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RESEARCH**

APPLICATION NUMBER:

204223Orig1s000

MEDICAL REVIEW(S)

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	June 1, 2012
PDUFA Goal Date	April 1, 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:	Complete Response

Material Reviewed/Consulted	
OND Action Package, including:	
CMC Review	Julia Pinto, Ph.D.
OBP Review	Elsbeth Chikhale, Ph.D., John Duan, Ph.D.
Pharmacology Toxicology Review	Carlic Hyunh, Ph.D, R. Daniel Mellon, Ph.D.
Clinical Pharmacology Review	Srikanth Nallani, Ph.D., Yun Xu, Ph.D.
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 Goen,
OSE/DMEPA	Vicky Borders-Hemphill, Pharm.D., Jamie Wilkins Parker, Pharm.D.
OPDP/DCDP	
OMP/DMPP	
Controlled Substances Staff	Stephen Sun, M.D., Michael Klein, Ph.D.

OND=Office of New Drugs

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Errors Prevention

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

Signatory Authority Review Template

1. Introduction

This is a 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, that 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 rationale for the IM route of administration in light of the differences in exposure for the subject of the NDA and the referenced product demonstrated in the bioavailability study and the deficiencies identified during the facilities inspection.

2. Background

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 staff 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 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)

(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 Dickenson 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 by Dr. Chikhale, the following is from her 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 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.

I concur with the conclusions reached by the chemistry reviewer and the product quality microbiology reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Stability data support a 24-month expiry. However, manufacturing site inspections were not acceptable and I concur that the deficiencies identified in the inspection must be rectified prior to approval.

4. Nonclinical Pharmacology/Toxicology

There were no nonclinical studies submitted nor required to support this 505(b)(2) application. In his review, Dr. Hyunh describes the evaluation of an impurity with a structural alert for genotoxicity and review of the leachables evaluation. According to his review:

(b)(4) (Impurity (b)(4)), which contains a structural alert for genotoxicity, was detected in the drug substance batch analysis; however, (b)(4) is predicted to be not genotoxic via QSAR analysis and therefore can be regulated as a non-genotoxic impurity. The drug substance and drug product specifications are below the ICH Q3A(R2) and Q3B(R2) qualification thresholds and therefore acceptable. There are no issues with the leachables identified in the container closure system. In fact, there are no issues with the container closure system as the contain closure system has been used in previously FDA-approved products. The Applicant has submitted osmolality data and their morphine sulfate injection drug product is deemed isotonic. As such, no blood compatibility studies are required. The Applicant is relying up the Agency's previous findings of safety to NDA 202515 (Hospira's Morphine Sulfate injection) and to NDA 19999 (Meridian Medical Technology's Morphine Sulfate injection). The label for the morphine sulfate injection drug product is the same as the label for NDA 202515.

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

5. Clinical Pharmacology/Biopharmaceutics

As described in the CMC section, the applicant has requested and been granted a biowaiver for PK studies for the IV route of administration and for the lower strengths for the IM route of administration. A relative bioavailability study was conducted to evaluate the exposure following an IM administration of morphine. The study was a Phase 1, single-center, randomized, open-label, single-dose, 2-period, 2-sequence crossover study in healthy, naltrexone-blocked subjects comparing a single 10 mg dose (1 mL dose of 10 mg/mL) of morphine by IM route delivered with a BD prefilled syringe administered over 1-2 seconds using a BD Eclipse™ 22G x 1 inch needle and a single injection of morphine from the Meridian auto-injector (NDA 19-999) which delivers 10 mg in 0.7 mL of 15 mg/mL solution. Details of the study design can be found in the review by Dr. Nallani and the following table and text are from page 4 of his review:

Statistical Analysis of Morphine Cmax, AUC0-t, and AUC0-∞ with and without Dose Normalization

Parameter ^a	Geometric LSMean (n=24)		Geometric LSMean Ratio (Trt A/Trt B)		
	BD Prefilled Syringe (Test)	Meridian morphine auto-injector (Reference)	Point Estimate	90% Confidence Interval	
				Lower	Upper
C _{max} (ng/mL)	64.28	90.54	0.710	0.651	0.775
nm ^d -C _{max} (ng/mL)	6.12	8.16	0.751	0.688	0.819
ne ^e -C _{max} (ng/mL)	6.13	8.17	0.750	0.687	0.819
AUC _{0-t} (ng*h/mL)	106.23	120.10	0.885	0.859	0.911
nm-AUC _{0-t} (ng*h/mL)	10.12	10.82	0.935	0.908	0.963
ne-AUC _{0-t} (ng*h/mL)	10.13	10.84	0.934	0.910	0.960
AUC _{0-∞} (ng*h/mL)	109.65	124.19	0.883	0.859	0.908
nm-AUC _{0-∞} (ng*h/mL)	10.44	11.19	0.933	0.908	0.960
ne-AUC _{0-∞} (ng*h/mL)	10.46	11.21	0.933	0.908	0.958

Before dose normalization, the geometric LSMean C_{max} for morphine after IM injection with the BD prefilled syringe (Treatment A) was about 71% of the corresponding C_{max} after IM injection with the Meridian morphine auto-injector. As shown in Table above, after normalization by either the mean or exact dose, C_{max} from Treatment A was about 75% that of Treatment B. The 90% CIs for C_{max} were not wholly contained within the 80-125% range for bioequivalence, regardless of dose normalization.

As described by Dr. Nallani, the C_{max} following the 10 mg dose from the BD prefilled syringe was lower by approximately 25% than the C_{max} of the referenced product, Meridian

autoinjector, below the range for bioequivalence. However, AUC was within the 80% to 125% range for bioequivalence. The significance of these findings is discussed in Section 7 below.

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

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

No efficacy data were submitted in support of this application. There is no reason, based on the formulation, to expect any difference in performance for efficacy or safety by the IV route of administration compared to the referenced product. While the C_{max} from a 10 mg dose of the proposed product, administered as 1 mL of 10 mg/mL solution by IM route of administration was lower than the C_{max} from a 10 mg dose by the Meridian autoinjector, the AUC was comparable and the exposure was adequate to expect efficacy. As discussed in the background, dosing parenteral morphine is based on a number of factors and patients receiving morphine by IM route will be followed clinically and managed based on their response to each dose of analgesic.

8. Safety

No new safety data were submitted in support of this application. The safety information in the referenced products is applicable and will be included in the labeling for this product, including all of the warnings relevant to morphine, a schedule II opioid agonist.

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

Inspections of Becton Dickinson and Company in Wilson, North Carolina were conducted on November 02, 2012. The following is from the memo by Dr. Shah:

An eight-item FDA 483 was issued to the firm on November 2nd, 2012. Although the establishment inspection report is unavailable at this time, Atlanta District Office (ATL-DO) had provided copies of Firm's responses, submitted to the Agency in three letters dated November 16, 2012, December 28, 2012 and January 11, 2013 respectively. The firm's response to observations 4 and 6, in particular with respect to the quality assurance of incoming container closure system (CCS) component, oxygen scavenger canister, have been found inadequate. The oxygen scavenger canister is one of the critical CCS components to ensure the stability of the drug product throughout its shelf life. This decision was reached after consultations with the lead investigator, CDR Jason Chancey, his findings surrounding this issue on the pre-approval inspection, and the CMC reviewer.

Dr. Shah describes in detail the findings of the failure of oxygen scavenger canisters from several batches to reduce the residual oxygen in the packages, with failure (b) (4)

The applicant described testing of the canisters by the vendor without providing any data and proposed future sampling of (b) (4) oxygen canisters without justification for the number chosen. Dr. Shah concludes:

In summary, the inspection and firm's response did not appear to demonstrate reliability of canister performance over the shelf-life of the product. Given the inadequacy of the firm response to observations 4 and 6, OMPQ concurs with the ATL-DO recommendation to withhold approval of the subject application due to significant deficiencies with the intended performance of oxygen canisters used in the proposed container closure system. For these reasons and per FDA CPGM 7346.832 "Pre-Approval Inspections" Part V, we recommend to *withhold* approval for NDA 204223 until corrections are determined to be adequate.

The withhold recommendation describes significant deficiencies that can affect product quality and must be satisfactorily addressed prior to product approval.

A review by Dr. Sun of the Controlled Substance Staff concluded:

Morphine sulfate is a well-documented DEA Schedule II opioid agonist that is proposed in varying concentrations of single-use, pre-filled syringes. Since the proposed dosage strengths in the routes of administration are within the previously approved dose ranges of existing products and the context for use are similar, the exposure risk profile of misuse, abuse, addiction, diversion, and overdose is not likely

to differ from the reference listed drugs for intravenous administration of Morphine Sulfate Injection USP by Hospira (NDA 202515) and for intramuscular administration by Meridian Medical (NDA 019999).

The applicant has filed a Form 3454 as required and certified that there were no financial arrangements with any clinical investigators. No clinical efficacy or safety studies were submitted in support of this application.

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 – Complete Response

- Risk Benefit Assessment

The only reason for the complete response at this time is the result of the facilities inspection which found deficiencies in controlling the exposure of the product to oxygen resulting in discoloration due to oxidation. Once corrected, the benefit of the product can be expected to outweigh the risks.

- Recommendation for Postmarketing Risk Management Activities

None.

- Recommendation for other Postmarketing Study Commitments

None.

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/s/

SHARON H HERTZ
04/01/2013