CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217812Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY
10903 NEW HAMPSHIRE AVENUE, BLDG 51, SILVER SPRING, MARYLAND 20993

Memorandum

NDA or BLA Number	NDA 217812
Link to EDR	\\Cdsesub1\evsprod\NDA217812
Submission Date	February 16, 2023
Submission Type	Standard, 505 (b)(2)
Brand Name	Hydromorphone Hydrochloride Injection, (b) (4) 40 mg/20 mL (2 mg/mL) multiple-dose vial
Generic Name	Hydromorphone Hydrochloride Injection, (b) (4) 40 mg/20 mL (2 mg/mL) multiple-dose vial
Dosage Form and Strength	Solutions; 2 mg/mL
Route of Administration	Intravenous (IV), Intramuscular (IM) or Subcutaneous (SC) injection
Proposed Indication	Management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate
Applicant	Hikma Pharmaceuticals USA
Associated IND	IND 157219
OCP Reviewer	Wei Qiu, PhD.
OCP Team Leader	Yun Xu, MD, PhD.

Recommendation:

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

On 2/16/2023, Hikma Pharmaceuticals submitted a 505(b)(2) NDA 217812 for Hydromorphone Hydrochloride (HCl) Injection solution for IV, IM, or SC use: 40 mg/20 mL (2 mg/mL) in a multiple-dose vial for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. For this

505(b)(2) NDA, the Applicant seeks approval of the proposed product by relying on the Agency's previous finding of safety and efficacy of the listed drug product, Dilaudid Injection (hydromorphone HCl) solution for IV, IM, or SC use, approved under NDA 019034. Dilaudid Injection 0.2 mg/mL, 0.5 mg/0.5 mL, 1 mg/mL and 2 mg/mL are available in single-dose prefilled syringes. Dilaudid Injection is an opioid agonist indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatment are inadequate. Hikma's proposed drug product contains the same active pharmaceutical ingredient in the same concentration and dosage form as Dilaudid Injection 2 mg/mL. The Applicant proposed the same indication and dosage regimen as Dilaudid Injection.

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.

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/

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