CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217812Orig1s000

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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PLLR Labeling Memorandum

Date: 11/15/23 **Date consulted:** 3/21/23

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To: Cooma Asonye, PharmD, MPH, Regulatory Project Manager (RPM)
Division of Anesthesia, Addiction Medicine, and Pain Medicine (DAAP)

Drug: Hydromorphone Hydrochloride Injection [New Drug Application (NDA) via 505(b)(2) regulatory pathway]

NDA: 217812

Applicant: Hikma Pharmaceuticals

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Recommendations

Indication: Proposed indication is for the management of pain severe enough to require an opioid analgesic and for which alternate treatments are inadequate.

Materials Reviewed:

- DPMH Immediate Release (IR) Opioids review. Miriam Dinatale DO, 8/3/2015. DARRTS Reference ID # 3800797[1].
- NDA 217812, submitted 2/16/23, SD#1, eCTD Sequence #0001.

[1] DPMH Immediate Release (IR) Opioids review. Miriam Dinatale DO, 8/3/2015. Darrts Reference ID # 3800797.

- Divisional Information Request (IR) for PLLR supporting data sent 4/13/23.
- PLLR supporting data submission received on 5/10/23, SD#2, eCTD Sequence #0002.

Consult Question:

DAAP requests DPMH consult to help with the clinical sections of the label re pregnancy and lactation.

INTRODUCTION AND BACKGROUND

- On 2/16/23, the applicant, Hikma Pharmaceuticals submitted NDA 217812, a new 505(b) (2) NDA for Hydromorphone Hydrochloride Injection. The listed drug relied upon (LD) product is Dilaudid, NDA 019034, approved January 1984.
- On 3/21/23, DAAP consulted DPMH to provide input for appropriate content and format of the pregnancy and lactation subsections of labeling.
- On 4/13/23, an information request (IR) for a review and summary of the available published literature regarding hydromorphone use in pregnant and lactating women was sent to the applicant. A response was received on 5/10/23.

Hydromorphone Drug Characteristics[2]

Drug Class	Opioid agonist
Mechanism of Action	Hydromorphone is a full opioid agonist and is relatively selective for the mu-opioid receptor, although it can bind to other opioid receptors at higher doses.
Dose and Administration	40 mg/20 mL (2 mg/mL) multiple-dose vial. - Intramuscular or Subcutaneous Use: The usual starting dose is 1 mg to 2 mg every 2 to 3 hours as necessary. - Intravenous Use: The usual starting dose is 0.2 mg to 1 mg every 2 to 3 hours. The injection should be given slowly, over at least 2 to 3 minutes.
Molecular Weight	321.80 Daltons
Protein Binding	8-19%
Terminal Elimination Half-Life	2.3 hours after an IV dose

Current State of Labeling for the LD Dilaudid

- The most recently approved labeling for Dilaudid is in Physicians Labeling Rule (PLR) format, complies with PLLR regulations and is dated January 2020.
- "Boxed Warnings" include "Life-Threatening Respiratory Depression" and "Neonatal Opioid Withdrawal Syndrome"
- "Warnings and Precautions" include
    - Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

[2] Working label for NDA 217812, 10/25/23

- Adrenal Insufficiency
- Severe Hypotension
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness
- Sulfite Sensitivity

- Under Subsection 8.1 Pregnancy, the labeling states

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (5.3)]*. There are no available data with DILAUDID injection in pregnant women to inform a drug-associated risk for major birth defects and miscarriage.

In animal reproduction studies, reduced postnatal survival of pups, and decreased body weight were noted following oral treatment of pregnant rats with hydromorphone during gestation and through lactation at doses 0.8 times the human daily dose of 24 mg/day (HDD), respectively. In published studies, neural tube defects were noted following subcutaneous injection of hydromorphone to pregnant hamsters at doses 6.4 times the HDD and soft tissue and skeletal abnormalities were noted following subcutaneous continuous infusion of 3 times the HDD to pregnant mice. No malformations were noted at 4 or 40.5 times the HDD in pregnant rats or rabbits, respectively [*see Data*]. Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.3)]*.

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be

available for reversal of opioid-induced respiratory depression in the neonate. DILAUDID INJECTION is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including DILAUDID INJECTION, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data

Animal Data
Pregnant rats were treated with hydromorphone hydrochloride from Gestation Day 6 to 17 via oral gavage doses of 1, 5, or 10 mg/kg/day (0.4, 2, or 4 times the HDD of 24 mg based on body surface area, respectively). Maternal toxicity was noted in all treatment groups (reduced food consumption and body weights in the two highest dose groups). There was no evidence of malformations or embryotoxicity reported.

Pregnant rabbits were treated with hydromorphone hydrochloride from Gestation Day 7 to 19 via oral gavage doses of 10, 25, or 50 mg/kg/day (8.1, 20.3, or 40.5 times the HDD of 24 mg based on body surface area, respectively). Maternal toxicity was noted in the two highest dose groups (reduced food consumption and body weights). There was no evidence of malformations or embryotoxicity reported.

In a published study, neural tube defects (exencephaly and cranioschisis) were noted following subcutaneous administration of hydromorphone hydrochloride (19 to 258 mg/kg) on Gestation Day 8 to pregnant hamsters (6.4 to 87.2 times the HDD of 24 mg/day based on body surface area). The findings cannot be clearly attributed to maternal toxicity. No neural tube defects were noted at 14 mg/kg (4.7 times the human daily dose of 24 mg/day).

In a published study, CF-1 mice were treated subcutaneously with continuous infusion of 7.5, 15, or 30 mg/kg/day hydromorphone hydrochloride (1.5, 3, or 6.1 times the human daily dose of 24 mg based on body surface area) via implanted osmotic pumps during organogenesis (Gestation Days 7 to 10). Soft tissue malformations (cryptorchidism, cleft palate, malformed ventricles and retina), and skeletal variations (split supraoccipital, checkerboard and split sternebrae, delayed ossification of the paws and ectopic ossification sites) were observed at doses 3 times the human dose of 24 mg/day based on body surface area. The findings cannot be clearly attributed to maternal toxicity.

Increased pup mortality and decreased pup body weights were noted at 0.8 and 2 times the human daily dose of 24 mg in a study in which pregnant rats were treated with hydromorphone hydrochloride from Gestation Day 7 to Lactation Day 20 via oral gavage doses of 0, 0.5, 2, or 5 mg/kg/day (0.2, 0.8, or 2 times the HDD of 24 mg based on body surface area respectively). Maternal toxicity (decreased food consumption and body weight gain) was also noted at the two highest doses tested.

- Under Subsection 8.2 Lactation, the labeling states

  Risk Summary

  Low levels of opioid analgesics have been detected in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DILAUDID INJECTION and any potential adverse effects on the breastfed infant from DILAUDID INJECTION or from the underlying maternal condition.

  Clinical Considerations

  Monitor infants exposed to DILAUDID INJECTION through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of hydromorphone is stopped, or when breast-feeding is stopped.

- Under Subsection 8.3 Females and Males of Reproductive Potential, the labeling states

  Infertility

  Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6), Clinical Pharmacology (12.2), Nonclinical Toxicology (13.1)]*.

REVIEW

Pregnancy

Opioids and Pregnancy

Opioid medications may be needed during pregnancy to manage severe pain associated with many conditions, including both acute and chronic medical conditions and surgical procedures. [3] The prevalence of opioid abuse or dependence during pregnancy in the US increased from 0.17% (1998) to 0.39% (2011)[3]. Recent studies indicate that 14 to 22% of pregnant women in the United States receive an opioid prescription during their pregnancy.[4]

[3] PMHS-MHT Review- Xartemis XR (NDA 204031). Leyla Sahin, MD. 10/28/2013.
[3] Maeda, Ayumi. Opioid Abuse and Dependence during Pregnancy: Temporal Trends and Obstetrical Outcomes. 2014. Anesthesiology. 121(6): 1158-65.
[4] Volkow, Nora. Opioids in Pregnancy. BMJ. 2016; 352.

Nonclinical Experience

In animal reproduction studies, reduced postnatal survival of pups, and decreased body weight were noted following oral treatment of pregnant rats with hydromorphone during gestation and through lactation at doses 0.8 times the human daily dose of 24 mg/day (HDD), respectively. In published studies, neural tube defects were noted following subcutaneous injection of hydromorphone to pregnant hamsters at doses 6.4 times the HDD and soft tissue and skeletal abnormalities were noted following subcutaneous continuous infusion of 3 times the HDD to pregnant mice. No malformations were noted following oral doses 4 or 40.5 times the HDD during the period of organogenesis to pregnant rats or rabbits, respectively.

Applicant Review of Published Literature Regarding Hydromorphone HCL Use during Pregnancy

The Applicant completed a review of published literature regarding hydromorphone use in pregnant and lactating women and the effects of hydromorphone on male and female fertility from 01/1/15 to April 2023. A total of 233 unique publications were identified. If considered potentially relevant, the abstract was reviewed. A total of 52 abstracts were reviewed and 29 abstracts were adjudicated as possibly or likely relevant. Of these full articles that were reviewed 21 were considered relevant to pregnancy. See Attachment A for a tabular summary of these publications.

Reviewer's Comments

There were no new safety concerns or signals identified in the publications identified by the applicant.

DPMH Review of Literature Regarding Hydromorphone HCL Use during Pregnancy

On 8/22/23, DPMH conducted a search of published literature in PubMed using the search terms "hydromorphone and pregnancy" "Hydromorphone and pregnancy and birth defects," "Hydromorphone and pregnancy and congenital malformations," "Hydromorphone and pregnancy and stillbirth," "Hydromorphone AND teratogenicity" and "Hydromorphone AND prematurity", "Hydromorphone AND low birth weight" and "Hydromorphone and pregnancy and miscarriage" covering the time-period 1/1/15 to the present. No reports of adequate and well-controlled studies of Hydromorphone use in pregnant women were identified beyond what the applicant provided. No additional publications were identified beyond those cited by the applicant and included in the Table in Attachment A.

Opioid Analgesic Drug Products' Class Labeling

In an FDA Drug Safety Communication issued on 1/9/15, the Agency reviewed published studies that reported on the potential risks of three types of pain medicine, including prescription non-steroidal anti-inflammatory drugs, acetaminophen and opioids, used during pregnancy. The Agency reviewed data related to opioid use (oxycodone, hydrocodone, hydromorphone, morphine and codeine) during pregnancy and evaluated the risk of birth defects of the brain, spine or spinal cord in infants born to women who took these products during the first trimester of pregnancy. The Agency found that all of the studies reviewed have limitations in their designs; therefore, it is not

possible to draw any conclusions regarding the risks of malformations following exposure to opioids during pregnancy. On 3/22/16, the FDA issued a safety labeling change (SLC) notification that updated the pregnancy, lactation and females and males of reproduction sections of opioid labeling.

Reviewer's Comments
The division noted during labeling meetings that some minor revisions to the class labeling for opioids was in draft form and would be incorporated into the labeling for this product. This included "If opioid use is required for an extended period of time in a pregnant woman" to replace "Prolonged use of Hydromorphone Hydrochloride Injection during pregnancy". DPMH agrees with this revision.

Lactation

Applicant Summary Regarding Hydromorphone Use during Lactation
The Applicant completed a review of published literature using PubMed regarding hydromorphone use in lactating women. Four publications regarding use of opiates in general and hydromorphone in particular during lactation were identified. See Attachment A for a tabular summary of these publications by Patricelli, Schultz and LactMed. An earlier publication by Edwards[5] which contains pharmacokinetic data is being considered by the Clinical Pharmacology team for inclusion in Subsection 8.2 of labeling is summarized below.

- Edwards et al. (2003)- A pharmacokinetic study that collected breastmilk samples in 8 lactating women after a single 2-mg intranasal dose of hydromorphone reported a milk/plasma (M/P) ratio of 2.56, peak milk levels occurred 2 hours after the dose, and half-life of elimination from milk was 10.5 hours. Calculated relative infant dose (adjusted for infant and maternal body weight) was 0.67%.

DPMH Review of Literature Regarding Hydromorphone Use during Lactation
On 8/22/23, DPMH conducted a search of Hale's *Medications and Mother's Milk*[6] , the Drugs and Lactation Database (LactMed),[7] and of published literature in PubMed using the search terms "hydromorphone AND lactation" and "hydromorphone AND breastfeeding" covering the time-period 1/1/15 to the present. No additional publications were identified beyond those cited by the applicant and included in the Table in Attachment A.

[5]Edwards JE et al. Hydromorphone Transfer into Breast Milk After Intranasal Administration. Pharmacotherapy. 2003;23 (2):153-158.
[6] Hale, Thomas. Medications and Mothers' Milk. Amarillo, Texas Hale Publishing, Accessed on-line on 10/25/23.
[7] http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

Hale[6] summarizes both the Edwards[5] publication and the case report by Schultz[8] included in the Table in Attachment A of this review.

Reviewer's Comments
The publication by Edwards concerning 8 lactating women treated with a single dose of intranasal hydromorphone was considered for inclusion in labeling under Subsection 8.2 by the Clinical Pharmacology team. An information request (IR) for more detailed information was sent to the applicant asking for a response by 10/30/23. The applicant subsequently requested more time to obtain the details of the Edwards publication with a postponed due date for the IR of 11/30/23. After discussion with the division, it was decided to proceed with labeling for Subsection 8.2 based on what is currently available, in order to have labeling ready for the PDUFA date. When the IR response is received, if the data is such that the Clinical Pharmacology team recommends revising Subsection 8.2 language, this can be done through a labeling supplement.

LactMed[7] in the "Summary of Use during Lactation" notes:

> Limited data indicate that hydromorphone is excreted into breastmilk in small amounts, but large maternal dosages have caused neonatal central nervous system depression. In general, Maternal use of oral narcotics during breastfeeding can cause infant drowsiness, and severe central nervous system depression. Hydromorphone use should be limited in nursing mothers.[9] Newborn infants seem to be particularly sensitive to the effects of even small dosages of narcotic analgesics. Once the mother's milk comes in, it is best to provide pain control with a nonnarcotic analgesic and limit maternal intake of hydromorphone to 2 to 3 days at a low dosage with close infant monitoring. If the baby shows signs of increased sleepiness (more than usual), difficulty breastfeeding, breathing difficulties, or limpness, a physician should be contacted immediately.

Females and Males of Reproductive Potential

Applicant Review of Literature Regarding Hydromorphone and its Effect on Fertility
No publications relevant to the topic of hydromorphone and its effects on fertility were identified by the Applicant.

DPMH Review of Literature Regarding Hydromorphone and its Effect on Fertility
DPMH conducted a search of published literature in PubMed using the search terms "hydromorphone AND fertility" and "hydromorphone AND infertility" covering 1/1/15 to the present. No relevant publications were identified.

[8] Schultz ML et al. A Case of Toxic Breast-feeding? Pediatric Emerg Care.2017 Jan.35(1):e9-e10.
[9] Lamvu G, Feranec J, Blanton E. Perioperative pain management: An update for obstetrician-gynecologists. Am J Obstet Gynecol. 2018; 218:193–9.

DISCUSSION/CONCLUSIONS

Pregnancy

The cumulative data on opioid exposure during pregnancy (including hydromorphone exposure) and the association with congenital malformations is very limited. During the 2015 DPMH review[1], the Agency found that all of the studies reviewed have limitations in their designs; therefore, it is not possible to draw any new conclusions regarding the risks of malformations following exposure to opioids during pregnancy.[10] Adverse reactions such as Neonatal Opioid Withdrawal syndrome (NOWS) and the effects of opioid use during labor and delivery will be included in labeling for hydromorphone. No new information was found in the updated literature review so no revisions to the class language for Subsection 8.1 is needed.

No pregnancy PMR is needed since there is no new safety information relative to the hydromorphone.

Lactation

Immediate-release (IR) opioids, including hydromorphone, may be needed by the mother for treatment of postpartum pain from cesarean section and for other acute medical conditions. According to LactMed, oral opioid use should be limited to a few days and a non-opioid analgesic should be used once the mother's milk comes in. Therefore, the Risk Summary will contain the following risk and benefit statement:

> The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for hydromorphone and any potential adverse effects on the breastfed infant from hydromorphone or from the underlying maternal condition.

However, given the potential risk that opioid use in the mother can cause sedation and respiratory depression in a breastfeeding infant, the Clinical Considerations heading under subsection 8.2 Lactation should state the following:

> Infants exposed to hydromorphone through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

No lactation PMR is needed since there is no new safety information relative to hydromorphone.

Females and Males of Reproductive Potential

Based on conclusions reached during Agency discussions, the immediate and extended-release opioid labelings were updated to include information about the potential for

[10] FDA Drug Safety Communication: FDA has reviewed possible risks of pain medicine use during pregnancy. January 9, 2015. http://www.fda.gov/Drugs/DrugSafety/ucm429117.htm

chronic opioid use to influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency. Subsection 8.3, Females and Males of Reproductive Potential, of opioid labeling now includes the following statement:

> Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible (b) (4)

RECOMMENDATIONS

DPMH revised the Highlights, and subsections 5.3, 8.1, 8.2, 8.3 and section 17 of hydromorphone labeling for compliance with the PLLR (see below). DPMH discussed labeling recommendations with DAAP on 9/27/23 and again on 10/12/23. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Hydromorphone Hydrochloride Pregnancy and Lactation Labeling

(b) (4)

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Attachment A Table 1: Tabulated Summaries of Relevant Clinical Publications for Hydromorphone Use in Pregnancy and Lactation[11]

[11] Publications by Patricelli, LactMed and Schultz include reference to lactational exposure.

Author/Year	Type of Study	Number Exposed/Unexposed	Endpoints/Outcomes/Point Estimates	P-value/Confidence Interval (CI)
Patricelli CJ, 2023	Case Report	n = 1 32-year-old woman (38 + 6 days gestational week) for CS **Hydromorphone** (IV): starting dose 20 mg, and titration to 120 mg TID.	Delivery complications: postpartum hemorrhage requiring intrauterine balloon tamponade, blood transfusion, and anesthesia support for IV access At discharge, infant had no clinically relevant apneas, bradycardias, desaturations, signs of respiratory depression, or excessive sedation.	NA
Patricelli CJ, 2023	Case Series	n = 13 total (n = 8 pregnant; n = 3 in labor; n = 2 postpartum) **Hydromorphone** (IV), 30-520 mg max daily doses	Average length of NICU stay (11.5 d; n = 11) Morphine (PO) for NOWS (n = 13, 21 days avg) Uncomplicated deliveries, infant APGAR > 7 (1 and 5 min), and no significant postpartum obstetrical complications (n = 6) Hemorrhage or hypertension, maternal seizure in labor, infant APGAR < 6 (1 and 5 min), and infant resuscitation (n=7)	NA
Brogly SB, 2023	Retrospective, cohort study	n = 15,724 Pregnancies exposed to first trimester opioid analgesics (beneficiary cohort) n = 11,903 Pregnancies exposed to first trimester opioid analgesics (population-based cohort)	Risk ratios between first trimester exposure and congenital abnormalities (CA): (1) RR in beneficiary cohort > population-based cohort for any CA with **hydromorphone** (2) RR in beneficiary cohort > population-based cohort for major CA with **hydromorphone**	(1) RR = 2.34, 95% CI: 1.65, 3.30 (2) RR = 2.74, 95% CI: 1.91, 3.94 (3) RR = 12.86, 95% CI: 8.67, 19.10

Author/Year	Type of Study	Number Exposed/Unexposed	Endpoints/Outcomes/Point Estimates	P-value/Confidence Interval (CI)
			RR in beneficiary cohort > population-based cohort for musculoskeletal anomalies with **hydromorphone**	
Zhang Y, 2022	Prospective, randomized, cohort study	n = 90 Patients receiving **hydromorphone** (IV, PCIA, 10 mg) 24 h post-CS n = 45 Butorphanol after PCIA n = 45 Saline after PCIA	VAS: (1) Butorphanol < saline at 3 and 4 hours post-PCIA No significant difference in the adverse effects or the birth weight and APGAR score between groups.	(1) $p < 0.05$
Drugs and Lactation Database (LactMed®), 2022	Summary	NA	Advises use of **hydromorphone** should be limited in breastfeeding mothers to a low dosage for 2 to 3 days. If the baby displays symptoms such as excessive sleepiness, difficulty breastfeeding, breathing problems, or limpness, medical assistance should be sought without delayed. Suggests that an appropriate dose for infants is 10 µg/kg parenterally or 30 µg/kg orally every 4 hours as needed without providing a reference. However, the recommended dosage in infant is not indicated in the prosed label.	NA
Esposito DB, 2022	Retrospective, Cohort study	n = 48,202 total Neonates exposed to opiates during pregnancy n = 90 Neonates exposed to **hydromorphone**	(1) Increased RR of NOWs in hydromorphone group (2) Increased RR of NOWs with strong agonists (i.e. hydromorphone) compared to weak agonists	(1) RR = 2.03; 95% CI 1.09-3.78 (2) RR = 1.97; 95% CI 1.78-2.17 (3) RR = 1.33; 95% CI 1.12-1.56

Author/Year	Type of Study	Number Exposed/Unexposed	Endpoints/Outcomes/Point Estimates	P-value/Confidence Interval (CI)
			(3) Longer half-life opioids associated with increased RR of NOWS compared to shorter half-life opioids	
Herbert et al, 2022	Retrospective, Cohort study	n = 278 **Hydromorphone** after CS n = 41 **Hydromorphone** (0.6 mg at 2 h) n = 109 **Hydromorphone** (1.0 mg at 24 h) n = 128 **Hydromorphone** (1.2 mg at 48 h)	No significant differences between the two protocols that both included **hydromorphone** use in: (1) Gestational age (2) Birth weights (3) CS delivery priority There is no discussion of hydromorphone safety or effect on newborn or lactation potential.	(1) p = 0.48 (2) p = 0.89 (3) p = 0.42
Zhao JP, 2021	Retrospective, Cohort study	n = 20,291 Pregnancies with opioid exposure	**Hydromorphone** exposure (11% overall) (1998-2015) Increase (8.4-fold) in **hydromorphone** prescriptions during pregnancy (2.92% in 1998, 19.49% in 2015)	NA
Griffiths S, 2021	Case report	n = 1 39 yr old pregnant woman with OUD, multiple admittance to hospital (gestational week 7-32) Fentanyl: up to 1g/day IV throughout pregnancy Methadone: (60 mg/day oral) throughout pregnancy Methadone following delivery: 135 mg daily	Infant delivered successfully APGAR score of 6 (1 min) APGAR score of 9 (5 min) Patient successfully reduced fentanyl (IV) use during hospitalization.	NA

Author/Year	Type of Study	Number Exposed/Unexposed	Endpoints/Outcomes/Point Estimates	P-value/Confidence Interval (CI)
		Hydromorphone (IM/IV) at 32 weeks gestation: maximum of 90 mg IM/IV BID **Hydromorphone** (IM/IV) following delivery: 75 mg IV/IM BID Morphine sulfate: 600 mg oral (after delivery)		
Mother To Baby Fact Sheet, 2021	Summary	NA	There are no differences on the factsheet's information compared to the prosed label regarding use of hydromorphone in pregnancy, lactation, and fertility.	NA
Wu Z, 2021	Randomized controlled parallel-group trial	n = 410 Pregnant women receiving intravenous **hydromorphone** (0.04 mg/mL) n = 410 Tramadol (4 mg/mL) n = 410 Ropivacaine (1.5 mg/mL)	Reported AEs were mostly mild; no woman or infant discontinued treatment. (1) Incidence of nausea and vomiting, pruritus, and headache were not significantly different among groups (2) Dizziness was not significantly different between tramadol and hydromorphone group No patients in hydromorphone group reported hypoesthesia. No cases of abnormal sleepiness, difficulty breastfeeding, or breathing problems for infants reported.	(1) p = 0.072, p = 0.803, and p = 0.803 (2) 4/410 (4%), p = 0.162, 95% CI 0.13–1.44,
Stanislaus MA, 2020	Case report	n = 1 Patient with OUD received **hydromorphone** epidural (140 µg/h,	Compared to previous delivery (no hydromorphone), the **hydromorphone**-based treatment plan:	NA

Author/Year	Type of Study	Number Exposed/Unexposed	Endpoints/Outcomes/Point Estimates	P-value/Confidence Interval (CI)
		40 h, PCA 20 µg, 30 min lockout) amounting to 3.36 mg after 24 h Comparisons made to patient's previous CD that did not include hydromorphone-based treatment plan	• Reduced average daily oral opioid consumption by 97% • Reduced self-reported pain score (from 8 to 5) • Shortened length of hospitalization • Improved ability to ambulate • Improved overall satisfaction with CD Patient did not experience nausea, pruritus, respiratory depression, or somnolence	
Puhto T, 2020	Pilot study	n = 7 healthy parturients, single epidural dose of **hydromorphone** n = 1 (1.5 mg), n = 2 (0.75 mg), n = 4 (0.5 mg) Additional levobupivacaine as requested	Hydromorphone dose decreased from 1.5 mg (n = 1) to 0.5 mg due to prolonged nausea and vomiting. Common adverse advents: • Nausea (n = 5) • Vomiting (n = 3) • Pruritus (n = 3) • Hypotension (n = 1) No respiratory suppression observed Half-life = 162 min C_{max} = 0.97-1.58 µg/L Fetal/maternal hydromorphone ratios were less than unity in one case (0.8 to 1.1 range) All but one newborn NACS ≥ 35 One newborn had NACS of 30 at 180 min, but recovery was uneventful	NA

Author/Year	Type of Study	Number Exposed/Unexposed	Endpoints/Outcomes/Point Estimates	P-value/Confidence Interval (CI)
Huang CY, 2020	Randomized, controlled, comparative trial	n = 114 total Parturients with elective CS n = 38 (LN) **Hydromorphone** (0.05 mg/mL) + nalbuphine (0.5 mg/mL) n = 38 (MN) **Hydromorphone** (0.05 mg/mL) + nalbuphine (0.75 mg/mL) N = 38 (HN) **Hydromorphone** (0.05 mg/mL) + nalbuphine (0.9 mg/mL)	<u>VAS scores:</u> (1) LN + MN > HN for uterine cramping at rest and after breastfeeding (2) LN > MN + HN when oxytocin was infused post-CS Day 3 (3) No significant differences between groups for incisional pain <u>PCA bolus demands and cumulative PCA dose:</u> (4) LN > MN = HN during first 48 hours post-CS <u>Ramsay sedation scores:</u> (5) HN > MN at 8 and 12 h post-CS (6) HN > LN at 4, 8, 12, and 24 h post-CS <u>Urinary retention:</u> (7) HNC > MN + LN No significant differences in 5-min APGAR scores (all groups n = 0) No significant differences in incidence of vomiting among three groups (LN = 1, 2.6%; MN = 0, 0; HN = 2, 5.6%)	(1) $p < 0.01$ (2) $p < 0.05$ (3) $p > 0.05$ $p < 0.05$ (compared to MN), $p < 0.01$ (compared to HN) (4) $p < 0.01$ (5) All p's < 0.05 (6) All p's < 0.05 (7) $p < 0.05$
Duan G, 2019	Prospective, cohort study	n = 168 Women undergoing CS with post-operative PCA	(1) RR inadequate analgesia on incision pain: multiparas > primiparas (2) Incidence of pain 4 w post-CS: primiparas > multiparas	(1) $p = 0.001$ (2) $p = 0.025$ (3) $p = 0.011$ (4) $p = 0.683$

Author/Year	Type of Study	Number Exposed/Unexposed	Endpoints/Outcomes/Point Estimates	P-value/Confidence Interval (CI)
		Hydromorphone (0.2 mg) + flurbiprofen (4 mg/kg, IV) n = 67, primiparas n = 101, multiparas	Incidence did not vary between groups: (3) Adverse events (4) Nausea (P: n = 3, R: n = 4) (5) Pruritus (P: n = 2, R: n = 3) Significant bleeding (> 500 mL) (P: n = 5, R: n = 6)	(5) p = 0.645 *(6)* p = 0.696
Choi SK, 2019	Observational Study	n = 3,428 total Pregnant women n = 103 **Hydromorphone**	**Hydromorphone** ranked 10th out of 20 most commonly reported individual drug causing ADRs **Hydromorphone**-associated ADRs among pregnant women: (1) Age 15-24 (2) Age 25-34 (3) Age 35-49 **Hydromorphone** was not reported to cause serious ADRs	(1) n = 4 (total 189) – 2.12% (2) n = 59 (total 3,543) – 1.67% (3) n = 40 (total 1,919 – 2.09%)
Yang M, 2019	Randomized, controlled	n = 80 Term laboring women aged 21-45 years who underwent elective CS under epidural anesthesia: n = 20 (H0) Unexposed n = 20 (H1) **Hydromorphone**, 0.2 mg n = 20 (H2) **Hydromorphone**, 0.4 mg n = 20 (H3) **Hydromorphone**, 0.6 mg	VAPS and the additional sulfentanil requirement: (1) H2 < H0 at 4 and 6 h post-CS (2) H3 < H0 at 4, 6, 12, and 45 h post CS No significant difference in incidence of nausea, vomiting, pruritus, and in antiemetics received at 24 h post-CS between groups 1/20 patients in H2 and 4/20 patients in H3 experience pruritus, but all cases were mild and nature and did not require treatment	(1) p < 0.05 (2) p < 0.05

Author/Year	Type of Study	Number Exposed/Unexposed	Endpoints/Outcomes/Point Estimates	P-value/Confidence Interval (CI)
			No reported episodes of significant respiratory depression	
Schultz ML, 2019	Case Report	n = 2 Mother (40 y): **hydromorphone** (4 mg, PO, q4h) during and after CS Infant: **hydromorphone** in breastmilk	Infant experienced decreased urine output, lethargy, reduced oral intake, intermittent bradycardia, respiratory arrest/apnea. Treatment with 3 doses of 0.36 naloxone resolved the apnea, and remained stable in the PICU with all subsequent testing negative	NA
Duan G, 2018	Prospective, 1:1 parallel, randomized, controlled and double-blind	n = 106 Patients receiving secondary CS under spinal anesthesia receiving PCIA n = 53 Tramadol (4 mg/kg) + flurbiprofen (4 mg/kg) n = 53 **Hydromorphone** (0.04 mg/kg) + flurbiprofen (4 mg/kg)	<u>Visceral pain:</u> (1) Tramadol > **hydromorphone** (4 h) (2) Tramadol > **hydromorphone** (8 h) <u>Anxiety:</u> (3) Tramadol < **hydromorphone** <u>Depression:</u> (4) Tramadol < **hydromorphone** <u>Early walking time:</u> (5) Tramadol < **hydromorphone** <u>Length of hospital stay:</u> (6) Tramadol < **hydromorphone** <u>Post-op nausea and vomiting:</u> (7) Tramadol (4/52, 7.7%) = **hydromorphone** (6/51, 11/8%) No significant difference in mean arterial pressure, heart rate, respiratory rate, and Ramsay scale between groups. No respiratory depression, pruritus, excessive sedation or agitation or other intraoperative and postoperative complications noted.	(1) p = 0.011 (2) p = 0.028 (3) p = 0.033 (4) p = 0.023 (5) p = 0.016 (6) p = 0.008 (7) p = 0.485

Author/Year	Type of Study	Number Exposed/Unexposed	Endpoints/Outcomes/Point Estimates	P-value/Confidence Interval (CI)
O'Reilly-Shah V, 2018	Prospective Dixon's up-and-down sequential allocation study	n= 20 **Hydromorphone** (12 µg, adjusted by 2 µg based on previous patient's response)	9/20 patients achieved effective pain management 1/20 patients experienced nausea and pruritus Median time of pain effectiveness = 24 min (14 -29 min range) ED50: 10.9 µg No other patients experienced side effects. One baby had a one-minute APGAR score < 7 and all babies had five-minute APGAR scores ≥ 8. None required intubation or ventilation greater than five minutes.	ED50: 95% CI 5.6-16.2 µg
Lu YY, 2017[a]	Prospective with open and randomized components	n = 140 total Nulliparous women selected for delivery with epidural anesthesia n = 50 **Hydromorphone** (20 µg/mL) + ropivacaine (0.12%) n = 30 (H1) **Hydromorphone** (15 µg/mL) + ropivacaine (0.08%) n = 30 (H2) **Hydromorphone** (15 µg/mL) + ropivacaine (0.10%) n = 30 (H3) **Hydromorphone** (15 µg/mL) + ropivacaine (0.12%)	ED50 = 10.49 µg/ml ED95 = 15.15 µg/ml Onset time of anesthesia: (1) H1 (14.23 ± 3.82) > H2 (11.32 ± 2.16) and H3 (10.83 ± 2.56) VAS: (2) H1 > H2 and H3 (3) H1 > H3 (at withdrawal) (4) H1 > H2 and H3 (at 4th, 5th, and 6th contractions) Motor nerve block: (5) H3 (26.67%) > H1 (6.66%) and H2 (3.33%) No safety concerns were mentioned in the abstract.	95% CI: 8.89-11.79 95% CI: 13.25-22.25 (1) p's < 0.05 (2) p's < 0.05 (3) p < 0.05 (4) p's < 0.05 (5) p's < 0.05

Author/Year	Type of Study	Number Exposed/Unexposed	Endpoints/Outcomes/Point Estimates	P-value/Confidence Interval (CI)
Marroquin B, 2017	Retrospective	n = 450 Morphine (200 µg, IT) n = 387 **Hydromorphone** (60 µg, IT) n = 81 Morphine (3 mg, epidural) n = 102 **Hydromorphone** (0.6 mg, epidural)	**Morphine vs. hydromorphone (IT)** (1) Mean to first opioids (17.0h vs. 14.6) (2) Opioids consumption (26.4mg vs. 37.0mg) (3) Side effects: mean nausea/vomiting doses requested (0.44 vs 0.47). (4) Percentage of patients requesting pruritus medication (35.8% vs 38%). (5) Mean antipruritic doses requested (0.7 vs 0.73) **Morphine vs. hydromorphone (epidural)** (6) Mean to first opioids (13.0h vs. 20.2h) (7) Opioids consumption (35.3 mg vs. 27.9 mg) (8) Side effects: mean nausea/vomiting doses requested (0.38 vs 0.22). (9) Percentage of patients requesting pruritus medication (29.6% vs 24.5%). (10) Mean antipruritic doses requested (0.37 vs 0.41)	(1) $p < 0.0001$ (2) $p < 0.001$ (3) $p = 0.65$ (4) $p = 0.56$ (5) $p = 0.75$ (6) $p = 0.0007$ (7) $p = 0.07$ (8) $p > 0.05$ (9) $p = 0.5$ (10) $p = 0.75$
Lynde GC, 2016	Blinded, up–down sequential allocation study	n = 20 **Hydromorphone** (6 µg, ± 2 µg) with 0.5% bupivacaine (12.5 mg, IT) + fentanyl (25 µg, IT)	10/20 (50%) patients reported an effective **hydromorphone** dose 12 h post-injection ED50 = 4.6 µg (10/20) No significant side effects or adverse outcomes reported	ED50: 95% CI 3.72-5.48 µg
Sviggum HP, 2016	Double-blind, up–down sequential allocation	n = 40	ED90 = 75 µg (**hydromorphone**)	95% CI 46–93 µg (**hydromorphone**)

Author/Year	Type of Study	Number Exposed/Unexposed	Endpoints/Outcomes/Point Estimates	P-value/Confidence Interval (CI)
	study with a biased-coin design	**Hydromorphone** (IT) n = 40 Morphine (IT)	ED90 = 150 µg (morphine)	95% CI 145–185 µg (morphine)
Miller EC, 2015	Case Report	n = 1 (Pregnant woman 26 weeks gestational age at beginning of treatment) Initial treatment (26 weeks): Oral hydromorphone (1-2mg every 4-6 hours as needed, up to 10mg/d for 21 days) Secondary treatment (~28 weeks): escalating doses of IV **hydromorphone** (total of 30 mg/d) while hospitalized + increased oral dosages of **hydromorphone** when discharged Tertiary treatment (~29 weeks): 75 µg/h fentanyl patch + 50 mg/d intravenous **hydromorphone** during hospitalization Final Treatment (at 34 weeks gestational age): transversus abdominis plane (TAP) block with 0.25% bupivacaine (2x) + TAP block with 0.5% ropivacaine (once)	Initial treatment: No significant improvement of pain (patient returned after 21 days from discharge) Secondary treatment: No significant improvement of pain (patient returned after 5 days from discharge) Tertiary treatment: minimal pain alleviation achieved Final treatment: complete pain resolution (0/10 VAPS) following 0.25% bupivacaine 30 min after administration. Pain returned 10 and 14 h post administration. Complete pain resolution following one administration of 0.5% ropivacaine. Uneventful cesarean delivery under spinal anesthesia at 37 weeks' gestational age	NA

a The full publication for Lu et al, 2017 is in Chinese, only information from the abstract is presented here.
ADR = adverse drug reaction; AE=adverse event; APGAR = Appearance, pulse, grimace, activity, and respiration; BID = Twice daily; CA = Congenital abnormality; CI = Confidence interval; Cmax = Maximum serum concentration; CS = Cesarean section; ED50 = Median effective dose; ED95 = 95% effective dose; IT = Intrathecal; IV = intravenous; NA = Not applicable/No answer; NACS = Neurologic adaptive capacity score; NICU = Neonatal intensive care unit; NOWS = Neonatal opioid withdrawal syndrome; OUD = Opioid use disorder; PCA = Patient-controlled analgesia; PCIA = Patient-controlled intravenous analgesia; PICU = pediatric intensive care unit; PO = Orally administered; PONV= Postoperative nausea and vomiting; RR = Risk ratio; VAPS = Visual analogue pain scale; VAS = Visual analogue score.

Source: Applicant's Submission Response to Information Request – Clinical, recieved 5/10/23, pages 19-29.

Table 2: Bibliography for Applicant's Table 1

Patricelli CJ, Gouin IJ, Gordon S, Carter N, Albert A, Paquette V, Stewart K, George S, Urbanoski K. Breastfeeding on Injectable Opioid Agonist Therapy: A Case Report. J Addict Med. 2023 Mar;17(2):222–226. doi: 10.1097/ADM.0000000000001055. PMID: 36001061.
Patricelli CJ, Chai J, Gordon S, Gouin IJ, Carter N, Stewart K, Paquette V, Urbanoski K, Albert A. Perinatal Injectable Opioid Agonist Therapy (iOAT) Administration: A Case Series. J Addict Med. 2023 Feb 20;(00):1–8. doi: 10.1097/ADM.0000000000001152. PMID: 36804862.
Brogly SB, Bowie AC, Li W, Camden A, Velez MP, Guttmann A, Werler MM. Safety of prenatal opioid analgesics: Do results differ between public health insurance beneficiary and population-based cohorts? Birth Defects Res. 2023 Mar 15;115(5):555–562. doi: 10.1002/bdr2.2147. PMID: 36628593.
Zhang Y, Xie S, Zhang G, Gong X. Analgesic effect of butorphanol tartrate combined with hydromorphone on patients with cesarean section: A prospective cohort study. Medicine. 2022 Dec 2;101(48):e31901. doi: 10.1097/MD.0000000000031901. PMID: 36482626.
Drugs and Lactation Database (LactMed®) [Internet]. Bethesda (MD): National Institute of Child Health and Human Development; 2006-. Hydromorphone. [Updated 2022 Sep 19].
Esposito DB, Huybrechts KF, Werler MM, Straub L, Hernández-Díaz S, Mogun H, Bateman BT. Characteristics of Prescription Opioid Analgesics in Pregnancy and Risk of Neonatal Opioid Withdrawal Syndrome in Newborns. JAMA Netw Open. 2022 Aug 1;5(8):e2228588. doi: 10.1001/jamanetworkopen.2022.28588. PMID: 36001312.
Herbert KA, Yurashevich M, Fuller M, Pedro CD, Habib AS. Impact of a multimodal analgesic protocol modification on opioid consumption after cesarean delivery: a retrospective cohort study. J Matern Fetal Neonatal Med. Taylor & Francis; 2022 Dec 11;35(24):4743–4749. doi: 10.1080/14767058.2020.1863364. PMID: 33393401.
Zhao JP, Berthod C, Sheehy O, Kassaï B, Gorgui J, Bérard A. Prevalence and duration of prescribed opioid use during pregnancy: a cohort study from the Quebec Pregnancy Cohort. BMC Pregnancy Childbirth. BioMed Central; 2021 Dec 1;21(1):800. doi: 10.1186/s12884-021-04270-x. PMID: 34847870.

Griffiths S, Campbell DM, Caudarella A, Guimond T, Lamba W, Lurie E, Nader M, Sgro M, Turner S. Use of Injectable Opioid Agonist Therapy in a In-Patient Setting for a Pregnant Patient With Opioid Use Disorder: A Case Report. J Addict Med. 2021 Sep;15(5):435–438. doi: 10.1097/ADM.0000000000000776. PMID: 33234803.

Mother To Baby | Fact Sheets [Internet]. Brentwood (TN): Organization of Teratology Information Specialists (OTIS); 1994-. Hydromorphone (Dilaudid®) 2021 Aug 1. Available from: https://www.ncbi.nlm.nih.gov/books/NBK582753/.

Wu Z, Zhao P, Peng J, Fang L, Ding J, Yan G, Wang Y, Zhu J, Wang D, Li Y, Chen Z, Zhang Q, Deng Q, Duan G, Zuo Z, Li H. A Patient-Controlled Intravenous Analgesia With Tramadol Ameliorates Postpartum Depression in High-Risk Woman After Cesarean Section: A Randomized Controlled Trial. Front Med (Lausanne). 2021;8(May):679159. doi: 10.3389/fmed.2021.679159. PMID: 34124111.

Stanislaus MA, Reno JL, Small RH, Coffman JH, Prasad M, Meyer AM, Carpenter KM, Coffman JC. Continuous Epidural Hydromorphone Infusion for Post-Cesarean Delivery Analgesia in a Patient on Methadone Maintenance Therapy: A Case Report. J Pain Res. 2020 Apr;13:837–842. doi: 10.2147/JPR.S242271. PMID: 32425588.

Puhto T, Kokki M, Hakomaki H, Spalding M, Gunnar T, Alahuhta S, Vakkala M. Single dose epidural hydromorphone in labour pain: maternal pharmacokinetics and neonatal exposure. Eur J Clin Pharmacol. 2020;76:969-977. PMID: 32363420.

Huang CY, Li SX, Yang MJ, Xu LL, Chen XZ. A comparative study of three concentrations of intravenous nalbuphine combined with hydromorphone for post-cesarean delivery analgesia. Chin Med J (Engl). 2020 Mar 5;133(5):523–529. doi: 10.1097/CM9.0000000000000067. PMID: 32142492.

Duan G, Yang G, Peng J, Duan Z, Li J, Tang X, Li H. Comparison of postoperative pain between patients who underwent primary and repeated cesarean section: a prospective cohort study. BMC Anesthesiol. 2019 Oct 22;19(1):189. doi: 10.1186/s12871-019-0865-9. PMID: 31640565.

Choi SK, Kim YH, Kim SM, Wie JH, Lee DG, Kwon JY, Song JH, Lee SJ, Park IY. Opioid analgesics are the leading cause of adverse drug reactions in the obstetric population in South Korea. Medicine. 2019 May;98(21):e15756. doi: 10.1097/MD.0000000000015756. PMID: 31124960.

Yang M, Wang L, Chen H, Tang Y, Chen X. Postoperative Analgesic Effects of Different Doses of Epidural Hydromorphone Co administered with Ropivacaine after Cesarean Section: A Randomized Controlled Trial. Pain Res Manag. 2019; 2019: 9054538. doi: 10.1155/2019/9054538. PMID: 30944686.

Schultz ML, Kostic M, Kharasch S. A Case of Toxic Breast-feeding? Pediatr Emerg Care. 2019 Jan;35(1): e9–e10. doi: 10.1097/PEC.0000000000001009. PMID: 28067687.

Duan G, Bao X, Yang G, Peng J, Wu Z, Zhao P, Zuo Z, Li H. Patient-controlled intravenous tramadol versus patient-controlled intravenous hydromorphone for analgesia after secondary cesarean delivery: a randomized controlled trial to compare analgesic, anti-anxiety and anti-depression effects. J Pain Res. 2019 Dec; 12:49–59. doi: 10.2147/JPR.S184782. PMID: 30588079.

O'Reilly-Shah V, Lynde GC. Determination of ED50 and time to effectiveness for intrathecal hydromorphone in laboring patients using Dixon's up-and-down sequential allocation method. BMC Anesthesiol. 2018 Oct 5;18(1):140. doi: 10.1186/s12871-018-0603-8. PMID: 30290794.

Lu YY, Huang H, Mao WL, Liu RH, Hu MJ, Shao LX, Hu MP, Li J. A concentration-response observation of hydromorphone combined with ropivacaine in labor analgesia. Zhonghua Yi Xue Za Zhi. 2017 Nov 14; 97(42):3297-3300. doi: 10.3760/cma.j.issn.0376-2491.2017.42.005. PMID: 29141373.

Marroquin B, Feng C, Balofsky A, Edwards K, Iqbal A, Kanel J, Jackson M, Newton M, Rothstein D, Wong E, Wissler R. Neuraxial opioids for post-cesarean delivery analgesia: can hydromorphone replace morphine? A retrospective study. Int J Obstet Anesth. Elsevier Ltd; 2017 May;30(March 2012):16–22. doi: 10.1016/j.ijoa.2016.12.008. PMID: 28185794.

Lynde GC. Determination of ED50 of hydromorphone for postoperative analgesia following cesarean delivery. Int J Obstet Anesth. Elsevier Ltd; 2016 Dec; 28:17–21. doi: 10.1016/j.ijoa.2016.07.005. PMID: 2764109.

Sviggum HP, Arendt KW, Jacob AK, Niesen AD, Johnson RL, Schroeder DR, Tien M, Mantilla CB. Intrathecal Hydromorphone and Morphine for Post-cesarean Delivery Analgesia: Determination of the ED90 Using a Sequential Allocation Biased-Coin Method. Anesth Analg. Elsevier B.V.; 2016 Sep;123(3):690–7. doi: 10.1213/ANE.0000000000001229. PMID: 26974022.

Miller EC, Szeto M, Boet S. Unilateral Transversus Abdominis Plane Block Catheter for the Treatment of Abdominal Wall Pain in Pregnancy: A Case Report. Reg Anesth Pain Med. 2015;40(6):720–2. doi: 10.1097/AAP.0000000000000296. PMID: 26398168.

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/

JANE E LIEDTKA
11/16/2023 12:13:34 PM

TAMARA N JOHNSON
11/16/2023 04:47:10 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 27, 2023
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 217812
Product Name, Dosage Form, and Strength:	hydromorphone hydrochloride injection, 40 mg/20 mL (2 mg/mL)
Applicant/Sponsor Name:	Hikma Pharmaceuticals USA Inc. (Hikma)
TTT ID #:	2023-3729
DMEPA 1 Safety Evaluator:	Damon Birkemeier, PharmD, FISMP, NREMT
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on September 18, 2023 for hydromorphone hydrochloride. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised container label and carton labeling for hydromorphone hydrochloride (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Birkemeier D. Label and Labeling Review for hydromorphone hydrochloride (NDA 217812). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 JUL 13. TTT ID No.: 2023-3729.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON SEPTEMBER 18, 2023

- Response to recommendations from Hikma available from: \\CDSESUB1\EVSPROD\nda217812\0009\m1\us\12-cover-letters\cover-letter-0009.pdf

Container labels

(b) (4)

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

DAMON A BIRKEMEIER
09/27/2023 12:42:32 PM

VALERIE S VAUGHAN
09/27/2023 01:25:34 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	July 13, 2023
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 217812
Product Name, Dosage Form, and Strength:	hydromorphone hydrochloride injection 40 mg/20 mL (2 mg/mL)
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Hikma Pharmaceuticals USA Inc. (Hikma)
FDA Received Date:	February 16, 2023
TTT ID #:	2023-3729
DMEPA 1 Safety Evaluator:	Damon Birkemeier, PharmD, FISMP, NREMT
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 REASON FOR REVIEW

As part of the approval process for hydromorphone hydrochloride injection, the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the proposed hydromorphone hydrochloride container label, carton labeling, and prescribing information (PI) for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

NDA 217812 is a 505(b)(2) NDA and the listed drug product is Dilaudid, NDA 019034. We note that the proposed hydromorphone hydrochloride injection, (b) (4) 40 mg/20 mL multiple-dose vial is a legacy unapproved drug product under NDC 0641-2341-41 which has a listed start marketing date of 1972, and that the proposed product has since been acquired by Hikma from Baxter.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed container label, carton labeling, and prescribing information (PI) may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Hikma Pharmaceuticals USA Inc.

4 RECOMMEDATIONS FOR DIVISION OF ANESTHESIOLOGY, ADDICTION MEDICINE, AND PAIN MEDICINE (DAAP)

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	The strength lacks adequate spacing between the numerical dose and unit of measure.	Lack of adequate spacing may impact readability and might result in wrong strength errors.	We recommend placing adequate space between the numerical dose and unit of measure (e.g., 40 mg/20 mL instead of 40mg/20mL) to improve readability.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	Each numeric value presented in the storage statement is not immediately followed by its intended unit of measurement (i.e., °C or °F).	The presentation of the storage statement should be clearly stated to avoid storage errors.	Revise “20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F)” to “20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

5 RECOMMENDATIONS FOR HIKMA PHARMACEUTICALS USA INC.

Table 3. Identified Issues and Recommendations for Hikma Pharmaceuticals USA Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	As currently presented, the statement of dosage includes the term (b) (4).	The term (b) (4) is inconsistent with terminology used in the Prescribing Information.	Revise the usual dosage statement to "Dosage: See Prescribing Information."
2.	Each numeric value presented in the storage statement is not immediately followed by its intended unit of measurement (i.e., °C or °F).	The presentation of the storage statement should be clearly stated to avoid storage errors.	Revise “20° to 25°C (68° to 77°F)” to “20°C to 25°C (68°F to 77°F).

Table 3. Identified Issues and Recommendations for Hikma Pharmaceuticals USA Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label			
1.	As currently presented, there is no space for end-users to write the beyond-use date which is the date the product must be discarded after opening.	Since the product has a different expiration date after opening, the container label should have a designated space and format for end-users to write the beyond-use date to minimize the risk of administration of deteriorated drug medication errors.	If space permits, we recommend including space for end users to write the beyond-use date on the container label. For example: Discard after __/__/____ [Time ____]
Carton Labeling			
1.	The product identifier is missing.	In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and repackagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a	We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).[a] If you determine that the product identifier requirements apply to your product's labeling, we request you add a place holder to the carton labeling.

[a] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act - Questions and Answers. 2021. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers

Table 3. Identified Issues and Recommendations for Hikma Pharmaceuticals USA Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format.	

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table presents relevant product information for hydromorphone hydrochloride that Hikma Pharmaceuticals USA Inc. submitted on February 16, 2023, and the listed drug (LD).

Table 4. Relevant Product Information for Listed Drug and hydromorphone hydrochloride		
Product Name	Dilaudid	hydromorphone hydrochloride
Initial Approval Date	January 11, 1984	N/A
Active Ingredient	Hydromorphone hydrochloride	Hydromorphone hydrochloride
Indication	Opioid agonist indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate	
Route of Administration	Intravenous, intramuscular, or subcutaneous	
Dosage Form	Injection	
Strength	1 mg/mL, 2 mg/mL, 4 mg/mL, and 10 mg/mL	40 mg/20 mL (2 mg/mL)
Dose and Frequency	<u>Use as the first opioid analgesic:</u> *Subcutaneous or Intramuscular Administration:* Usual starting dose is 1 to 2 mg every 2 to 3 hours as necessary *Intravenous Administration:* 0.2 to 1 mg every 2 to 3 hours, given slowly over 2 to 3 minutes *Do not use Dilaudid-HP for patients who are not tolerant to the respiratory depressant or sedating effects of opioid	
How Supplied	Dilaudid: 1 mg/mL, 2 mg/mL, (b) (4) (b) (4) prefilled syringes Dilaudid-HP: 10 mg/mL (b) (4)	40 mg/20 mL multiple-dose glass vial
Storage	20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]	20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Use or discard multiple-dose vials within 28 days of first use

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following hydromorphone hydrochloride labels and labeling submitted by Hikma Pharmaceuticals USA Inc.

- Container label received on February 16, 2023
- Carton labeling received on February 16, 2023
- Prescribing Information (Image not shown) received on February 16, 2023, available from \\CDSESUB1\EVSPROD\nda217812\0001\m1\us\anno-draft-text.pdf OR \\CDSESUB1\EVSPROD\nda217812\0001\m1\us\draft-labeling-text.doc

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

DAMON A BIRKEMEIER
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VALERIE S VAUGHAN
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M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date:	April 20, 2023
To:	Rigoberto Roca, M.D., Director Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Through:	Dominic Chiapperino, Director Silvia Ph.D., Senior Pharmacologist Controlled Substance Staff
From:	James M. Tolliver, Ph.D., Senior Pharmacologist Controlled Substance Staff
Subject:	NDA 217812, Hydromorphone Hydrochloride (HCl) Injection **Indication:** Treatment of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. **Dosages:** 40 mg Hydromorphone HCl / 20 mL sterile aqueous solution (2 mg/1 ml) in multiple dose vials intended for subcutaneous, intramuscular and slow intravenous injection **Sponsor:** Hikma Pharmaceuticals USA, Inc.
Materials reviewed:	Materials submitted under NDA 217812

I. Background

This memorandum is in response to a consult request dated March 21, 2023, from the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) pertaining to NDA 217,812 for Hydromorphone Hydrochloride 40 mg/20 mL (2 mg/mL) Multiple Dose Vial, under development by Hikma Pharmaceuticals USA, Inc.

The Sponsor is seeking approval via a 505(b)(2) pathway relying on the Agency's previous finding of safety and efficacy of the listed drug, Dilaudid Injection (Hydromorphone Hydrochloride) for IV, IM, or SC use; NDA 019034) held by Fresenius Kabi USA LLC. Proposed indication for use will be the same as that for Dilaudid Injection

II. Conclusions

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.

III. Recommendations to the Division

Based on the information provided, CSS need not be involved in the review of this NDA. Consequently, CSS will not submit a filing checklist for NDA 217812.

CSS requests that the Division consult CSS if the label of the product is to be revised

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/s/

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