PRESCRIBING INFORMATION

INCLUDING PATIENT MEDICATION INFORMATION

[N] HYDROmorphone Hydrochloride Injection, USP

High Potency
(Hydromorphone Hydrochloride Injection, USP)
Solution; 10 mg / mL

Intramuscular, Intravenous, and Subcutaneous

Opioid agonist

NOT A PRODUCT MONOGRAPH

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[N]HYDROmorphone Hydrochloride Injection, USP

(Hydromorphone Hydrochloride Injection, USP)

Solution; 10 mg / mL

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
Intramuscular, Intravenous, Subcutaneous	Solution / 10 mg / mL	Citric acid, sodium citrate, water for injection

INDICATIONS AND CLINICAL USE

Analgesia

Adults:

HYDROmorphone Hydrochloride Injection, USP (Hydromorphone Hydrochloride Injection, USP) is indicated for the relief of severe pain only in patients who require subcutaneously, intravenously or intramuscularly administered opioids in doses or concentrations higher than those usually needed. Because hydromorphone is highly soluble, a smaller injection volume can be used and discomfort associated with the intramuscular or subcutaneous injection of larger volumes of solution can be minimized.

Geriatrics (> 65 years of age)

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range and titrated slowly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or other drug therapy (see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics).

Pediatrics (< 18 years of age)

The safety and efficacy of hydromorphone has not been studied in the pediatric population. Therefore the use of HYDROmorphone Hydrochloride Injection, USP is not recommended in patients under 18 years of age.

Supervised Injectable Opioid Agonist Therapy (siOAT)

HYDROmorphone Hydrochloride Injection, USP is indicated as supervised injectable opioid agonist therapy in adult patients with severe opioid use disorder who are using injectable opioids and have failed previous attempts at opioid agonist therapy.

Injectable opioid agonist therapy with HYDROmorphone Hydrochloride Injection, USP should only be administered under the supervision of a physician experienced in treatment of severe opioid use disorder and trained in injectable opioid agonist therapy, in accordance with provincial or territorial professional requirements and guidance, as applicable. To be safely used as a supervised injectable opioid agonist therapy, the product has to be administered in

facilities that allow for prompt recognition of serious adverse reactions, including potentially fatal respiratory depression, and initiation of immediate resuscitation measures (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINSTRATION).

In the clinical trial which demonstrated efficacy of injectable hydromorphone, supervised injectable opioid agonist therapy could be supplemented with oral opioid agonist therapy (methadone), in order to avoid withdrawal symptoms.

Supervised injectable opioid agonist therapy should be monitored and provided within a framework of medical, social and psychological support, as part of a comprehensive opioid dependence treatment program.

Geriatrics (> 65 years of age)

Supervised injectable agonist therapy with hydromorphone for severe opioid use disorder has not been evaluated in patients older than 65 years. Caution is advised, in recognition of the likelihood of concomitant disease and drug therapies and the greater frequency of decreased hepatic, renal, or cardiac function (see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics).

Pediatrics (< 18 years of age)

The safety and efficacy of siOAT with hydromorphone for severe opioid use disorder have not been studied in the pediatric population, therefore HYDROmorphone Hydrochloride Injection, USP is not indicated for siOAT in patients under 18 years of age.

CONTRAINDICATIONS

General

Administration is contraindicated in:

- Patients who are hypersensitive to the active substance (Hydromorphone) or other opioid analgesics or to any ingredient in the formulation. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Prescribing Information.
- Patients who are not already receiving high doses or high concentrations of opioids.
- Patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction or strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).
- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis)
- Patients with mild pain that can be managed with other pain medications.
- Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus.
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood and/or cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and/or head injury.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).
- Women who are breast-feeding, pregnant or during labour and delivery (see Serious Warnings and Precautions, and WARNINGS AND PRECAUTIONS).

For the Supervised Injectable Opioid Agonist Therapy (siOAT) indication
In addition to the above **CONTRAINDICATIONS**, administration is contraindicated in:

- Patients with signs of intoxication, including due to centrally-acting sedatives and/or stimulants, or in any other acute clinical condition that would increase the risk of an adverse event with the use of HYDROmorphone Hydrochloride Injection, USP.

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

General
HYDROmorphone Hydrochloride Injection, USP is a highly concentrated solution of hydromorphone hydrochloride. It should be used only in opioid tolerant patients requiring a high dose or a high concentration of opioid agonist. Do not confuse HYDROmorphone Hydrochloride Injection, USP, 10 mg / mL with the lower concentration of the HYDROmorphone Hydrochloride Injection, USP, 2 mg / mL since overdosage and death could result.

When used at a high concentration, the delivery of a precise lower dose of HYDROmorphone Hydrochloride Injection, USP may be difficult. Therefore, high concentration hydromorphone preparations should be used only if the amount of hydromorphone required can be delivered accurately.

Addiction, Abuse, and Misuse
HYDROmorphone Hydrochloride Injection, USP poses risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Each patient's risk should be assessed prior to prescribing HYDROmorphone Hydrochloride Injection, USP, and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS). HYDROmorphone Hydrochloride Injection, USP should be stored securely to avoid theft or misuse.

Life-threatening Respiratory Depression: OVERDOSE
Serious, life-threatening, or fatal respiratory depression may occur with use of HYDROmorphone Hydrochloride Injection, USP. Infants exposed *in utero* or through breast milk are at risk of life-threatening respiratory depression upon delivery or when nursed. Patients should be monitored for respiratory depression, especially during initiation of HYDROmorphone Hydrochloride Injection, USP or following a dose increase.

Further, instruct patients of the hazards related to taking opioids including fatal overdose.

Accidental Exposure
Accidental ingestion of even one dose of HYDROmorphone Hydrochloride Injection, USP, especially by children, can result in a fatal overdose of hydromorphone (see DOSAGE AND ADMINISTRATION, Disposal, for instructions on proper disposal).

Neonatal Opioid Withdrawal Syndrome
Prolonged maternal use of HYDROmorphone Hydrochloride Injection, USP during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see WARNINGS AND PRECAUTIONS).

Interaction with Alcohol
The co-ingestion of alcohol with HYDROmorphone Hydrochloride Injection, USP should be avoided as it may result in dangerous additive effects, causing serious injury or death (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see WARNINGS AND PRECAUTIONS, Neurologic and DRUG INTERACTIONS).

- **Reserve concomitant prescribing of HYDROmorphone Hydrochloride Injection, USP and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

Analgesia-Specific SERIOUS WARNINGS AND PRECAUTIONS
In addition to all the above SERIOUS WARNINGS AND PRECAUTIONS:

Limitations of Use
Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the risks of overdose and death with immediate release opioid formulations, HYDROmorphone Hydrochloride Injection, USP should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide appropriate management of pain (see DOSAGE AND ADMINISTRATION).

Supervised Injectable Opioid Agonist Therapy-Specific SERIOUS WARNINGS AND PRECAUTIONS
In addition to all the above SERIOUS WARNINGS AND PRECAUTIONS:

HYDROmorphone Hydrochloride Injection, USP should not be injected into the jugular or femoral vein.

General
Where high concentration hydromorphone preparations are indicated; the patient is presumed to be receiving an opioid to which tolerance has developed and the initial dose of hydromorphone selected should therefore be estimated on the basis of the relative potency of hydromorphone and the opioid previously used by the patient (see DOSAGE AND ADMINISTRATION).

In diseases, such as malignant cancers, where pain control is the primary focus, opioid administration at very high doses has been associated with seizures and myoclonus.

Hyperalgesia that will not respond to a further dose increase of hydromorphone may occur at particularly high doses. A hydromorphone dose reduction or change in opioid may be required.

HYDROmorphone Hydrochloride Injection, USP should be stored securely to avoid theft or misuse.

HYDROmorphone Hydrochloride Injection, USP should only be prescribed by healthcare professionals who are knowledgeable in the continuous administration of potent opioids, in the management of patients receiving potent opioids, and in the detection and management of respiratory depression, including the use of opioid antagonists.

Patients should be cautioned not to consume alcohol while taking HYDROmorphone Hydrochloride Injection, USP as it may increase the chance of experiencing serious adverse events, including death.

Abuse and Misuse

Like all opioids, HYDROmorphone Hydrochloride Injection, USP are potential drugs of abuse and misuse, which can lead to overdose and death. Therefore, HYDROmorphone Hydrochloride Injection, USP should be prescribed and handled with caution.

Analgesia

Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse and abuse.

Opioids, such as HYDROmorphone Hydrochloride Injection, USP should be used with particular care in patients with a history of alcohol and illicit/prescription drug abuse. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

Supervised Injectable Opioid Agonist Therapy (siOAT)

In the Phase 3 clinical trial which demonstrated the efficacy of injectable hydromorphone in siOAT for patients with severe, refractory opioid use disorder, the supervised therapy included measures to ensure compliance and prevent diversion, and allowed close monitoring for safety.

Cardiovascular

Severe Hypotension: Hydromorphone administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of such drugs as phenothiazines and other tranquilizers, sedatives, hypnotics, tricyclic antidepressants or general anesthetics. These patients should be monitored for signs of hypotension after initiating or titrating the dose of HYDROmorphone Hydrochloride Injection, USP.

The use of HYDROmorphone Hydrochloride Injection, USP in patients with circulatory shock should be avoided as it may cause vasodilation that can further reduce cardiac output and blood pressure.

Rapid intravenous injection of opioid analgesics increases the possibility of hypotension and respiratory depression and should be avoided (see DOSAGE AND ADMINISTRATION).

Dependence/Tolerance

Analgesia

As with other opioids, tolerance and physical dependence may develop upon repeated administration of HYDROmorphone Hydrochloride Injection, USP and there is a potential for development of psychological dependence.

Physical dependence and tolerance reflect the neuroadaptation of the opioid receptors to chronic exposure to an opioid, and are separate and distinct from abuse and addiction. Tolerance, as well as physical dependence, may develop upon repeated administration of opioids, and are not by themselves evidence of an addictive disorder or abuse.

Patients on prolonged therapy should be tapered gradually from the drug if it is no longer required for pain control. Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist. Some of the symptoms that may be associated with abrupt withdrawal of an opioid analgesic include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, anxiety, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning (see ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage).

Patients with a history of addiction to drugs or alcohol may be at higher risk of becoming addicted to HYDROmorphone Hydrochloride Injection, USP; extreme caution and awareness is warranted to mitigate the risk.

Supervised Injectable Opioid Agonist Therapy (siOAT)
Withdrawal symptoms may occur following missed doses and are expected after abrupt discontinuation of therapy. In addition, if siOAT is interrupted, re-initiation of dose titration may be necessary, starting at a decreased dose for patient safety, since rapid loss of tolerance may occur, posing a significant risk of overdose (see DOASGE AND ADMINISTRATION).

Endocrine
Adrenal Insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Gastrointestinal Effects
Hydromorphone and other morphine-like opioids have been shown to decrease bowel motility. Hydromorphone may obscure the diagnosis or clinical course in patients with acute abdominal conditions (see CONTRAINDICATIONS).

Neonatal Opioid Withdrawal Syndrome (NOWS)
Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening.

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.

Use of HYDROmorphone Hydrochloride Injection, USP is contraindicated in pregnant women (see CONTRAINDICATIONS).

Neurologic

Interactions with CNS Depressants (including benzodiazepines and alcohol): Hydromorphone should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics, general anesthetics, phenothiazines and other tranquilizers, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, benzodiazepines, centrally-active anti-emetics and other CNS depressants. Respiratory depression, hypotension and profound sedation, coma or death may result.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (see DRUG INTERACTIONS). If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when HYDROmorphone Hydrochloride Injection, USP is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see DRUG INTERACTIONS).

HYDROmorphone Hydrochloride Injection, USP should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see CONTRAINDICATIONS and ADVERSE REACTIONS, Sedation, and DRUG INTERACTIONS).

Severe pain antagonizes the subjective and respiratory depressant actions of opioid analgesics. Should pain suddenly subside, these effects may rapidly become manifest.

Serotonin Syndrome: HYDROmorphone Hydrochloride Injection, USP could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs (e.g. anti-depressants, migraine medications). Treatment with the serotonergic drug should be

discontinued if such events (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated. HYDROmorphone Hydrochloride Injection, USP should not be used in combination with MAO inhibitors or serotonin- precursors (such as L-tryptophan, oxitriptan) and should be used with caution in combination with other serotonergic drugs (triptans, certain tricyclic antidepressants, lithium, tramadol, St. John's Wort) due to the risk of serotonergic syndrome (see DRUG INTERACTIONS).

Head Injury: The respiratory depressant effects of hydromorphone, and the capacity to elevate cerebrospinal fluid pressure, may be greatly increased in the presence of an already elevated intracranial pressure produced by trauma. Also, hydromorphone may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, hydromorphone must be used with extreme caution and only if it is judged essential (see CONTRAINDICATIONS).

Peri-Operative Considerations

HYDROmorphone Hydrochloride Injection, USP is not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative pain).

HYDROmorphone Hydrochloride Injection, USP injections should be used with caution pre- and intra-operatively and within the first 24 hours post-operatively. Severe pain antagonizes the subjective and respiratory depressant actions of hydromorphone. However, should pain suddenly subside, these effects may rapidly become manifest. Patients who are scheduled for cordotomy or other interruptions of pain transmission pathways should not receive hydromorphone within 24 hours of the procedure. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. Thereafter, if HYDROmorphone Hydrochloride Injection, USP is to be continued after the patient recovers from the post-operative period, a new dosage should be administered in accordance with the changed need for pain relief. The risk of withdrawal in opioid-tolerant patients should be addressed as clinically indicated.

The administration of analgesics in the peri-operative period should be managed by healthcare providers with adequate training and experience (e.g., by an anesthesiologist).

Hydromorphone and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common post-operative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in post-operative patients receiving opioids. Standard supportive therapy should be implemented.

Psychomotor Impairment

HYDROmorphone Hydrochloride Injection, USP may impair the mental and/or physical abilities needed for certain potentially hazardous activities such as driving a car or operating machinery. Patients should be cautioned accordingly. Patients should also be cautioned about the combined effects of hydromorphone with other CNS depressants, including other opioids, phenothiazine, sedatives, hypnotics and alcohol.

Respiratory

General

Respiratory Depression: Serious, life-threatening, or fatal respiratory depression has been reported

with the use of opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Hydromorphone should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia (see CONTRAINDICATIONS).

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of HYDROmorphone Hydrochloride Injection, USP, the risk is greatest during the initiation of therapy or following a dose increase. Patients should be closely monitored for respiratory depression when initiating therapy with HYDROmorphone Hydrochloride Injection, USP and following dose increases.

Life-threatening respiratory depression is more likely to occur in the elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

To reduce the risk of respiratory depression, proper dosing and titration of HYDROmorphone Hydrochloride Injection, USP is essential. Overestimating the HYDROmorphone Hydrochloride Injection, USP dose when converting patients from another opioid product can result in a fatal overdose with the first dose. In these patients, the use of non-opioid analgesics should be considered, if feasible (see WARNINGS AND PRECAUTIONS, Special Populations, Special Risk Groups, and DOSAGE AND ADMINISTRATION).

Supervised Injectable Opioid Agonist Therapy (siOAT)
Concomitant Oral Methadone Treatment: Due to the pharmacokinetic properties of methadone (such as its long half-life and slow bioaccumulation) compared to other opioids, as well as the high degree of individual variability in absorption rates, metabolism, potency and cross-tolerance with other opioids, a dose increase of methadone may take several days to reach a steady-state concentration and maximum therapeutic effect, and this can cause delayed emergence of serious adverse effects like respiratory depression. Health care professionals assessing patients undergoing siOAT with concomitant oral methadone should be familiar with the risks of such treatment and procedures to mitigate these. Refer also to the corresponding Product Monographs for methadone products indicated for treatment of opioid use disorder.

Use in Patients with Chronic Pulmonary Disease:
Analgesia
Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression for respiratory depression, particularly when initiating therapy and titrating with HYDROmorphone Hydrochloride Injection, USP as in these patients, even usual therapeutic doses of HYDROmorphone Hydrochloride Injection, USP may decrease respiratory drive to the point of apnea. In these patients, use of alternative non-opioid analgesics should be considered, if possible. The use of HYDROmorphone Hydrochloride Injection, USP is contraindicated in patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see CONTRAINDICATIONS).

Supervised Injectable Opioid Agonist Therapy (siOAT)

Caution should be exercised in prescribing siOAT to patients with chronic pulmonary disease due to risks associated with respiratory depression.

In the Phase 3 clinical trial which demonstrated the efficacy of injectable hydromorphone in siOAT for patients with severe, refractory opioid use disorder, patients with chronic respiratory disease resulting in a resting respiratory rate greater than 20 per minute were excluded from the trial.

Patient Counselling Information

A patient information sheet should be provided to patients when HYDROmorphone Hydrochloride Injection, USP injection is dispensed to them.

Patients receiving HYDROmorphone Hydrochloride Injection, USP should be given the following instructions:

1. Patients should be informed that accidental use or administration by individuals (including children) other than the patient for whom it was originally prescribed, may lead to severe, even fatal consequences. HYDROmorphone Hydrochloride Injection, USP should be kept under lock and out of sight and out of reach of children.

2. Patients should be advised that HYDROmorphone Hydrochloride Injection, USP contains hydromorphone, is an opioid pain medicine.

3. Patients should be advised that HYDROmorphone Hydrochloride Injection, USP should only be used as directed. The dose of HYDROmorphone Hydrochloride Injection, USP should not be adjusted without consulting with the prescriber.

4. Patients should be advised that high concentration HYDROmorphone Hydrochloride Injection, USP preparations should only be used by patients who are already receiving high doses or high concentrations of opioids.

5. Patients should not combine HYDROmorphone Hydrochloride Injection, USP with alcohol or other central nervous system depressants (sleep aids, tranquilizers) because dangerous additive effects may occur, resulting in serious injury or death.

6. Patients should be advised to consult the prescriber or pharmacist if other medications are being used or will be used with HYDROmorphone Hydrochloride Injection, USP.

7. Patients should be advised that if they have been receiving treatment with HYDROmorphone Hydrochloride Injection, USP and cessation of therapy is indicated, they should not abruptly stop without consulting the prescriber.

8. Patients should be advised of the most common adverse reactions that may occur while taking HYDROmorphone Hydrochloride Injection, USP: constipation, dizziness, light-headedness, nausea, sedation, sweating and vomiting. If symptoms worsen, patients should seek immediate medical attention.

9. Patients should be advised that HYDROmorphone Hydrochloride Injection, USP may cause drowsiness, dizziness or light-headedness and may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating

machinery).

Patients started on HYDROmorphone Hydrochloride Injection, USP or patients whose dose has been adjusted should be advised not to drive a car or operate machinery unless they are tolerant to the effects of HYDROmorphone Hydrochloride Injection, USP.

10. Patients should be advised that HYDROmorphone Hydrochloride Injection, USP are potential drugs of abuse. They should protect it from theft or misuse.

11. Patients should be advised that HYDROmorphone Hydrochloride Injection, USP should never be given to anyone other than the individual for whom it was prescribed.

12. Women of childbearing potential who become or are planning to become pregnant should be advised to consult a physician prior to initiating or continuing therapy with HYDROmorphone Hydrochloride Injection, USP. Women who are breastfeeding or pregnant should not use HYDROmorphone Hydrochloride Injection, USP.

Special Considerations for Supervised Injectable Opioid Agonist Therapy (siOAT)

HYDROmorphone Hydrochloride Injection, USP should only be administered under the supervision of a physician experienced in treatment of severe opioid use disorder and trained in supervised injectable opioid agonist therapy, in accordance with provincial or territorial professional requirements and guidance, as applicable.

The greater inherent risk of overdose with injectable treatments compared to oral OAT should be individually considered in each case.

Prescribers should carefully consider drug interactions (see DRUG INTERACTIONS).

Use Extreme Caution with siOAT in case of the following:

- **Existing injection-related infection (e.g., septicemia, endocarditis, pneumonia, infective osteomyelitis)**
- **Coagulation disorders (e.g., due to concomitant anticoagulants, severe hepatic disease)**

In the above situations, *oral treatment should be preferentially prescribed*.

Use caution with siOAT in case of the following:

- **Patients who cannot safely self-inject their medication, due to either inadequate venous access in 'low-risk' sites (with consequent injecting in neck or groin veins), or persistently poor injecting technique not remedied by education about injection**
- **Patients with chronic medical conditions such as respiratory, hepatic or renal disease, or a history of recent head injury**
- **Older adults**

In the above situations, oral OAT or other forms of treatment may be more appropriate.

Sexual Function / Reproduction

Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (see ADVERSE REACTIONS, Post-Marketing

Experience).

Special Populations

Special Risk Groups: Hydromorphone should be administered with caution to patients with a history of alcohol and drug abuse and in a reduced dosage to debilitated patients, and in patients with severely impaired pulmonary function, Addison's disease, hypothyroidism, myxedema, toxic psychosis, prostatic hypertrophy or urethral stricture.

The administration of opioid analgesics, including hydromorphone, may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Opioid analgesics including hydromorphone should also be used with caution in patients about to undergo surgery of the biliary tract, since it may cause spasm of the sphincter of Oddi.

Pregnant Women: Studies in humans have not been conducted. HYDROmorphone Hydrochloride Injection, USP crosses the placental barrier and is contraindicated in pregnant women.

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal Opioid Withdrawal Syndrome (NOWS), unlike opioid withdrawal syndrome in adults, can be life-threatening (see WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome (NOWS), ADVERSE REACTIONS, Post-Marketing Experience).

Pregnant women using opioids should not discontinue their medication abruptly as this can cause pregnancy complication such as miscarriage or still-birth. Tapering should be slow and under medical supervision to avoid serious adverse events to the fetus.

Labour, Delivery and Nursing Women: Since opioids can cross the placental barrier and are excreted in breast milk, HYDROmorphone Hydrochloride Injection, USP is contraindicated in nursing women and during labour and delivery. Life-threatening respiratory depression can occur in the infant if opioids are administered to the mother. Naloxone, a drug that counters the effects of opioids, should be readily available if HYDROmorphone Hydrochloride Injection, USP is used in this population.

Pediatrics (< 18 years of age): The safety and efficacy of hydromorphone hydrochloride has not been studied in the pediatric population. Therefore, use of HYDROmorphone Hydrochloride Injection, USP is not recommended in patients under 18 years of age.

Geriatrics (> 65 years of age): In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range and titrated slowly, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy (see DOSAGE AND ADMINISTRATION).

Supervised Injectable Opioid Agonist Therapy (siOAT)

Pregnant Women: Data are limited regarding the relative safety of siOAT with hydromorphone in pregnant women with severe opioid use disorder who have been continuing to inject illicit opioids, and for whom treatment options such as methadone have been ineffective.

Geriatrics (> 65 years of age): Supervised injectable agonist therapy with hydromorphone for severe opioid use disorder has not been evaluated in patients older than 65 years. Caution is advised, in recognition of the likelihood of concomitant disease and drug therapies and the greater frequency of decreased hepatic, renal, or cardiac function.

Pediatrics (< 18 years of age): The safety and efficacy of siOAT with hydromorphone for severe opioid use disorder have not been studied in the pediatric population, therefore HYDROmorphone Hydrochloride Injection, USP is not indicated as siOAT in patients under 18 years of age.

Patients with Hepatic Impairment:

General

The pharmacokinetics of hydromorphone following an oral administration of hydromorphone at a single 4 mg dose (2 mg hydromorphone immediate-release tablets) are affected by hepatic impairment. Mean exposure to hydromorphone (C_{max} and AUC_{∞}) is increased 4-fold in patients with moderate (Child-Pugh Group B) hepatic impairment compared with subjects with normal hepatic function. The pharmacokinetics of hydromorphone in patients with severe hepatic impairment has not been studied. A further increase in C_{max} and AUC of hydromorphone in this group is expected and should be taken into consideration when selecting a starting dose.

Supervised Injectable Opioid Agonist Therapy (siOAT)

In the Phase 3 clinical trial which demonstrated the efficacy of injectable hydromorphone in siOAT for patients with severe, refractory opioid use disorder, patients were excluded if they had a serum bilirubin >2.5 x normal or Stage II or greater hepatic encephalopathy.

Caution should be exercised in prescribing siOAT to patients with chronic hepatic disease. Oral treatment options should be preferentially prescribed in individuals with greater degrees of hepatic impairment.

Patients with Renal Impairment:

General

The pharmacokinetics of hydromorphone following an oral administration of hydromorphone at a single 4 mg dose (2 mg hydromorphone immediate-release tablets) are affected by renal impairment. Mean exposure to hydromorphone (C_{max} and $AUC_{0-\infty}$) is increased by 2-fold in patients with moderate (CLcr = 40 - 60 mL/min) renal impairment and increased by 4-fold in patients with severe (CLcr < 30 mL/min) renal impairment compared with normal subjects (CLcr > 80 mL/min). In addition, in patients with severe renal impairment, hydromorphone appeared to be more slowly eliminated with a longer terminal elimination half-life (40 hr) compared to patients with normal renal function (15 hr).

Supervised Injectable Opioid Agonist Therapy (siOAT)

Caution should be exercised in prescribing siOAT to patients with chronic renal disease.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The adverse effects of HYDROmorphone Hydrochloride Injection, USP is similar to those of other opioid analgesics and represent an extension of pharmacological effects of the drug class. The major hazards include respiratory depression, central nervous system depression and apnea. To a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest have occurred.

Supervised Injectable Opioid Agonist Therapy and Opioid Withdrawal Symptoms
Opioid agonist treatment is designed to prevent withdrawal symptoms. Withdrawal symptoms and signs include lacrimation, rhinorrhea, sneezing, yawning, excessive perspiration, gooseflesh, fever, chilliness alternating with flushing, restlessness, irritability, weakness, anxiety, depression, dilated pupils, tremors, tachycardia, abdominal cramps, body aches, involuntary twitching and kicking movements, anorexia, nausea, vomiting, diarrhea, intestinal spasms, and weight loss. Withdrawal symptoms should be recognized and managed accordingly.

The most frequently observed adverse effects of hydromorphone are constipation, lightheadedness, dizziness, sedation, nausea, vomiting and hyperhidrosis.

Sedation: Sedation is a common side effect of opioid analgesics, especially in opioid naïve individuals. Sedation may also occur partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Most patients develop tolerance to the sedative effects of opioids within three to five days and, if the sedation is not severe, will not require any treatment except reassurance. If excessive sedation persists beyond a few days, the dose of the opioid should be reduced and alternate causes investigated. Some of these are: concurrent CNS depressant medication, hepatic or renal dysfunction, brain metastases, hypercalcemia and respiratory failure. If it is necessary to reduce the dose, it can be carefully increased again after three or four days if it is obvious that the pain is not being well controlled. Dizziness and unsteadiness may be caused by postural hypotension, particularly in elderly or debilitated patients, and may be alleviated if the patient lies down.

Nausea and Vomiting: Nausea is a common side effect on initiation of therapy with opioid analgesics and is thought to occur by activation of the chemoreceptor trigger zone, stimulation of the vestibular apparatus and through delayed gastric emptying. The prevalence of nausea declines following continued treatment with opioid analgesics. When instituting prolonged therapy with an opioid for chronic pain, the routine prescription of an antiemetic should be considered. In the cancer patient, investigation of nausea should include such causes as constipation, bowel obstruction, uremia, hypercalcemia, hepatomegaly, tumor invasion of celiac plexus and concurrent use of drugs with emetogenic properties. Persistent nausea which does not respond to dosage reduction may be caused by opioid-induced gastric stasis and may be accompanied by other symptoms including anorexia, early satiety, vomiting and abdominal fullness. These symptoms respond to chronic treatment with gastrointestinal prokinetic agents.

Constipation: Practically all patients become constipated while taking opioids on a persistent basis. In some patients, particularly the elderly or bedridden, fecal impaction may result. It is essential to caution the patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged opioid therapy. Stimulant laxatives, stool softeners, and other appropriate measures should be used as required. As fecal impaction may present as overflow diarrhea, the presence of constipation should be excluded in patients on opioid therapy prior to initiating treatment for diarrhea.

The following adverse effects occur with opioid analgesics and include those reported in hydromorphone clinical trials, for indications other than siOAT, as well as post-marketing adverse events related to hydromorphone. The reactions are categorized by body system and frequency according to the following definitions: Very common (≥ 1/10); Common (≥ 1/100 to <1/10); Uncommon (≥ 1/1,000 to <1/100); Rare (≥ 1/10,000 to <1/1000); Very rare (< 1/10,000), Not known (cannot be estimated from the available data).

Immune System Disorders:
Not known: Anaphylactic reactions and hypersensitivity reactions (including oropharyngeal swelling).

Metabolism and Nutrition Disorders:
Common: decreased appetite

Psychiatric Disorders:
Common: anxiety, confusional state, insomnia, euphoric mood, dysphoria
Uncommon: agitation, depression, hallucination, nightmares, mood altered
Not known: drug dependence, nervousness, disorientation

Nervous System Disorders:
Very common: dizziness, somnolence, sedation
Common: headache
Uncommon: myoclonus, paraesthesia, tremor, presyncope
Rare: lethargy
Not known: convulsions, dyskinesia, hyperalgesia, syncope, increased intracranial pressure, nystagmus

Eye Disorders:
Uncommon: visual impairment
Not known: blurred vision, miosis, diplopia

Cardiac Disorders:
Rare: bradycardia, palpitations, tachycardia

Vascular Disorders:
Very common: flushing
Uncommon: hypotension
Not known: hypertension

Respiratory, Thoracic and Mediastinal Disorders:
Uncommon: dyspnea
Rare: respiratory depression
Not known: bronchospasm, and laryngospasm

Gastrointestinal Disorders:
Very common: constipation, nausea
Common: abdominal pain, dry mouth, vomiting
Uncommon: diarrhea, dysgeusia
Not known: paralytic ileus

Hepatobiliary Disorders:
Uncommon: hepatic enzymes increased
Not known: biliary colic

Skin and Subcutaneous Tissue Disorders:
Common: pruritus, hyperhidrosis

Uncommon: rash
Not known: urticaria

Musculoskeletal and Connective Tissue Disorders
Common: muscle contractions involuntary
Not known: muscle rigidity

Renal and Urinary Disorders:
Uncommon: urinary hesitancy, urinary retention

Reproductive System and Breast Disorders:
Uncommon: erectile dysfunction

General Disorders and Administration Site Conditions:
Common: asthenia, injection site reaction, weakness
Uncommon: drug withdrawal syndrome, fatigue, malaise, peripheral edema
Not known: drug tolerance, chills, drug withdrawal syndrome neonatal, feeling abnormal

Supervised Injectable Opioid Agonist Therapy (siOAT) Adverse Reactions
In the 6-month Phase 3 clinical trial which demonstrated the efficacy of injectable hydromorphone in siOAT for patients with severe, refractory opioid use disorder, adverse events considered drug-related occurred in 48% of patients taking hydromorphone and serious adverse events considered drug-related occurred in 3% of patients taking hydromorphone. In these patients, immediate post-injection reaction or injection site pruritus occurred in 16% of patients and somnolence in 16% of patients. There were serious adverse events of opioid overdose requiring naloxone in 2% of patients.

Post-Marketing Experience
The following adverse reactions have been identified during post approval use of hydromorphone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use (see **WARNINGS AND PRECAUTIONS-Endocrine**).

Anaphylaxis: Anaphylactic reaction has been reported with ingredients contained in **HYDROmorphone Hydrochloride Injection, USP**.

There have also been post-marketing reports of Neonatal Opioid Withdrawal Syndrome (NOWS) in patients treated with hydromorphone (see **WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome (NOWS)**).

Androgen deficiency: Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in

studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

DRUG INTERACTIONS

Overview

Interaction with Benzodiazepines and Other CNS Depressants: Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants (e.g. other opioids, sedatives/hypnotics, antidepressants, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, phenothiazines, neuroleptics, antihistamines, antiemetics, and alcohol) as well as beta-blockers, increases the risk of respiratory depression, profound sedation, coma, and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see WARNINGS AND PRECAUTIONS, Neurologic, Interactions with CNS Depressants (including benzodiazepines and alcohol) and Psychomotor Impairment). HYDROmorphone Hydrochloride Injection, USP should not be administered when alcohol is consumed as this may increase the chance of experiencing dangerous side effects.

Drug-Drug Interactions

Administration with Mixed Activity Agonist/Antagonist Opioids:

Analgesia

Mixed agonist/antagonist opioid analgesics (i.e., pentazocine, nalbuphine, butorphanol, and buprenorphine) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as hydromorphone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of hydromorphone and/or may precipitate withdrawal symptoms in these patients.

Supervised Injectable Opioid Agonist Therapy (siOAT)

The use of mixed agonist/antagonist or partial agonist analgesics in patients receiving siOAT with hydromorphone may precipitate withdrawal symptoms.

MAO Inhibitors: MAO Inhibitors intensify the effects of opioid drugs which can cause anxiety, confusion and decreased respiration. HYDROmorphone Hydrochloride Injection, USP is contraindicated in patients receiving MAO Inhibitors or who have used them within the previous 14 days (see CONTRAINDICATIONS).

Serotonergic Agents: Coadministration of hydromorphone with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor or a Serotonin Norepinephrine Re-uptake Inhibitor, may increase the risk of serotonin syndrome, a potentially life-threatening condition (see WARNINGS AND PRECAUTIONS, Neurologic).

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

The concomitant use of alcohol should be avoided (see WARNINGS AND PRECAUTIONS, General).

DOSAGE AND ADMINISTRATION

HYDROmorphone Hydrochloride Injection, USP is a highly concentrated solution of hydromorphone hydrochloride. It should be used only in opioid tolerant patients requiring a high dose or a high concentration of opioid agonist. Do not confuse HYDROmorphone Hydrochloride Injection, USP, 10 mg / mL with the lower concentration of the HYDROmorphone Hydrochloride Injection, USP, 2 mg / mL since overdosage and death could result.

Dosing Considerations

Analgesia

- **For acute pain, it is recommended that HYDROmorphone Hydrochloride Injection, USP be used for a maximum of 7 days at the lowest dose that provides adequate pain relief.**

- All doses of opioids carry an inherent risk of fatal or non-fatal adverse events. This risk is increased with higher doses. For the management of chronic non-cancer, non-palliative pain, it is recommended that 13.5 mg (90 mg morphine milligram equivalent) of HYDROmorphone Hydrochloride Injection, USP not be exceeded. Each patient should be assessed for their risk prior to prescribing HYDROmorphone Hydrochloride Injection, USP as the likelihood of experiencing serious adverse events can depend upon the type of opioid, duration of treatment, level of pain as well as the patient's own level of tolerance. In addition, the level of pain should be assessed routinely to confirm the most appropriate dose and the need for further use of HYDROmorphone Hydrochloride Injection, USP (see Dosage And Administration - Adjustment or reduction of Dosage).

- **HYDROmorphone Hydrochloride Injection, USP should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics).**

- HYDROmorphone Hydrochloride Injection, USP should be used with caution within 12 hours pre-operatively and within the first 12-24 hours post-operatively (see WARNINGS AND PRECAUTIONS, Peri-Operative Considerations).

- See **Recommended Dose and Dose Adjustment – Analgesia.**

Supervised Injectable Opioid Agonist Therapy (siOAT)

- Dosing must be individualized for each patient. Patients prescribed hydromorphone for supervised injectable opioid agonist therapy of severe, refractory opioid use disorder should be carefully monitored and provided appropriate supportive psychological and social services.

- Prescribers should be experienced in siOAT, and are referred to regional and/or national clinical treatment guidelines regarding recommended dosing protocols.

- See **Recommended Dose and Dose Adjustment – siOAT.**

Recommended Dose and Dosage Adjustment

Analgesia

High concentration hydromorphone preparations are indicated for relief of severe pain in opioid tolerant patients. Thus, these patients will already have received opioid analgesics. If the patient is being changed from one injectable form of hydromorphone to higher concentration hydromorphone preparations, similar doses should be used, depending on the patient's clinical response to the drug. If high concentration hydromorphone preparations are substituted for a different opioid analgesic, Table 1 is provided as a guide to determine the approximate equivalent dose of hydromorphone. Further dose reductions should be considered due to incomplete cross- tolerance between opioids.

Opioid Rotation in Analgesia: Conversion ratios for opioids are subject to variations in kinetics governed by genetics and other factors. When switching from one opioid to another, consider **reducing the calculated dose by 25-50%** to minimize the risk of overdose. Subsequently, up-titrate the dose, as required, to reach the appropriate maintenance dose.

Table 1: Opioid Analgesics - Approximate Analgesic Equivalences[a]

Drug	Equivalent Dose (mg)[b] (compared to morphine 10 mg IM)		Duration of Action (hours)
	Parenteral	Oral	
Strong Opioid Agonists:			
Morphine	10	60[c]	3 - 4
Oxycodone	15	30[d]	2 - 4
Hydromorphone	1.5	7.5	2 - 4
Anileridine	25	75	2 - 3
Levorphanol	2	4	4 - 8
Meperidine[f]	75	300	1 - 3
Oxymorphone	1.5	5 (rectal)	3 - 4
Methadone[e]	-	-	-
Heroin	5 - 8	10 - 15	3 - 4
Weak Opioid Agonists:			
Codeine	120	200	3 - 4
Propoxyphene	50	100	2 - 4
Mixed Agonist-Antagonist[g]			
Pentazocine[f]	60	180	3 - 4
Nalbuphine	10	-	3 - 6
Butorphanol	2	-	3 - 4

Footnotes:

[a] References:
Expert Advisory Committee on the Management of Severe Chronic Pain in Cancer Patients, Health and Welfare Canada. Cancer pain: A monograph on the management of cancer pain. Ministry of Supplies and Services Canada, 1987. Cat. No. H42-2/5-1984E.

Foley KM. The treatment of cancer pain. N Engl J Med 1985;313(2):84-95
Aronoff, GM, Evans WO. Pharmacological management of chronic pain: A review. In: Aronoff GM, editor. Evaluation and Treatment of Chronic Pain, 2nd Ed. Baltimore (MD): Williams and Wilkins, 1992. p. 359-68.
Cherny, NI. and Portenoy, RK. Practical issues in the management of cancer pain. In: Wall PD, Melzack R, editors. Textbook of Pain, 3rd Ed. P.H. Wall and R. Melzack (Eds.) New York: Churchill Livingstone; 1994. p. 1437-67.

[b] **Most of these data were derived from single-dose, acute pain studies and should be considered an approximation for selection of doses when treating chronic pain. As analgesic conversion factors are approximate and patient response may vary, dosing should be individualized according to relief of pain and side effects. Because of incomplete cross-tolerance, dose reductions of 25-50% of the equianalgesic dose may be appropriate in some patients when converting from one opioid to another, particularly at high doses.† Upward titration may be required to reach appropriate maintenance doses.**
†Levy MH. Pharmacologic treatment of cancer pain. N Engl J Med 1996;335:1124-32.

[c] **For acute pain, the oral or rectal dose of morphine is six times the injectable dose. However, for chronic dosing, clinical experience indicates that this ratio is 2 - 3:1 (i.e., 20-30 mg of oral or rectal morphine is equivalent to 10 mg of parenteral morphine).**

[d] Based on single entity oral oxycodone in acute pain.

[e] Extremely variable equianalgesic dose. Patients should undergo individualized titration starting at an equivalent to 1/10 of the morphine dose.

[f] Not recommended for the management of chronic pain.

[g] Mixed agonist-antagonists can precipitate withdrawal in patients on pure opioid agonists.

Dose Titration in Analgesia: Dose titration is the key to success with opioid analgesic therapy. Proper optimization of doses scaled to the relief of the individual's pain should aim at the administration of the lowest dose which will achieve the overall treatment goal of satisfactory pain relief with acceptable side effects.

Dosage adjustments should be based on the patient's clinical response.

Adjustment or Reduction of Dosage in Analgesia:
Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including HYDROmorphone Hydrochloride Injection, USP. Withdrawal (abstinence) symptoms may occur following abrupt discontinuation of therapy. These symptoms may include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning.

Following successful relief of severe pain, periodic attempts to reduce the opioid dose should be made. Smaller doses or complete discontinuation may become feasible due to a change in the patient's condition or mental state. Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal for the drug, these symptoms are usually mild (see WARNINGS AND PRECAUTIONS). Tapering should be individualized and carried out under medical supervision.

Patients should be informed that reducing and/or discontinuing opioids decreases their tolerance to these drugs. If treatment needs to be re-initiated, the patient must start at the lowest dose and titrate up to avoid overdose.

Opioid analgesics may only be partially effective in relieving dysesthetic pain, postherpetic neuralgia, stabbing pains, activity-related pain and some forms of headache. That is not to say that patients with advanced cancer suffering from some of these forms of pain should not be given an

adequate trial of opioid analgesics, but it may be necessary to refer such patients at an early time to other forms of pain therapy.

A gradual increase in dose may be required if analgesia is inadequate, tolerance occurs, or if pain severity increases. The first sign of tolerance is usually a reduced duration of effect.

Supervised Injectable Opioid Agonist Therapy (siOAT)
Initiation and titration of hydromorphone should be done carefully and individually to minimize hazards, particularly those related to opioid overdose.

In the phase 3 clinical trial which demonstrated the efficacy of supervised injectable hydromorphone for severe, refractory opioid use disorder, by the end of the titration period hydromorphone was dosed up to three times per day, supplemented with oral methadone as needed. Following titration, the average total daily dose of hydromorphone received in the trial was approximately 261 mg per day. Serious adverse events in the trial were not confined to the titration phase, indicating that patient supervision and monitoring remains essential throughout treatment to minimize serious risks associated with injectable hydromorphone use in siOAT.

Missed Dose / Treatment Interruption
Withdrawal symptoms may occur following missed doses and are expected after abrupt discontinuation of therapy. If siOAT is interrupted, re-initiation of dose titration may be necessary, starting at a decreased dose, for patient safety, since rapid loss of tolerance may occur, posing a significant risk of overdose. Prescribers are referred to regional and/or national clinical treatment guidelines regarding recommended dosing protocols, including missed dose protocols.

Prescribers are also referred to the Product Monographs for methadone products indicated for treatment of opioid use disorder, as appropriate.

Patients with Hepatic Impairment:
Due to increased exposure of hydromorphone, patients with moderate hepatic impairment should be started at one-fourth to one-half the recommended starting dose depending on the degree of hepatic dysfunction and closely monitored during dose titration.

Patients with Renal Impairment:
Start patients with renal impairment on one-fourth to one-half the usual starting dose depending on the degree of impairment. Patients with renal impairment should be closely monitored during dose titration.

Geriatrics:
Respiratory depression has occurred in the elderly following administration of large initial doses of opioids to patients who were not opioid-tolerant or when opioids were co-administered with other agents that can depress respiration. HYDROmorphone Hydrochloride Injection, USP should be initiated at a low dose and slowly titrated to effect (see WARNINGS AND PRECAUTIONS).

Administration
General
HYDROmorphone Hydrochloride Injection, USP is to be visually inspected prior to use. Only clear solutions practically free from particles should be used. The injection should be given immediately after opening the vial. Once opened, any unused portion should be discarded.

HYDROmorphone Hydrochloride Injection, USP has been reported to be physically or chemically incompatible with solutions containing sodium bicarbonate and thiopenthal sodium.

Rapid intravenous injection of opioid analgesics increases the possibility of hypotension and respiratory depression.

In open clinical trials with hydromorphone in patients with terminal cancer, both subcutaneous and intramuscular injections of hydromorphone were well-tolerated, with minimal pain and/or burning at the injection site. Mild erythema was rarely noted after intramuscular injection. Subcutaneous injections of hydromorphone were particularly well-tolerated when administered with a short, 30 gauge needle. In addition, continuous subcutaneous infusions of hydromorphone have been shown to be well-tolerated. The most common adverse reaction is local tissue redness which can be relieved with more frequent site changes. Experience with administration of hydromorphone by the intravenous route is limited. Should intravenous administration be necessary for analgesia, the injection should be given slowly, over at least 2 to 3 minutes. Rapid intravenous injection of opioid analgesics increases the possibility of hypotension and respiratory depression. The intravenous route is usually painless.

Disposal

General

HYDROmorphone Hydrochloride Injection, USP should be kept in a safe place, such as under lock and out of the sight and reach of children before, during and after use. HYDROmorphone Hydrochloride Injection, USP should not be used in front of children, since they may copy these actions.

HYDROmorphone Hydrochloride Injection, USP should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired HYDROmorphone Hydrochloride Injection, USP should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets. HYDROmorphone Hydrochloride Injection, USP should not be shared with others and steps should be taken to protect it from theft or misuse. The patient should speak to their pharmacist about temporary storage options, if required, until the medication can be returned to the pharmacy for safe disposal.

OVERDOSAGE

For management of a suspected drug overdose, contact your Regional Poison Control Centre immediately.

Symptoms: Serious overdosage with HYDROmorphone Hydrochloride Injection, USP (Hydromorphone hydrochloride) is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), dizziness, confusion, extreme somnolence progressing to stupor or coma, pneumonia aspiration, skeletal muscle flaccidity, cold and clammy skin, constricted pupils and sometimes bradycardia and hypotension. In severe overdosage, particularly following intravenous injection, apnea, circulatory collapse, cardiac arrest and death may occur.

Treatment: In the treatment of overdosage, primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. It should be borne in mind that for individuals who are physically dependent on opioids and are receiving large doses of these drugs, the administration of the usual dose of opioid antagonist will precipitate an acute withdrawal syndrome. The severity will depend on the degree of physical dependence and the dose of the antagonist administered. Use of an opioid antagonist in such persons should be avoided. If necessary to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care and by titration, commencing with 10 to 20% of the usual recommended initial dose.

Respiratory depression which may result from overdosage, or unusual sensitivity to hydromorphone in a non-opioid-tolerant patient, can be managed with the opioid antagonist naloxone. A dose of naloxone (usually 0.4 to 2.0 mg) should be administered intravenously, if possible, simultaneously with respiratory resuscitation. The dose can be repeated in 3 minutes. Naloxone should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Naloxone should be administered cautiously to persons who are known or suspected to be physically dependent on hydromorphone. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome.

Since the duration of action of hydromorphone may exceed that of the antagonist, the patient should be kept under continued surveillance; repeated doses of the antagonist may be required to maintain adequate respiration. Other supportive measures should be applied when indicated.

Supportive measures, including oxygen and vasopressors, should be employed in the management of circulatory shock and pulmonary edema accompanying overdose, as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Hydromorphone hydrochloride is a hydrogenated ketone of morphine. It is an opioid analgesic with many of the effects common to the class of drugs.

Opioid analgesics have multiple actions but exert their primary effects on the central nervous system and organs containing smooth muscle. The principal actions of therapeutic value are analgesia and sedation. Opioid analgesics also suppress the cough reflex and cause respiratory depression, mood changes, mental clouding, euphoric mood, dysphoria, nausea, vomiting, increased cerebrospinal fluid pressure, pinpoint constriction of the pupils, increased biliary tract pressure, increased parasympathetic activity and transient hyperglycemia.

The precise mode of analgesic action of opioid analgesics is unknown. However, specific CNS opiate receptors have been identified. Opioids are believed to express their pharmacological effects by combining with these receptors.

Pharmacodynamics

The relationship between plasma concentration of hydromorphone and analgesic effect has not been well established. In patients with chronic pain, hydromorphone should be titrated to the dose required to adequately relieve pain without unmanageable side effects. There is no intrinsic limit to

the analgesic effect of hydromorphone; adequate doses will relieve even the most severe pain. Clinically, however, dosage limitations are imposed by the adverse effects, primarily respiratory depression; nausea and vomiting which can result from high doses.

Cardiovascular System:
Hydromorphone may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, flushing, red eyes, hyperhidrosis and/or orthostatic hypotension.

Central Nervous System:
Hydromorphone produces respiratory depression by direct action on brain stem respiratory centres. The respiratory depression involves both a reduction in the responsiveness of the brain stem centres to increases in CO_2 tension and to electrical stimulation.

Hydromorphone depresses the cough reflex by direct effect on the cough centre in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia. Hydromorphone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of hydromorphone overdose.

Endocrine System:
Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may be manifest from these hormonal changes.

Gastrointestinal Tract and Other Smooth Muscle:
Hydromorphone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Hepatobiliary System:
Opioids may induce biliary spasm.

Immune System:
In vitro and animal studies indicate that opioids have a variety of effects on immune functions, depending on the context in which they are used. The clinical significance of these findings is unknown.

Pharmacokinetics
Distribution: Following intravenous administration of hydromorphone to normal volunteers, the mean t½ of elimination was 2.65 +/- 0.88 hours. The mean volume of distribution was 91.5 liters, suggesting extensive tissue uptake. Hydromorphone is rapidly removed from the bloodstream and distributed to skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen and brain. It also crosses the placental membranes.

Metabolism: In normal human volunteers hydromorphone is metabolized primarily in the liver.

Elimination: It is excreted predominantly as the glucuronidated conjugate, with small amounts of parent drug and minor amounts of 6-hydroxy reduction metabolites.

Estimates of the relative analgesic potency of parenterally administered hydromorphone to morphine in acute pain studies in man range from approximately 7:1 to 11:1. After intramuscular administration, hydromorphone has a slightly more rapid onset and slightly shorter duration of action than morphine. The duration of analgesia in the non-tolerant patient with usual doses may be up to 4 to 5 hours. However, in opioid tolerant subjects, duration of analgesia will vary substantially depending on tolerance and dose. Dose should be adjusted so that 3 to 4 hours of pain relief may be achieved.

Special Populations and Conditions

Pediatrics:

Individuals under 18 years of age should not use HYDROmorphone Hydrochloride Injection, USP.

STORAGE AND STABILITY

Store at 15 °C to 30°C. Protect from light. Do not use beyond the expiry date indicated on the label. Discard unused portion.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition:

HYDROmorphone Hydrochloride Injection, USP: Each mL contains hydromorphone hydrochloride 10 mg, citric acid 2 mg, sodium citrate 2 mg, and water for injection.

Packaging:

HYDROmorphone Hydrochloride Injection, USP is available in 1 mL, 5 mL and 50 mL single use vials. The 1 mL and 5 mL vials are available in boxes of 10. The 50 mL vial is available in boxes of 1.

Dilution For Intravenous Use:

HYDROmorphone Hydrochloride Injection, USP may be diluted for IV infusion in 5% Dextrose Injection, 0.9% Sodium Chloride Injection or Ringer's Injection. The diluted preparations are chemically stable for 24 hours at room temperature when diluted to 0.08 mg / mL with 5% Dextrose Injection, 0.9% Sodium Chloride Injection or Ringer’s Injection.

All presentations of HYDROmorphone Hydrochloride Injection, USP are for single use only.

Discard any unused portions.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

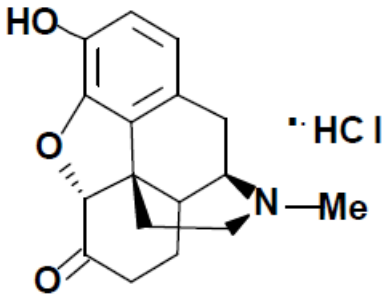
Proper Name: Hydromorphone Hydrochloride

Chemical Name: Morphinan-6-one, 4,5-epoxy-3-hydroxy-17-methyl-, hydrochloride, (5α)-
4,5α-Epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride

Molecular Formula: $C_{17}H_{19}NO_3 \cdot HCl$

Molecular Mass: 321.80 g/mol

Structural Formula:



Physicochemical Properties

Appearance: White to off-white odorless powder

Solubility: Soluble in 3 parts water and sparingly soluble in alcohol.

Melting Point: Decomposes at 305 °C to 315 °C.

pKa: 8.095 ± 0.013 (basic)
9.190 ± 0.013 (acidic)

REFERENCES

Sandoz Canada Inc., Prescribing Information: [N]Hydromorphone HP 10. Control No.: 223245. Date of Revision: April 30, 2019.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

[N]HYDROmorphone Hydrochloride Injection, USP

(Hydromorphone Hydrochloride Injection, USP)

Solution; 10 mg / mL

Read this carefully before you start taking HYDROmorphone Hydrochloride Injection, USP and each time you get a refill if you use it for pain. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about HYDROmorphone Hydrochloride Injection, USP.

Serious Warnings and Precautions

- **HYDROmorphone Hydrochloride Injection, USP is a highly concentrated solution of hydromorphone hydrochloride. You should only be taking this medication if you are already taking high doses or high concentrations of opioids.**
- **Even if you take HYDROmorphone Hydrochloride Injection, USP as prescribed you are at a risk for opioid addiction, abuse and misuse. This can lead to overdose and death.**
- **You may get life-threatening breathing problems while taking HYDROmorphone Hydrochloride Injection, USP. This is less likely to happen if you take it as prescribed by your doctor. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.**
- **You should never give anyone your HYDROmorphone Hydrochloride Injection, USP. They could die from taking it. If a person has not been prescribed HYDROmorphone Hydrochloride Injection, USP, taking even one dose can cause a fatal overdose. This is especially true for children.**
- **If you took HYDROmorphone Hydrochloride Injection, USP while you were pregnant, whether for short or long periods of time or in small or large doses, your baby can suffer life-threatening withdrawal symptoms after birth. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has any of the following symptoms:**
  - **has changes in their breathing (such as weak, difficult or fast breathing)**
  - **is unusually difficult to comfort**
  - **has tremors (shakiness)**
  - **has increased stools, sneezing, yawning, vomiting, or fever**

  Seek immediate medical help for your baby.
- **Taking HYDROmorphone Hydrochloride Injection, USP with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.**
- **If you are taking HYDROmorphone Hydrochloride Injection, USP for treatment for opioid use disorder, do not inject it into your neck or groin.**

What is HYDROmorphone Hydrochloride Injection, USP used for?
HYDROmorphone Hydrochloride Injection, USP is used in adults (18 years of age and older) for the:

- Relief of severe pain. It is used only in patients who need an injectable opioid in doses or concentrations higher than usually needed.
- Treatment of severe opioid use disorder. It is used for patients who are using injectable opioids who have not been helped by other medication. Patients take HYDROmorphone Hydrochloride Injection, USP:
    - under the care of a doctor
    - in a safe, supervised place for injection treatment
    - as part of a complete treatment program that includes medical, social and psychological support

How does HYDROmorphone Hydrochloride Injection, USP work?
HYDROmorphone Hydrochloride Injection, USP belongs to the class of drugs known as opioids. This class of drugs also include heroin, codeine, fentanyl, morphine and oxycodone. Opioids relieve pain by acting on specific nerve cells of the spinal cord and brain. They may also be used to help people who are dependent on injected opioids who have not been helped by other medication, such as methadone.

What are the ingredients in HYDROmorphone Hydrochloride Injection, USP?
Medicinal ingredient: hydromorphone hydrochloride
Non-medicinal ingredients: citric acid, sodium citrate, and water.

HYDROmorphone Hydrochloride Injection, USP comes in the following dosage forms:
Solution; 10 mg / mL: 1 mL, 5 mL and 50 mL single-use vials.

Do not use HYDROmorphone Hydrochloride Injection, USP if:

- your doctor did not prescribe it for you
- you are not already taking high doses or high concentrations of opioids
- you are allergic to hydromorphone, other opioids, or to any of the other ingredients in HYDROmorphone Hydrochloride Injection, USP (see **What the non-medicinal ingredients list above**);
- you are taking this medication for pain, and you can control your pain by the occasional use of other pain medications. This includes those available without a prescription
- you have severe asthma, trouble breathing, or other breathing problems
- you have any heart problems
- you have bowel blockage or narrowing of the stomach or intestines or you have severe pain in your abdomen
- you have a head injury
- you are at risk for seizures
- you suffer from alcoholism
- you are taking or have taken within the past 2 weeks a monoamine oxidase (MAO) inhibitor (such as phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline)
- you are going to have, or recently had, a planned surgery
- you are pregnant or planning to become pregnant or you are in labour
- you are breastfeeding
- you are taking this medication for the supervised treatment of opioid use disorder and you also had alcohol, benzodiazepines (also known as “downers”), stimulants (also known as “uppers”) or other street drugs

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take HYDROmorphone Hydrochloride Injection, USP. Talk about any health conditions or problems you may have, including if you:

- have a history of illicit or prescription drug or alcohol abuse
- have severe kidney disease, liver or lung disease
- have heart disease
- have low blood pressure
- have past or current depression
- suffer from chronic or severe constipation
- have problems with your thyroid, adrenal or prostate gland
- have, or had in the past hallucinations or other severe mental problems
- suffer from migraines
- have suffered a head injury
- take any other medicines, especially tranquilizers, sedatives, medicine for depression, or mania (manic depression) or for other mental health conditions or pain, or if you take any street drugs
- are taking this medicine for supervised treatment of opioid use disorder and:
    - you have missed a dose or doses. Your doctor may need to change your dose before you can restart your medication to help prevent serious side effects and overdose
    - you don't feel well and have a fever (in case you have an infection)
    - you are taking methadone
    - you are taking blood thinners

Other warnings you should know about:

Opioid dependence and addiction: There are important differences between physical dependence and addiction. It is important that you talk to your doctor if you have questions or concerns about abuse, addiction or physical dependence.

Pregnancy, nursing, labour and delivery: Do not use HYDROmorphone Hydrochloride Injection, USP while pregnant, nursing, during labour or delivery. Opioids can be transferred to your baby through breast milk, or while still in the womb. HYDROmorphone Hydrochloride Injection, USP can then cause life-threatening breathing problems in your unborn baby or nursing infant.

If you are pregnant and are taking HYDROmorphone Hydrochloride Injection, USP, it is important that you don't stop taking your medication all of a sudden. If you do, it can cause a miscarriage or a still-birth. Your doctor will monitor and guide you on how to slowly stop taking Hydrochloride Injection, USP. This may help avoid serious harm to your unborn baby.

Driving and using machines: Before you do tasks which may require special attention, you should wait until you know how you react to HYDROmorphone Hydrochloride Injection, USP. It can cause:

- drowsiness
- dizziness or
- light headedness

This can usually occur after you take your first dose and when your dose is increased.

Disorder of the adrenal gland: You may develop a disorder of the adrenal gland called adrenal insufficiency. This means that your adrenal gland is not making enough of certain hormones. You may experience symptoms such as:

- nausea, vomiting
- feeling tired, weak or dizzy
- decreased appetite

You may be more likely to have problems with your adrenal gland if you have been taking opioids for longer than one month. Your doctor may do tests, give you another medication, and slowly take you off HYDROmorphone Hydrochloride Injection, USP.

Serotonin Syndrome: HYDROmorphone Hydrochloride Injection, USP can cause Serotonin Syndrome, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop Serotonin Syndrome if you take HYDROmorphone Hydrochloride Injection, USP with certain anti-depressants or migraine medications.

Serotonin Syndrome symptoms include:
- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

Sexual Function/Reproduction: Long term use of opioids may lead to a decrease in sex hormone levels. It may also lead to low libido (desire to have sex), erectile dysfunction or being infertile.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with HYDROmorphone Hydrochloride Injection, USP:
- Alcohol. This includes prescription and non-prescription medications that contain alcohol. **Do NOT** drink alcohol while you are taking HYDROmorphone Hydrochloride Injection, USP. It can lead to:
  - drowsiness
  - unusually slow or weak breathing
  - serious side effects or
  - a fatal overdose
- other sedative drugs which may enhance the drowsiness caused by HYDROmorphone Hydrochloride Injection, USP
- other opioid analgesics (drugs used to treat pain)
- general anesthetics (drugs used during surgery)
- benzodiazepines (drugs used to help you sleep or that help reduce anxiety)
- antidepressants (for depression and mood disorders). **Do NOT** use HYDROmorphone Hydrochloride Injection, USP with MAO inhibitors (MAOi) or if you have taken MAOi's in the last 14 days.
- drugs used to treat serious mental or emotional disorders, such as mania (manic depression) or schizophrenia
- antihistamines (drugs used to treat allergies)
- anti-emetics (drugs used for the prevention of vomiting)
- drugs used to treat muscle spasms and back pain
- some heart medication (such as beta blockers)

- drugs used to treat migraines (e.g. triptans)
- St. John's Wort

How to take HYDROmorphone Hydrochloride Injection, USP:

HYDROmorphone Hydrochloride Injection, USP is a highly concentrated solution of hydromorphone hydrochloride. You should only be taking this medication if you are already taking high doses or high concentrations of opioids.

Before you take HYDROmorphone Hydrochloride Injection, USP check the vial. Only clear solutions free from particles should be used.

The injection should be taken right away after opening the vial. Once opened, any unused portion should be thrown away. HYDROmorphone Hydrochloride Injection, USP is taken as an injection:

- under the skin (subcutaneously) or
- into the muscle (intramuscularly) or
- into the vein (intravenously)

If you are taking this medication for the relief of severe pain:

- Your doctor will prescribe this medication at the lowest dose that works to control your pain.
- Take your medication **exactly** as your doctor has told you.
- You should only take this medication for a maximum of 7 days. If you need to take it for longer, your doctor will determine the best dose for you to lower the risk of side effects. Taking higher doses can lead to more side effects and a greater chance of overdose.
- You should review your pain regularly with your doctor to determine if you still need to take HYDROmorphone Hydrochloride Injection, USP.
- Tell your doctor right away if your pain gets worse while taking HYDROmorphone Hydrochloride Injection, USP
- Tell your doctor if you have missed a dose or several doses in a row. Your doctor may need to change your dose before you can restart your medication.

Refilling your Prescription:

- A new written prescription is required from your doctor each time you need more HYDROmorphone Hydrochloride Injection, USP. Therefore, it is important that you contact your doctor before your current supply runs out.
- Only obtain prescriptions for this medicine from the doctor in charge of your treatment. **Do NOT** seek prescriptions from other doctors unless you switch to another doctor for your pain management.

If you are taking this medication for the supervised treatment of opioid use disorder:

- You should only be given this medication under the supervision of a doctor who has experience in the treatment of opioid use disorder and in a medically supervised place where there is equipment available to the doctor in case you experience any serious side effects.
- To lower your risk of feeling side effects or having an overdose and to ensure you take your dose on time, it is important you take this medication **exactly** as your doctor tells you.
- Tell your doctor if you have missed a dose or several doses in a row. Your doctor may need to change your dose before you can restart your medication.
- Your doctor may also prescribe methadone to help you with cravings.
- Tell your doctor **right away** if you have:

- body aches,
- diarrhea,
- goosebumps,
- loss of appetite,
- nausea,
- feeling nervous or restless,
- runny nose,
- sneezing,
- tremors or shivering,
- stomach cramps,
- rapid heart rate,
- have trouble sleeping,
- an unusual increase in sweating,
- heart palpitations,
- an unexplained fever,
- weakness
- yawning

Your doctor may need to change your medication or your dose.

If you develop any side effects (see **What are possible side effects from using HYDROmorphone Hydrochloride Injection, USP) tell your doctor right away.**

Usual Adult Dose:
Your doctor will decide your dose based on your health and age. Your dose is tailored/personalized just for you. Be sure to follow your doctor's dosing instructions **exactly. Do NOT** increase or decrease your dose without first talking to your doctor.

Stopping your Medication:
If you have been taking HYDROmorphone Hydrochloride Injection, USP for more than a few days you should not stop taking it all of a sudden. Your doctor will monitor and guide you on how to slowly stop taking it. You should stop slowly to avoid withdrawal symptoms such as:

- body aches
- diarrhea
- goosebumps
- loss of appetite
- nausea
- feeling nervous or restless
- runny nose
- sneezing
- tremors or shivering
- stomach cramps
- rapid heart rate (tachycardia)
- having trouble sleeping
- an unusual increase in sweating
- heart palpitations
- an unexplained fever
- weakness
- yawning

By reducing or stopping your opioid treatment, your body will become less used to opioids. If you start treatment again, you will need to start at the lowest dose. You may overdose if you restart at the last dose you took before you slowly stopped taking HYDROmorphone Hydrochloride Injection, USP.

Overdose:

If you think you have taken too much HYDROmorphone Hydrochloride Injection, USP**,** contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Signs of overdose may include:

- unusually slow or weak breathing
- dizziness
- confusion
- extreme drowsiness

Missed Dose:
Your doctor will tell you what to do if you miss the dose. **Do NOT** take two doses at once. If you miss a dose or several doses in a row, talk to your doctor before restarting your medication.

What are possible side effects from using HYDROmorphone Hydrochloride Injection, USP?
These are not all the possible side effects you may feel when taking HYDROmorphone Hydrochloride Injection, USP. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Drowsiness
- Insomnia
- Dizziness
- Fainting
- Nausea, vomiting, or a poor appetite
- Dry mouth
- Headache
- Problems with vision
- Weakness, uncoordinated muscle movement
- Lack of muscle strength
- Itching at the site of injection
- Light headedness
- Sweating
- Constipation
- Confusion
- Anxiety
- Feeling agitated
- Abdominal pain
- Injection site reaction
- Low sex drive, impotence (erectile dysfunction), infertility

Talk with your doctor or pharmacist about ways to prevent constipation when you start using

Serious side effects and what to do about them				
Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
RARE	**Overdose:** hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone, cold and clammy skin.			√
	Respiratory Depression: slow, shallow or weak breathing.			√
	Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
	Bowel Blockage (impaction): abdominal pain, severe constipation, nausea			√
	Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite.		√	
	Fast, Slow or Irregular Heartbeat: heart palpitations.		√	
	Low Blood Pressure: dizziness, fainting, light- headedness.	√		
	Serotonin Syndrome: agitation or restlessness, loss of muscle control or muscle twitching, tremor, diarrhea			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- **Keep unused or expired HYDROmorphone Hydrochloride Injection, USP in a secure place to prevent theft, misuse or accidental exposure.**

- **Keep HYDROmorphone Hydrochloride Injection, USP under lock, out of sight and reach of children and pets.**

- Never take medicine in front of small children as they will want to copy you. Accidental ingestion by a child is dangerous and may result in death. If a child accidentally takes HYDROmorphone Hydrochloride Injection, USP, get emergency **help right away**.

- Store at 15 °C to 30 °C. Protect from light. Do not use beyond the expiry date indicated on the label.

Disposal:

HYDROmorphone Hydrochloride Injection, USP should never be thrown into household trash, where children and pets may find it. It should be returned to a pharmacy for proper disposal.

If you want more information about HYDROmorphone Hydrochloride Injection, USP:

- Talk to your healthcare professional
- Find the full prescribing information that is prepared for healthcare professionals and includes this patient medication information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacture's website (https://www.fresenius-kabi.com/en-ca/products/iv-drugs), or by calling 1-877-821-7724 (toll-free-telephone).

This Information is current up to the time of the date of preparation shown below, but more current information may be available from Fresenius Kabi.

Fresenius Kabi Canada Ltd.
165 Galaxy Blvd, Suite 100
Toronto, ON M9W 0C8
Questions or concerns? 1-877-821-7724

Date of Preparation: August 19, 2019