Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesiology, Addiction Medicine and Pain Medicine
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Cross-Discipline Team Leader and Division Director Summary Review

Date	See signature sheet
From	Robert Shibuya, MD Rigoberto Roca, MD
NDA # and Supplement#	202515, S-025
Applicant	Hospira
Date of Submission	June 29, 2020
PDUFA Goal Date	April 29, 2021
Proprietary Name	MORPHINE SULFATE INJECTION
Established or Proper Name	Morphine Sulfate Injection
Dosage Form	Injection
Applicant Proposed Indication/Population	Morphine Sulfate Injection is an opioid agonist indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate
Applicant Proposed Dosing Regimen	The proposed labeling is truncated for brevity in this table. Adults: 0.02 to 0.1 mg mg/kg/hr as needed. The dose should be be titrated according to the patient's response. Pediatric: Per a request from DAAP, the applicant submitted pediatric labeling. Weight-based dosing recommendations were proposed

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment
This supplement proposes to bring a presentation of morphine sulfate injection under NDA. While currently not approved, the presentation under review is currently marketed and is characterized as high-concentration [redacted] (b) (4) 50 mg/mL), high-quantity (as much as 2,500 mg/vial) formulations packaged in "Fliptop" vials. The presentation under review differs from the approved presentations in that the Fliptop vials must be diluted into normal saline or D5W and administered via continuous IV infusion. As a new dosing regimen, this supplement "triggered" the Pediatric Research Equity Act. The Applicant responded to requests for a Pediatric Research Plan and for new pediatric labeling by summarizing and referencing existing literature. Those literature are adequate to support the supplement, including new pediatric labeling.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Pain is an unpleasant, universal human experience. • Opioids are considered to be the most potent analgesic class of which morphine is the prototype moiety. • Given that this particular product requires preparation in a pharmacy, intravenous (IV) access, and an infusion metering device ("buretrol"), its use is effectively limited to the treatment of inpatients and most likely, short-term use. It can also be used in the hospice setting for severe pain.	The method of use for this potent opioid is established and is an important element of medical practice for management of acute pain and in certain hospice scenarios.
Current Treatment Options	• Severe acute pain is currently managed with multimodal analgesia to potentially include parenteral and orally administered opioids, acetaminophen, NSAIDs, long-acting local anesthesics, continuous peripheral nerve catheters, continuous epidural analgesia, and adjunctive systemic analgesics such as gabapentinoids.	The current armamentarium includes IV opioids including bolus intermittent injection and continuous IV infusion. The literature is inconclusive with regard to comparative benefits of either method of administration and both forms of IV morphine are used in practice.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• IV opioids are well established in clinical practice. • The literature cited by the applicant, describing clinical trials that used morphine via continuous IV injection generally support a conclusion that painful conditions can be successfully managed with morphine by the proposed method of use.	Morphine by IV infusion is effective.
Risk and Risk Management	• The adverse reaction profile of morphine is well established and includes respiratory depression, nausea, vomiting, pruritus, constipation, CNS depression, and addiction. • Given the method of use for this particular presentation, patients are expected to have medical supervision and the known risks of morphine are expected to be well managed. • The available data do not suggest that the high-contentration and high-quantity presentations present unacceptable risk from a medication error perspective.	The product under review does not pose any particular risks beyond the recognized hazards of opioids.

1. Background

MORPHINE SULFATE INJECTION (MSI) was an unapproved, marketed product for many years. The unapproved products fell into two conceptual categories, single-use, low-quantity (SULQ) products for bolus intravenous (IV) injection and high-concentration, high-quantity (HCHQ) products to be diluted into crystalloid and administered IV via continuous infusion. The SULQ products are either proprietary pre-filled syringes (iSecure) or a cartridge that fits into a proprietary syringe system (Carpuject). All SULQ products deliver 1 mL. Approved SULQ products contain 2, 4, 8, 10, or 15 mg of morphine per mL.The SULQ products are pictured below. Distribution data from the most recent Annual Report (October 2018 to September 2019) shows (b) (4)

(b) (4)

The HCHQ products are vials containing morphine solution, pictured below.

(b) (4)

Pursuant to CDER's Unapproved Drugs Program, Hospira, the Applicant, submitted a NDA which was approved in November 2011. In the January 2011 505(b)(2) application, Hospira requested approval of both the SULQ and HCHQ products. In 2011, only the SULQ products were approved due to GMP compliance issues at the Rocky Mount, NC facility that manufactures the HCHQ products. Conditions have improved at the Rocky Mount facility and Hospira is currently seeking approval of the "Fliptop" presentations of the HCHQ products (b) (4) 50 mg/mL (20 mL and 50 mL vials). (b) (4) this application is limited to the Fliptop vials.

Hospira initially applied for approval to market the HCHQ presentations via a CMC supplement. Upon review, the Divison determined that, due to the difference in manner of use (dilution and continuous infusion as opposed to bolus), the CMC supplement should be withdrawn and resubmitted as a Prior Approval Efficacy supplement.

The Applicant was advised to submit additional data from literature or other sources to support the continuous dosing proposed. Hospira was also told to provide information to assuage safety concerns around the high concentration (50 mg/mL) products.

2. Product Quality

What follows is largely a summary provided by the Office of Product Quality.

This OND-managed prior-approval Efficacy Supplement provides for the following cross referencing to CMC Supplement (b) (4):

- Addition of Morphine Sulfate Injection 50 mg/mL (1,000 mg/20 mL and 2,500 mg/50 mg) in single-dose Fliptop Vial presentations for the preparation of large volume parenteral solutions
- Addition of Hospira, Inc. located at Highway 301 North, Rocky Mount, NC 27801 [FEI: 1021343] as the manufacturing site of Morphine Sulfate Injection in Fliptop vials and the packaging and testing site for Morphine Sulfate Injection

The proposed Fliptop Vial configurations were included in the NDA 202515 original submission dated January 14, 2011. These Fliptop vial configurations (b) (4) were subsequently withdrawn on November 9, 2011 due to the compliance status of the Hospira Rocky Mount, NC facility at that time. All presentations have been evaluated in CMC review #1 dated 10/5/2011 and all CMC review deficiencies have been resolved except for an overall WITHHOLD recommendation from the Office of Compliance.

The PA Supplement (b) (4) was submitted on 12/30/2014 for the morphine sulfate injection USP (b) (4) 50 mg/mL, packaged in the Fliptop (b) (4) presentations (which were withdrawn from the original NDA). All CMC information have been evaluated in CMC reviews dated 4/22/2015 and 3/29/2016. See NDA 202515 (b) (4).pdf and NDA 202515 (b) (4).pdf for CMC Assessments by Drs. Pramoda Maturu and Ramesh Raghavachari.

In this Supplement, Hospira is refiling the Morphine Sulfate Injection USP (b) (4) 50 mg/mL Fliptop Vial presentations as a Prior Approval Efficacy Supplement with updated literature-based evidence for the continuous infusion dosing recommendation and supportive safety information for the higher-concentration product to address the Agency's concern. In an Amendment dated April 9, 2021, the applicant is no longer seeking to register the (b) (4) presentation through the Supplement-25. (b) (4) The marketed, unapproved product (50 mg/mL) is still in use in the United States.

The Agency has agreed to allow Hospira to cross-reference the CMC content in S (b) (4), including associated amendments, to ensure that the prior CMC review of the supplement is not disregarded. Details of the cross-referenced documents and changes made to the application are outlined in the Summary of Change document. The proposed changes that have been made since the withdrawal of the supplement (b) (4) have been evaluated in this review and the product quality microbiology review. The risk associated with the proposed changes and impact to product quality and safety is low. See CMC Assessment for Details.

The product quality microbiology recommendation for this supplement is adequate (See N202515S025MR01) by Drs. Koushik Paul and Jesse Wells.

Hospira, Inc. located at Highway 301 North, Rocky Mount, NC 27801 [FEI: 1021343] the manufacturer of morphine sulfate injection USP Fliptop Vial presentations and relevant facilities were submitted to OPMA in conjunction with this supplemental NDA and were recommended for approval

The CMC team recommended approval for this supplement.

3. Nonclinical Pharmacology/Toxicology

No new pharmacology/toxicology data were submitted. The information below was extracted essentially verbatim from the Nonclinical Pharmacology/Toxicology review for this supplement.

The drug substance impurity specifications in the supplement are the same as the previously approved configurations in this NDA and are considered acceptable. The drug product degradant specifications in this supplement are the same as in the original NDA and exceed ICH Q3B qualification specifications. At the time of initial approval, PMRs were issued for toxicology studies to qualify the proposed specifications that exceeded ICH Q3B(R2) thresholds. The PMR studies were reviewed and adequately qualified the specifications. All drug product impurity specifications in this supplement are considered acceptable. The formulation in the fliptop vials is qualitatively identical to the previously approved configurations and is considered acceptable from the pharmacology toxicology perspective.

For the initial approval of NDA 202515 in 2011, a summary of an extractable study report was submitted and the configurations, including the fliptop vials, were deemed acceptable based on the standards at that time. Because of a manufacturing issue, the fliptop vial format was withdrawn from the NDA prior to approval. A comment was sent to the Applicant in the 74-day letter stating that at the time of the original approval, the best practices for extractable and leachable studies outlined in USP <1663> and USP <1664> were not yet established. Since the proposed vial format was not previously approved, the review team would consider the need for additional data to support the new drug product presentation taking into consideration the current standards for the safety qualification of the container closure system. The Applicant was asked to provide any additional data and or justification for the safety of the container closure. The Applicant communicated to the Division that they will submit the extractable/leachable assessment in September of 2021, which is after the PDUFA deadline for this supplement. Since the individual components of the proposed container closure system of the fliptop vial are used in multiple FDA-approved aqueous intravenous products with relatively similar chemical properties to this product, it was deemed acceptable to conduct the study postmarketing. An evaluation of the container closure up to current standards for the fliptop vials will be a postmarketing requirement for this supplement.

From a nonclinical pharmacology/toxicology perspective, Supplement 025 to NDA 202515 may be approved with the following postmarketing requirement. Potential leachables from the container closure system, specifically the (b) (4) Gray rubber stopper, for the Fliptop Vial configuration of the Morphine Sulfate Injection USP product have not been fully characterized for safety. A summary of an extractable study with the (b) (4) Gray rubber stopper material was submitted and potential extractables were assessed, however, no leachable study was conducted with the Fliptop Vial configuration. The PMR will evaluate leachables from the Fliptop Vial drug product at multiple timepoints across shelf-life to inform trend analysis. Any leachables that exceed 5 mcg/day should be identified and a toxicologic risk assessment should be conducted on the maximum levels achieved to adequately address the safety of the container closure system.

The Pharmacology/Toxicology Team has recommended the following regarding a Post-Marketing Requirement.

> Conduct a leachable safety assessment of the morphine sulfate injection USP product housed in the Fliptop Vial container closure that includes the (b) (4) Gray rubber stopper. This assessment must include leachable data from long-term stability studies, taking into consideration the product expiry date, testing at least three batches at multiple timepoints to determine if any identified extractables leach into the product over time and to inform trend analysis. Submit a toxicological risk assessment for all leachables greater than 5 mcg/day based on the maximum daily dose of the drug product. Following discussion with the Applicant, the following dates have been agreed to (the gap between the draft protocol and final protocol was considered acceptable because the Applicant has concluded that new extraction studies will be necessary to adequately inform the final protocol leachable targeting strategy).

Draft Protocol Submission: 07/2021
Final Protocol Submission: 03/2022
Study Completion: 04/2024
Final Report Submission: 07/2024

4. Clinical Pharmacology

No new clinical pharmacology data were submitted. The Applicant submitted literature to support pediatric and adult clinical pharmacology labeling. Given a lack of access to the raw data from the published studies, our clinical pharmacology team did not accept the literature as a basis for labeling and the labeling will remain silent on pediatric clinical pharmacology information.

5. Clinical Microbiology

See Section 2.

6. Clinical/Statistical- Efficacy

No clinical trials were conducted to support this supplement. In lieu of clinical trial data, the Applicant conducted a literature search to support the manner of use proposed in labeling for this supplement. Eight randomized, controlled studies that included a morphine IV continuous infusion arm were identified and summarized and full-text articles were submitted. I have summarized the eight articles in Table 1, below.

Table 1: Adult clinical trials informing safety and efficacy of morphine administered by continuous IV infusion

First Author	Year	Population	N (morphine)	Comparator	Dosing Scheme (morphine)	Conclusions/comments
Abu-Halaweh	2016	Laproscopic bariatric surgery	30	Dexmeditomidine	3 mg/hr	No difference between morphine and dex on outcome of rescue use.
Briggs	1985	Gynecologic cancer surgery	Unclear (42 total)	Bolus IM morphine	0.05 mg/kg push followed by 0.05 mg/kg/hr	No difference in pain control or safety.
Cuschieri	1985	Cholecystectomy	25	Bolus IM morphine and epidural bupivicaine	1 mg/min to initial pain relief (max 25 mg) followed by "3.5 times the initial pain relieving injection of morphine over 60 h"	Epidural bupivacaine was superior to morphine for efficacy and safety
Marshall	1985	Cholecystectomy	17	Placebo with bolus morphine rescue	0.02 mg/kg/hr	Placebo group required less rescue morphine and had less nausea and vomiting than the patients who received IV infusions.
Ohqvist	1991	Open-heart surgery	27	Meperidine, ketobemidone	4 mg/hr	There were no differences among the three arms.
Oztekin	2006	Open-heart surgery	10	Fentanyl, meperidine, remifentanil, tramadol	0.1 mg/kg/hr	The treatment groups appear similar.
Rabinov	1987	Cardiac surgery	6	IV buprenorphine	0.5mg/kg/hr	Both groups met the clinical needs for analgesia. There were no differences in the safety metrics although the sample size was low.
Rutter	1990	Cholecystectomy, vagotomy or other major surgery	15	IM bolus on a schedule IM bolus prn	Same as Cuschieri	Patients treated with morphine by continuous IV infusion had better analgesia with a low total dose administered.

There is adequate information in the literature and authoritative, consensus guidance on dosing morphine injection by continuous IV infusion to support a finding of efficacy and dosing information in labeling.

7. Safety

As no clinical trials were conducted to support this supplement, the available data are limited to the literature and post-marketing safety data. See Table 1, for a summary of the pertinent literature.

The Applicant conducted a review of the post-marketing data for a reporting period of January 1, 1900 to January 31, 2020. The safety database consists of spontaneous reports, reports from health authorities, cases from the literature, clinical trials, and other sources. The Applicant indicates that topics searched included death, abuse and dependence, overdose, lack of effect, and medication error. Key findings are summarized in Table w, following.

Table 2: Summary of Applicant's Postmarketing Database Search

Metric/Safety Topic	Applicant's Finding
Estimated worldwide exposure	The total sales include that nearly nearly 270 million milligrams have been sold during the reporting period. That converts to approximately 24,615 patient-years of use.
Post-marketing safety data	1. A total of 24,182 cases were reported on 46,231 adverse events of which 7,745 were reported as serious. 2. A total of 2,600 cases were coded as death and 694 cases were related to an injectable formulation of morphine. Hospira/Pfizer reported no deaths with fliptop vials or continuous IV infusion. Most of the cases of death were derived from the literature. The most common Preferred Terms (PTs) for deaths included overdose, completed suicide, and accidental overdose. 3. Given the high concentration of morphine in this product, the Agency had asked the Applicant to thoroughly review data related to medication errors for the (b) (4) 50 mg/mL formulations in this submission. Hospira reports 675 cases reporting 794 relevant events. Most of the cases (60%+) were spontaneous reports and about the same percentage were from the US. The most common error types were accidental exposure/overdose (29.8%), medication errors not elsewhere classified (25.6%), "maladministration" (24.0%), and dosing/scheduling error (14.2%). Examples of maladministration include incorrect route, wrong technique in produce usage process, wrong product administered, and product administration error. I infer that the preceding information pertains to all formulations of morphine injection. Specific to the high concentration products, Hospira reports 10 cases and 12 events, two of which were fatal. The PTs are not informative for this subset of morphine injection. The individual events described include an incorrect infusion rate (100 mg/hr vs. 10 mg/hr), intrathecal (IT) administration, and compounding error. Two of the IT infusions also represented overdoses. 4. Drug abuse/dependence comprise 2,496 cases, 653 of which cited the injectable formulation. There were no cases involving the fliptop vials and 2 were associated with continuous infusion. PTs in this category include concepts of substance abuse, drug withdrawal, drug

	dependence, drug screen positive. Most of these cases involved polydrug abuse. 5. There were 927 cases coded as overdose of which 263 involved an injectable formulation. Again, no cases were associated with fliptop vials. The vast majority of these cases were serious and approximately half involved another drug of abuse. Some of the overdose cases were also coded as suicide attempts. 6. Lack of effect comprised approximately 1500 cases and none involved fliptop vials.

The Divisions of Pharmacovigiliance and Division of Medication Errors and Prevention were consulted and did not find any unlabeled, new postmarket safety signals associated with the presentations under review. Thus, the literature and Applicant's postmarketing safety review adequately supports the safety of morphine sulfate injection by this proposed manner of use.

7. Advisory Committee Meeting

No Advisory Committee meeting was convened for this supplement.

8. Pediatrics

The currently approved package insert (for the SULQ presentations) contains the generic language "The safety and effectiveness of Morphine Sulfate Injection in pediatric patients below the age of 18 have not been established" in Section 8.4 (Pediatric Use).
The proposed labeling for this supplement (HCHQ) represents a new dosing regimen. Thus, the Pediatric Research Equity Act (PREA) is "triggered." The initial supplement contained no initial Pediatric Study Plan (iPSP). The Applicant was notified to submit an iPSP in an information request dated August 28, 2020 with reiteration in the Filing Letter ("74-Day Letter").

The iPSP was submitted on October 8, 2020, Briefly, the Applicant proposed a "waiver" of pediatric studies. The rationale not to conduct pediatric studies is that the literature contains sufficient information to inform the safety, efficacy and pharmacokinetics (PK) in the pediatric age range. To support this argument, Hospira cited and summarized 14 articles, 13 of which were pertinent. I have summarized this literature in the Table 3, following.

Table 3: Pediatric clinical trials informing safety, efficacy, and pharmacokinetics of morphine administered by continuous IV infusion

First Author	Year	Type of Research Reported	Ages studied	Pharmacokinetic (PK) data
Hendrickson	1990	Prospective (P), Safety (S), Efficacy (E) study comparing IM bolus vs. continuous IV morphine infusion in nonventilated post-surgical patients	Mean age 6.2 years	No
Lynn	1984	Single-arm, P study of continuous IV morphine in patients s/p repair of congenital heart defects	Not stated	No

Van Dijk	2002	P, R, DB study comparing IM bolus morphine vs continuous IV morphine in patients following major abdominal/thoracic surgery	0-3 years	No
Kopecky	2004	Post-hoc analysis of a R, controlled study comparing oral morphine vs. continuous IV morphine in patients with sickle cell crisis	5-17 years	Yes
Robieux	1992	P, controlled, "before-and-after" evaluation of continuous IV morphine vs. bolus meperidine/morphine/codeine in patients with veno-occlusive sickle cell crisis	3-18 years	No
Portenoy	1986	Retrospective assessment of continuous IV opioid infusion in patients with cancer pain. 36 of 46 infusions used morphine.	1.5 to 67 years	No
Chinyanga	1984	Assessment of post-general anesthesia recovery. Following termination of general anesthesia, patients received continuous IV morphine or an inhaled anesthetic agent under mechanical ventilation.	0-5 years	Yes
Dyke	1995	Placebo-controlled study comparing continuous IV morphine and 5% dextrose in mechanically ventilated preterm infants with hyaline membrane disease	Pre-term infants	No
El Sayed	2007	Retrospective study in full-term neonates who underwent thoracic or abdominal surgery and were managed with continuous IV morphine infusions.	Full term neonates	No
Chay	1992	Single-arm PK and pharmacodynamic (PD) study of continuous IV morphine infusion	Neonates	Yes
Hartley	1993	PK of a loading dose followed by continuous IV morphine infusion	Preterm neonates	Yes
Lynn	1998	PK study to evaluate the clearance of morphine administered by IV infusion	Infants	Yes
Vandenberghe	1983	PK of IV morphine in conjunction with balanced anesthesia.	0-5 years	Yes

The PSP also referenced Berde and Sethna's 2002 review article[1] published in the NEJM. This article summarizes the basic science underlying appropriate analgesic use in the pediatric population and includes concrete dosing recommendations for several analgesic classes including opioids and morphine by oral and parenteral routes.

[1] Berde CB, Sethna NF. Analgesics for the Treatment of Pain in Children. NEJM 347(14):1094-1103.

Internal discussions with a pediatric anesthesiologist within DAAP and personnel from the Office of Pediatric Therapeutics (OPT) was obtained. There was agreement that the literature and extensive clinical experience with morphine injection administered by IV infusion were adequate, even in preterm neonates. The experts from OPT also directed me to two randomized, placebo-controlled studies of morphine via continuous IV infusion in premature neonates. One study[2] ("NOPAIN") provided preliminary data suggesting that the neonates randomized to morphine benefited although a follow-up study[3] ("NEOPAIN") did not confirm those pilot findings. A study required under the Pediatric Research Equity Act (PREA) would enroll a small number of patients and collect data on safety and pharmacokinetics. While, under current policy, the Applicant might be asked to study efficacy in patients under two years of age, for ethical reasons, an acceptable study design has not been developed. Thus, a PREA study would likely be limited to safety and PK which would not substantively contribute to our understanding of the use of this drug by this method use in the pediatric population.

This application was discussed at the Pediatric Review Committee (PeRC) on December 1, 2020. PeRC agreed with the Division's assessment that the existing literature fulfills PREA and no additional pediatric studies would be required. However, PeRC opined that pediatric labeling should be included in labeling and the Applicant was asked to submit pediatric labeling in an Advice Letter dated December 23, 2020.

Proposed pediatric labeling was submitted via the Gateway on February 22, 2021. The February 22 request consolidated advice provided on February 3 and February 10 that requested that the Applicant specify some additional information around preparation for infusion and to consolidate the different presentations into one package insert.

Proposed pediatric labeling to the Full Prescribing Information is summarized here (congruent edits were proposed to the Highlights section).

Section 1 INDICATIONS AND USAGE

The Applicant proposes to add "in adult and pediatric patients"

Reviewer Comments: My review of the literature and expert opinion from within the Division and CDER support the safety and efficacy of morphine sulfate injection by the proposed manner of use. Acceptable.

Section 2.2 DOSAGE AND ADMINISTRATION (Important Dosage and Administration Instructions)

[2] Anand KJS, McIntosh N, Lagercrantz H, Young TE, Vasa R, Barton BA Analgesia and Sedation in Preterm Neonates Who Require Ventilary Support Arch Pediatr Adolesc Med 199;153:331-8

[3] Anand KJS, Whit Hall R, Desai N, Shephard B, Bergqvist LL, Young TE, Boyle EM, Carbajal R, Bhutani VK, Moore MB, Kronsberg SS, Barton, BA. Effects of morphine analgesia in ventilated preterm neonates: primary outcomes from the NEOPAIN randomized trial. Lancet 2004;363:1673-82

The Applicant proposes to separate adult and pediatric dosing and add:

Pediatric patients (see Table 1)
Patients 1 to less than 17 years old:
The usual starting dose for intravenous infusion in patients 1 to less than 17 years old is as follows:

- <50 kg body weight: 20-30 µg/kg/hour (0.02-0.03 mg/kg/hour)
- ≥50 kg body weight: 1500 µg/hour (1.5 mg/hour)

Patients less than 1 year old, including neonates:

- Initial infusion rates in neonates range from 0.005-0.01 mg/kg/hour.
- Cardiorespiratory function should be monitored in patients less than 3 months of age. The infusion rate should be adjusted based on clinical signs of inadequate pain relief and/or increased somnolence.
- For premature infants and former premature infants with chronic lung disease and up to 5 to 6 months of age, careful monitoring for depressed hypoxic drive is required following opioid administration.

Reviewer Comments: The annotated PI indicates that the dosing recommendations for this section are from the AMA Pediatric Pain Management statement. I verified the information used from the source document. Acceptable

Section 2.3 DOSAGE AND ADMINISTRATION (Titration and Maintenance of Therapy)

The Applicant proposes to add:

Pediatric patients (see Table 1)
Patients 1 to less than 17 years old:
Recommended maintenance dose for patients 1 to less than 17 years old is as follows:

- < (b) (4) kg body weight: 10–60 µg/kg/hour (0.01-0.06 mg/kg/hour)
- ≥ kg body weight: 0.8–3 mg/hour

(b) (4)

The maintenance dosage in pediatric patients should be adjusted based on individual patient's needs to obtain an appropriate balance between effective pain management and opioid-related adverse reactions.

(b) (4)

Reviewer Comments: The annoted PI indicates that these components were derived from the AMA guideline and two peer reviewed journal articles. I note that, for the maintenance dose, Playfor et al represents a consensus guideline from the PK Paediatric Intensive Care Society. Playfor cites a weight dichotomization at 60 kg, not (b) (4) *as shown in the draft PI.*

(b) (4)

Section 8.4 USE IN SPECIFIC POPULATIONS (Pediatric Use)

The Applicant proposes to strike "The safety and effectiveness of Morphine Sulfate Injection in pediatric patients below the age of 18 have not been established."

The Applicant proposes to add:

The safety and effectiveness of morphine continuous intravenous infusion in pain management have been established in pediatric patients for all age groups.

Use of morphine continuous intravenous infusion for pain management in pediatric patients is supported by evidence from randomized controlled studies in pediatric patients (b) (4)

Cardiorespiratory function should be monitored in patients less than 3 months of age. The infusion rate should be adjusted based on clinical signs of inadequate pain relief and/or increased somnolence [see Dosage and Administration (2.2)].

For premature infants and former premature infants with chronic lung disease and up to 5 to 6 months of age, careful monitoring for depressed hypoxic drive is required following opioid administration [see Dosage and Administration (2.2)].

In the first week of a newborn's life, the elimination half-life of morphine is more than twice as long as that in older children and adults. Therefore, a decreased infusion rate should be considered for adequate analgesia [see Table 1 and Clinical Pharmacology (12.3)].

Reviewer Comments: I reviewed the literature for this earlier in this section of this review. The Applicant also cited the AMA document. This section is acceptable.

(b) (4)

9. Other Relevant Regulatory Issues

Not applicable.

10. Labeling

Prescribing Information

During this review cycle, there has been discussion between the Applicant and the Division regarding consolidation of the package inserts (for the different presentations and manner of use) for this NDA. At this time, the Division is approving a separate package insert for the fliptop vial products. The package inserts may be consolidated at some time in the future. The approved SULQ package insert (PI) is the basis for the new PI. Key sections are discussed below.

- INDICATIONS AND USAGE:
  - The Applicant is not proposing to amend the indication the critical portion of which reads, "management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate."
  - *Comment: While the approved indication is very broad, realistically this product can only be used in an inpatient setting due to the requirement for IV access and a device to accurately control continuous infusion rate ("Buretrol"). Thus, the clinical scenarios for this product are largely limited to management of acute pain (postoperative and sickle cell crisis (in the pediatric population) predominantly). It may also be used in a hospice setting in patients with IV access. Thus, an argument could be made to narrow the indication. However, the indication for this class of drugs has been largely driven by opioid-class labeling changes over the years and to narrow the indication for this product would not serve any purpose but could result in unintended consequences.*

- DOSAGE AND ADMINISTRATION:
  - This is the key change for the HCHQ drug presentations. This section will delete the irrelevant information related to the SULQ products and proposes to add the following:

    - Add for IV use only. "It is not for intrathecal or epidural use."
    - Add "…after dilution (b) (4) ."
    - Add "Do not use if color is darker than pale yellow, if it is discolored in any other way, or if it contains a precipitate."
    - Modify Initial Dosage to read, "Continuous Intravenous Infusion. (b) (4)

- Add "For opioid-naïve patients, a maximum dosing rate should not exceed 10 mg/hour"
- Add "For opioid-tolerant patients, including patients who because of their condition have a high analgesic requirement (e.g., terminal cancer pain), dosing rates as needed high as 30 mg/hour or higher may be required to manage pain."
- Add subsection 2.5 (Preparation of Solutions for Infusion) to read:

> Morphine Sulfate Injection is incompatible with admixtures of soluble barbiturates, chlorothiazide, aminophylline, heparin, meperidine, methicillin, phenytoin, sodium bicarbonate, iodide, sulfadiazine and sulfisoxazole.
>
> Single-dose Flip Top Vial
> Morphine Sulfate Injection USP, (b) (4) 1000 mg/20 mL (50 mg/mL), and 2500 mg/50 mL (50 mg/mL) single-dose vials are for the preparation of large volume parenteral solutions and are not for direct injection.
>
> Dilute Morphine Sulfate Injection in either Dextrose 5% injection or Sodium Chloride 0.9% injection to a final concentration of (b) (4) mg/mL or (b) (4) mg/mL prior to administration. Preparations in Sodium Chloride 0.9% injection are stable for 14 days at room temperature or refrigerated. Preparations in Dextrose 5% injection are stable for up to 72 hours at room temperature and for 14 days refrigerated.

Comments:

- *The explicit prohibition against use in the neuraxis is due to the presence of edetate disodium,* (b) (4) *in the formulation. The addition of this language is acceptable.*
- *The starting dose proposed falls within the range of the published literature and guidelines. Given that this product is titrated to effect the language proposed is acceptable.*
- *The maximum dose of 10 mg/hr in opioid-naïve patients and dosing rate as high as 30 mg/hr is already in the PI for a similar product (NDA 19-916 [Morphine sulfate preservative-free injection solution for IV use]*
- *The instructions for preparation are pending review by DMEPA.*

- DOSAGE FORMS AND STRENGTHS:
  - Appropriately revised to reflect the HCHQ presentations.

- WARNINGS AND PRECATIONS
  - New label proposes to add to subsection 5.12 (Risks of Seizures) "Excitation of the CNS, resulting in convulsion, may accompany high doses of morphine given intravenously."

Comment: This also appears in the PI for NDA 19-916 and is acceptable.

- DESCRIPTION, HOW SUPPLIED, and INSTRUCTIONS FOR USE
  - Appropriate changes made to reflect the HCHQ presentation (b) (4)

New pediatric labeling. Discussed as Reviewer Comments in Section 8 (Pediatrics).

11. Postmarketing Recommendations

See Section 3 for the Pharmacology/Toxicology Postmarketing Requirement.

12. Recommended Comments to the Applicant

See Sections 3 and 11 for the Approval Letter.

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/s/

ROBERT B SHIBUYA
04/29/2021 03:04:01 PM

RIGOBERTO A ROCA
04/29/2021 03:05:25 PM