The updated OC report is attached below. The NDA resubmission provides for no additional CMC data or CMC labeling changes. Therefore from the CMC perspective this NDA is recommended for approval. (See Dr. Pinto's review for the OC report.)

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Stability data support a 24-month expiry. There are no outstanding CMC issues.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology or toxicology information was submitted with this complete response.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology information was submitted with this complete response.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

No new clinical efficacy information was submitted with this complete response.

8. Safety

No new clinical safety information was submitted with this complete response.

9. Advisory Committee Meeting

No advisory committee was convened for this 505(b)(2) application for a parenteral morphine for IV and IM administration. Neither the drug substance, route of administration, nor indication is novel.

10. Pediatrics

The applicant notes that active ingredient, dosage form, dosing regimens and administration routes for the proposed products do not differ from the two referenced drugs. This NDA is exempt from the requirements of the Pediatric Research Equity Act.

11. Other Relevant Regulatory Issues

The following is from Dr. Shah's review of the Applicant's responses to the deficiencies noted in the FDA Form 483:

> The Office of Manufacturing and Product Quality (OMPQ) has completed its review of the FDA 483 observations and the firm's responses to these observations for the inspection ending on November 02, 2012 of Becton Dickinson and Company in Wilson, North Carolina. In addition to providing CGMP coverage, this inspection specifically provided pre-approval coverage for NDA 204223. The profile covered during this CGMP inspection was (b) (4)
>
> This memo summarizes the final evaluation of firm's responses to the FDA 483 observations that were submitted to ATL-DO in letters dated November 16, 2012, December 28, 2012, January 11, 2013, and July 31, 2013.

Dr. Shah concludes the following:

> In summary, the firm's responses to the FDA 483 observations seem reasonable to ensure quality and reliable performance of oxygen absorbing canister. From a CGMP compliance perspective, OMPQ concurs with the ATL-DO's ACCEPTABLE recommendation for this facility and supports the approval of the subject application. OMPQ also recommends that on a subsequent inspection, ATL-DO verifies the effectiveness of the firm's implemented corrective and preventive measures to ensure quality of the drug product including the incoming container closure system (CCS) component - oxygen scavenger canister.

The applicant has submitted Paragraph I certification that states, in the opinion of the applicant, no patent information has been submitted to FDA for the listed drugs in this NDA.

The applicant has not requested exclusivity.

12. Labeling

No proprietary name has been proposed for this product. The labeling will be consistent with the labeling for the referenced products with the exception of a product specific set of instructions for use. The package insert including instructions for use, carton and container labeling have all been reviewed by DMEPA and the review team. Recommendations for changes have been communicated to the applicant and accepted.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Approval

- Risk Benefit Assessment

The Applicant has adequately addressed the issues cited during the manufacturing site inspections and can assure the quality of the drug product.

The risks associated with the use of opioid analgesics apply to this product. As a product intended for parenteral administration, morphine sulfate for injection is administered in a supervised setting and is stored and handled under the regulations applied to a Schedule II controlled substance. The package insert conveys the important information necessary to use the product safely and to understand the risks associated with the administration of parenteral morphine. Overall, the benefit of parenteral morphine, when used properly to manage pain not responsive to non-narcotic analgesics outweighs the risks.

- Recommendation for Postmarketing Risk Management Activities

None.

- Recommendation for other Postmarketing Study Commitments

None.

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/s/

SHARON H HERTZ
10/30/2013