CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217812Orig1s000

SUMMARY REVIEW

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	December 11, 2023
From	Timothy Jiang, MD, PhD; Clinical Reviewer Alla Bazini, MD; Associate Director for Therapeutic Review, Anesthesiology Rigoberto Roca, MD; Division Director
NDA#	217812
Applicant	Hikma Pharmaceuticals
Date of Submission	February 16, 2023
PDUFA Goal Date	December 15, 2023
Proprietary Name	Hydromorphone Hydrochloride Injection, (b) (4) 40 mg/20 mL (2 mg/mL) multiple-dose vial
Established or Proper Name	Hydromorphone hydrochloride
Dosage Form	Injection (40 mg/20 mL)
Applicant Proposed Indication	An opioid agonist indicated for the management of pain severe enough to require an opioid analgesic and for which alternate treatments are inadequate.
Applicant Proposed Dosing Regimen	Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. Reserve titration to higher doses of Hydromorphone Hydrochloride Injection for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial risks.
Regulatory Action	Approval

OND Action Package included reviews by the following:	
Medical Officer	Timothy Jiang, MD, PhD
Clinical Pharmacology Review Team	Wei Qiu, PhD.; Yun Xu, PhD
Pharmacology-Toxicology Review Team	Jessica Hoffman, PhD.; Jay Chang, PhD.;
Office of Product Quality Review Team Drug Substance Drug Product Microbiology Biopharmaceutics Review Team	Team Leader - Valerie Amspacher, PhD Katie Duncan, PhD.; Gaetan Ladouceur, PhD Mari Chelliah, PhD.; Valerie Amspacher, PhD Gouri Chattopadhyay PhD.; Paul Dexter PhD Bryan Erickson, PhD; Hansong Chen, PhD
Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis	Damon Birkemeier, Pharm D; Valerie Vaugham, PhD

1. Benefit-Risk Assessment

Acute pain is a serious clinical condition which when inadequately treated, may result in increased morbidity, prolonged hospital stays, and decreased patient satisfaction. Additionally, uncontrolled acute pain increases the risk of developing chronic pain as detailed in the Benefit-Risk Dimensions as below:

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Acute pain is commonly associated with tissue injury, inflammation, surgical procedures, childbirth, or a brief disease process • Symptoms can last hours, days, or weeks and are commonly associated with tissue injury, inflammation, a minor surgical procedure such as dental extraction, or a brief disease process • Clinical symptoms of minor aches and pains often include increased heart rate, blood pressure, and respiratory rate, shallow respiration, agitation or restlessness, facial grimaces, or splinting	Inadequate acute pain control can result in increased morbidity, prolonged hospitalization time, and decreased patient satisfaction
Current Treatment Options	• Current treatments for acute postoperative pain include opioids, acetaminophen (APAP), and NSAIDs	A combination of analgesics with different mechanisms of action and different safety profiles has the potential to provide greater analgesia than either agent alone without increasing the safety risk
Benefit	• The Applicant did not conduct any clinical studies in support of the efficacy of the study product	Applicant is relying on the Agency's previous findings of effectiveness for the listed drug, Dilaudid (NDA 019034)
Risk and Risk Management	• The Applicant did not conduct any clinical studies in support of the safety of the study product. The proposed product is currently available as a marketed unapproved product.	Applicant is relying on the Agency's previous findings of safety for the listed drug, Dilaudid (NDA 019034)

The Applicant requested a biowaiver for the proposed product in accordance with 21 CFR 320.24(b)(6). The Biopharmaceutics team concludes that the Applicant has provided an adequate scientific justification to establish a scientific bridge between the proposed drug product and Listed Drug (LD), permitting reliance on the Agency's findings of efficacy and safety of the LD, in accordance with 320.24(b)(6). See details in Section 3.

We conclude that the benefits of Hydromorphone Hydrochloride Injection, (b) (4) 40 mg/20 mL (2 mg/mL) multiple-dose vial outweigh the risks.

2. Background

This document will serve as the Cross-Discipline Team Leader and the Division Director Summary Review of NDA 217812 for the decision on regulatory action for the proposed product, Hydromorphone Hydrochloride Injection, 40 mg/20 mL.

The Applicant submitted NDA 217812 on February 16, 2023, through the 505(b)(2) marketing pathway with reliance on the Agency's previous findings of safety and effectiveness for Dilaudid (hydromorphone 1 mg/ml, and 2 mg/ml, NDA 019034). The Applicant's multiple dose vial has the same drug concentration as the referenced drug product with no change in dosage, administration methods or indication. The proposed multiple-dose vial formulation differs from the listed drug in the inclusion of (b) (4) (methylparaben and propylparaben), pH adjustors (hydrochloric acid and sodium hydroxide) and (b) (4) (edetate disodium) and exclusion of buffering agents (i.e., sodium citrate and citric acid). The proposed product is currently available as a marketed unapproved product.

The regulatory history for this application is briefly discussed as follows:

March 2023, PIND 157219 Written Response Only, the Division conveyed the following:

- 505(b)(2) regulatory pathway appears appropriate.
- "If your product is bioequivalent (BE) to Dilaudid and supports the same dosage and administration as listed for Dilaudid, then it appears reasonable that you may submit the NDA as a (b)(2) to Dilaudid and rely on safety and effectiveness of Dilaudid to support the filing."
- If a biowaiver/bio-bridge is granted for all the routes of administration, then no additional PK studies may be required to establish the scientific bridge between your proposed product and the LD.

3. Product Quality

The overall recommendation from the Office of Product Quality (OPQ) review team was for approval of the application with Summary of Rationale for Recommendation as follows:

CMC recommends approval for this application based on reviews by drug substance, drug product, process/facilities, biopharmaceutics, and microbiology.

The proposed expiry of 24 months is acceptable when stored at controlled room temperature (20°C to 25°C).

Specifically, for the drug substance, the team noted:

The drug substance in this NDA is hydromorphone hydrochloride, a well-known opioid agonist indicated for the management of pain. The CMC information for the hydromorphone hydrochloride drug substance is cross referenced to DMF (b) (4). DMF (b) (4) was reviewed by Fardokht Abulwerdi, Ph.D. on 24-Jul-2020 (Panorama) and found adequate. In this NDA, the Applicant provides brief descriptions of the general physicochemical properties of the drug substance. The submission includes adequate information on the potential impurities, including related substances, inorganic impurities, and residual solvents. The related substance impurities are adequately controlled to the ICH Q3A qualification threshold or to levels below those in the current USP monograph. There is negligible risk of the formation of (b) (4) impurities in the drug substance and no known impurities of genotoxic concern. The Applicant provides details on the tests performed upon the acceptance of the drugs substance from the DMF holder. The non-compendial analytical methods are adequately described and validated. Certificates of analysis are provided for two batches of the drug substance. These batches are within specification. The Applicant has set a retest period of (b) (4) months, which is acceptable, although the data in the DMF support a (b) (4) month retest period.

For the drug product, the team noted:

Hydromorphone hydrochloride 40 mg/20 mL (2 mg/mL) is a sterile, aqueous solution in a multi-dose vial for subcutaneous, intramuscular, and slow intravenous administration. The drug product strength is expressed in terms of hydromorphone hydrochloride salt - same as that of the listed drug product. All the excipients are of compendial grade, and their respective maximum daily exposures are considered qualified. The proposed formulation was marketed as an unapproved product since 1972. The Applicant seeks approval for this legacy unapproved product without any change to the legacy formulation's composition. The Applicant did not provide any development data for the legacy product. However, for the proposed product, the Applicant conducted additional studies, and optimized the target pH and sterilization time. The proposed specification complies with the requirement of USP <1>, ICH Q6A, and the USP monograph for Hydromorphone Hydrochloride Injection. The impurity limits meet the ICH Q3B identification and qualification thresholds. The Applicant's risk assessment for (b) (4) and elemental impurities are acceptable. The Applicant has adequately validated all the non-compendial analytical methods used for controlling the drug product quality. Furthermore, the batch data show that the Applicant can manufacture the drug product with consistent quality. The drug product is packaged in a clear, Type (b) (4) glass vial and closed with a rubber stopper and an aluminum overseal. The primary packaging components meet the appropriate USP requirements. They also have acceptable extractable and leachable profiles. The Applicant also assessed the vials for potential delamination – the risk is low. The Applicant has provided up to 18 months of long-term and 6 months accelerated stability data for three primary batches. No significant trending was noted - all batches met the stability criteria under all the tested time points.

For product microbiology, the team noted:

The finished drug product is a sterile solution supplied in a multi-dose 20 mL vial as 1 vial/carton. The drug product is [redacted] *into depyrogenated* [redacted] *glass vials. RS stoppers are d from* [redacted]

For biopharmaceutics, the team noted:

The Applicant proposes Hydromorphone Hydrochloride Injection, [redacted] */ 40 mg/20 mL (2 mg/mL). With the current submission, the Applicant seeks approval through 505(b)(2) regulatory pathway relying on the Agency's findings of efficacy and safety of the Listed Drug (LD), Dilaudid. The indication for the proposed drug is for the management of pain severe enough to require an opioid analgesic and for which alternate treatments are inadequate.*
The Applicant submitted a biowaiver request. The Applicant has provided an adequate scientific justification to establish a scientific bridge between the proposed drug product and LD, permitting reliance on the Agency's findings of efficacy and safety of the LD, in accordance with 320.24(b)(6) given the following consideration:
1) The proposed product is a clear liquid solution for intravenous, intramuscular, and subcutaneous administration and contains the same active pharmaceutical ingredient in the same concentration and dosage form as Dilaudid 2 mg/mL Injection.
2) The proposed drug product contains different excipients from those presented in the LD. The differences in formulations are not expected to affect the disposition of hydromorphone.
3) The proposed drug product and LD have comparable osmolarities and pHs. Comparative physicochemical data are provided including pH, osmolality, viscosity, and density. Although a 2-fold decrease in osmolality was observed in the proposed product compared to Dilaudid, this difference is insignificant considering plasma osmolality is approximately 300 mOsm/L. The Applicant noted that their other drug products with lower osmolality have been approved.
4) There is no drug-drug interaction between EDTA, parabens, and hydromorphone.

The biopharmaceutics team concludes:
From a Biopharmaceutics perspective, NDA-217812-ORIG-1 for Hydromorphone Hydrochloride Injection, [redacted] *40 mg/20 mL (2 mg/mL) is adequate.*

We concur with the conclusions reached by the OPQ review team, that from a product quality perspective, the application can be approved. For additional details, please refer to the integrated OPQ review by Dr. Amspacher dated November 9, 2023.

4. Nonclinical Pharmacology/Toxicology

Drs. Hoffman, Ahn, and Chang completed the nonclinical pharmacology and toxicology review of NDA 217812. In their summary of the nonclinical findings, they noted the following:

Hikma's Hydromorphone Hydrochloride Injection drug product has the same indication, dosage form, dosing regimen, and the concentration of hydromorphone hydrochloride as the listed drug, Dilaudid®, but it is formulated with different inactive ingredients and is packaged in a multiple-dose vial compared to the single-dose prefilled syringes for Dilaudid®.

The Applicant also notes that the drug product is the same as a legacy marketed unapproved IV hydromorphone hydrochloride drug product under NDC 0641-2341-41 (originally marketed by Baxter), with no changes in the drug product formulation composition.

Regarding excipients, the nonclinical team noted:

There are no novel excipients in the proposed drug product formulation. The highest and most frequent dosing regimen is for the SC and IM routes of administration and results in a total maximum daily volume of 12 mL. Based on this daily exposure, the maximum daily exposure (MDE) as well as the concentration of all the excipients are adequately covered for systemic and local safety for all three proposed routes of administration by FDA-approved products based on MDEs listed in the Inactive Ingredient Database (IID).

Regarding the container closure system, the nonclinical team noted:

Under the conditions of the leachable study, from the pharmacology/toxicology perspective, there is no leachable safety concern from the container closure components or the process contact materials. For the glass vial, all the extracted element concentrations were found to be lower than 30% of the PDEs listed in ICH Q3D for all 24 elemental impurities. For the rubber stopper, no non-volatile, volatile, and semi volatile organic compounds were detected in any of the stability samples above the AET.

Regarding Pregnancy and Lactation Labeling Rule (PLLR), the nonclinical team noted:

An acceptable updated nonclinical literature search was conducted and we agree with the Applicant that there was no new information from this review that warrants any changes to the nonclinical sections of the labeling.

We concur with the conclusions reached by the nonclinical reviewers that the application can be approved. For additional details, please refer to the review by Drs. Hoffman, Ahn, and Chang dated November 3, 2023.

5. Clinical Pharmacology

The Applicant did not conduct any clinical pharmacology or biopharmaceutics studies, and no clinical pharmacology published literature was submitted in support of this application. As previously discussed, a biowaiver was submitted and reviewed by the biopharmaceutics team. Refer to Section 3 of this review for additional information regarding the biopharmaceutics review.

The clinical pharmacology review team did not identify any issues that would prevent approval, and recommended by Drs. Qiu and Xu as follows:

The Office of Clinical Pharmacology/Division of Neuropsychiatric Pharmacology (OCP/DNP) has reviewed NDA 217812 submitted on February 16, 2023 and finds it acceptable.

The formulation of the proposed product differs from Dilaudid Injection 2 mg/mL in the inclusion of (b) (4) *(methylparaben and propylparaben), pH adjustors (hydrochloric acid and sodium hydroxide), and* (b) (4) *(edetate disodium) and exclusion of buffering agents (i.e., sodium citrate and citric acid). No clinical pharmacology study has been conducted or submitted for review. The Applicant requested a biowaiver/biobridge to waive the in vivo PK bridging study and to establish scientific bridge to Dilaudid Injection for this 505(b)(2) NDA. The review of the biowaiver/biobridge request is deferred to ONDQA/Biopharm team. Based on team discussion, Biopharm team concluded that the Applicant has provided an adequate scientific justification to establish a scientific bridge between the proposed drug product and listed drug product, permitting reliance on the Agency's findings of efficacy and safety of the listed drug product, in accordance with 21 CFR 314.24(b)(6) (see ONDQA/Biopharm review for more details). The proposed labeling is based on the approved label of Dilaudid Injection except for any differences between the products (e.g., formulations, presentation (multi-dose vials vs pre-filled syringes)).*
During the review, the following Information Request (IR) regarding hydromorphone exposure in breast milk was conveyed to the Applicant on 10/2/2023. The information requested is supposed to help inform lactation section of labeling:
"During review of NDA217812, the review team conducted search to identify literatures regarding hydromorphone exposure in breast milk to inform labeling. The attached article by Edwards et al. was identified. To ensure the pharmacokinetic information in the literature is accurate to support labeling, please contact author of the article to obtain relevant bioanalytical validation/performance information, such as precision, accuracy, stability, incurred- sample-reanalysis for quantifying the drug concentration. Also ask the author to provide raw PK data if available. Due diligence is required to acquire such information about the study. If such information could not be obtained from the author, indicate it in the response. Provide response by 10/30/23".
Because the Applicant was not able to provide response to IR by the requested date (10/30/2023) and the PUDFA goal date is 12/15/2023, there will not be adequate time to review the response. Thus, the review team decided to complete labeling based on the

current available information from the article. The Sponsor may submit a labeling supplement later if the Sponsor is able to find the requested bioanalytical validation/performance information and the information is up to standards.

We concur with the review team that the Applicant has provided sufficient clinical pharmacology information to support their application. For additional information refer to the clinical pharmacology team review dated November 16, 2023.

6. Clinical Microbiology

The proposed product is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

7. Clinical/Statistical- Efficacy

The Applicant did not conduct any clinical studies in support of the efficacy of their drug product and is relying on the Agency's previous findings of effectiveness for the listed drugs, Dilaudid (NDA 019034).

We have no efficacy concerns regarding this drug product that would preclude approval.

8. Safety

The Applicant did not conduct any clinical studies in support of the safety of the study product and is relying on the Agency's previous findings of safety for the listed drugs, Dilaudid (NDA 019034).

A comprehensive literature search was conducted to identify published information relevant to the clinical safety of Dilaudid (hydromorphone HCL) since the most recent label update on October 7, 2019. The investigation was limited to publicly available information from October 7, 2019 to September 29, 2022. A search in the FAERS public database was conducted to capture all adverse events (AEs) associated with Dilaudid that were reported in the system from 2019 through June 30, 2022. The search did not reveal new safety signal for hydromorphone.

We have no new safety concerns regarding this drug product that would preclude approval.

9. Advisory Committee Meeting

The Applicant is pursing the 505(b)(2) marketing pathway with reliance on the Agency's previous findings of safety and effectiveness for Dilaudid (hydromorphone 1 mg/ml, and 2 mg/ml, NDA 019034). The proposed multiple-dose vial formulation differs from the listed drug in the inclusion of (b) (4) pH adjustors and (b) (4), and exclusion of buffering agents. Furthermore, the proposed product is currently available as a marketed unapproved product. Because it was determined that this product does not represent a new

opioid analgesic to the US market, an advisory committee meeting was not convened for this application, as there were no issues that required presentation or discussion at an advisory committee meeting.

10. Pediatrics

Because this formulation does not represent a new route of administration, new indication, new dosage form, or new dosing regimen, and does not contain new active ingredients, pediatric studies under the Pediatric Research Equity Act (PREA) are not required.

11. Other Relevant Regulatory Issues

The Applicant did not conduct any clinical studies; therefore, financial disclosure statement was not submitted.

The Controlled Substance Staff (CSS) was consulted during review of NDA 217812, and did not identify any issues that would prevent approval with the conclusions as follows:

1. Hydromorphone Hydrochloride Injection, 40 mg/20 mL (2 mg/mL) multiple-dose vial is a sterile aqueous solution in a multi-dose vial containing 40 mg of Hydromorphone Hydrochloride in 20 mL vial for subcutaneous, intramuscular and slow intravenous administration, supplied as 1 vial per carton. The container closure is a glass vial with a rubber stopper. By contrast, Dilaudid injection is available as 0.5 mg/0.5 mL, 1 mg/mL or 2 mg/mL in single dose prefilled syringes.
2. The proposed formulation, while containing the same active ingredient (hydromorphone HCl) differs from Dilaudid in the inclusion of (b) (4) *(methylparaben and propylparaben), pH modifiers s (hydrochloric acid and sodium hydroxide),* (b) (4) *(edetate disodium) and the exclusion of buffering agents (i.e., sodium citrate and citric acid).*
3. Both the indications for use as well as the proposed dosing regimen for the proposed product will be the same as for the listed drug Dilaudid Injection.
4. Sponsor is seeking approval via a 505(b)(2) pathway with Dilaudid Injection (Hydromorphone Hydrochloride) for IV, IM, or SC use; NDA 019034) as the listed drug. Sponsor did not submit any clinical studies or preclinical studies.
5. Hydromorphone is an opioid designated as having a high potential for abuse and in Schedule II of the Controlled Substances Act (CSA). Sponsor is not pursuing any change in schedule of proposed drug product.

We concur there is no approvability issue from CSS perspective. For additional details, please refer to the CSS review by Drs. Tolliver and Calderon dated April 21, 2023.

12. Labeling

Consultation was obtained from the Division of Medication Error Prevention and Analysis

(DMEPA), who provided container label and carton labeling recommendations. The Applicant accepted and implemented all DMEPA recommendations. Refer to Drs. Birkemeier and Vaughan's Review of Revised Label and Labeling dated September 23, 2023, for details.

13. Decision/Action/Benefit:Risk Assessment

Regulatory Action
Approval.

Benefit:Risk Assessment
The benefits of Hydromorphone Hydrochloride Injection, (b) (4) 40 mg/20 mL (2 mg/mL) multiple-dose vial outweigh the potential risks.

Postmarketing Requirements
None.

14. Recommended Comments to the Applicant

None.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TIMOTHY T JIANG
12/11/2023 08:20:37 AM

ALLA T BAZINI
12/12/2023 08:26:19 PM

RIGOBERTO A ROCA
12/12/2023 10:39:53 PM