

PRESCRIBING INFORMATION

INCLUDING PATIENT MEDICATION INFORMATION

^NHYDROMorphone Hydrochloride Injection USP

Ready to use

0.4 mg/mL

(50 mL and 100 mL Flexible Plastic Containers)

Sterile Solution

THERAPEUTIC CLASSIFICATION

Opioid Analgesic

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TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION.....3

SUMMARY PRODUCT INFORMATION 3

INDICATIONS AND CLINICAL USE 3

CONTRAINDICATIONS.....3

WARNINGS AND PRECAUTIONS 4

ADVERSE REACTIONS 13

DRUG INTERACTIONS 16

DOSAGE AND ADMINISTRATION 17

OVERDOSAGE..... 21

ACTION AND CLINICAL PHARMACOLOGY..... 22

STORAGE AND STABILITY 24

SPECIAL HANDLING INSTRUCTIONS..... 24

DOSAGE FORMS, COMPOSITION AND PACKAGING 24

PART II: SCIENTIFIC INFORMATION 26

PHARMACEUTICAL INFORMATION 26

REFERENCES..... 27

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE 29

PATIENT MEDICATION INFORMATION..... 29

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0.4 mg/mL (50 and 100 mL Flexible Plastic Containers)

THERAPEUTIC CLASSIFICATION

Opioid Analgesic

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
Intravenous	Sterile Solution for Injection / 0.4 mg/mL	Citric acid, sodium citrate, sodium chloride in water for injection

INDICATIONS AND CLINICAL USE

Adults

HYDROMorphone Hydrochloride Injection USP is indicated exclusively for the relief of severe pain in patients who require intravenously administered opioids in doses or concentrations higher than those usually needed.

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 Hydrochloride Injection USP 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.

CONTRAINDICATIONS

- 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.

- In 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 cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and 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**).

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

HYDROmorphone Hydrochloride Injection USP is a high dose solution of HYDROmorphone hydrochloride. It should be used only in opioid tolerant patients requiring high doses of opioid agonists. Do not confuse HYDROmorphone Hydrochloride Injection USP with the lower dose of HYDROmorphone since overdose and death could result.

High dose HYDROmorphone Hydrochloride Injection USP preparations should be used only if the amount of HYDROmorphone Hydrochloride Injection USP required can be delivered accurately.

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).

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 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.

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 is 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.

Patients should be instructed not to give HYDROmorphone Hydrochloride Injection USP to anyone other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death. 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 for the treatment of pain, 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.

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

Abuse and Misuse

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

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.

Cardiovascular

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.

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

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**).

Use in Drug and Alcohol Addiction

HYDROmorphone is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia. 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.

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 of 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 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 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 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

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 Hydrochloride Injection USP 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 are 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**).

Use in Patients with Chronic Pulmonary Disease: 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**).

Patient Counselling Information

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

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

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, 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 a physician.
4. Patients should be advised that high concentration HYDROmorphone 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 their physician 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, do not abruptly stop without consulting their physician. 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, seek immediate medical attention.
8. 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.
9. Patients should be advised that HYDROmorphone Hydrochloride Injection USP is a potential drug of abuse. They should protect it from theft or misuse.
10. Patients should be advised that HYDROmorphone Hydrochloride Injection USP should never be given to anyone other than the individual for whom it was prescribed.

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.

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 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)**, and **ADVERSE REACTIONS, Post-Marketing Experience**).

Pregnant women using opioids should not discontinue their medication abruptly as this can cause pregnancy complications 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 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**).

Patients with Hepatic Impairment:

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.

Patients with Renal Impairment:

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 ($CL_{cr} = 40 - 60$ mL/min) renal impairment and increased by 4-fold in patients with severe ($CL_{cr} < 30$ mL/min) renal impairment compared with normal subjects ($CL_{cr} > 80$ 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).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The adverse effects of HYDROmorphone are 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.

The most frequently observed adverse effects are constipation, light-headedness, 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, 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 ($\geq 1/10$); Common ($\geq 1/100$ to $<1/10$); Uncommon ($\geq 1/1,000$ to $<1/100$); Rare ($\geq 1/10,000$ to $<1/1,000$); Very rare ($< 1/10,000$), Not known (cannot be estimated from the available data).

Immune System Disorders:

Not known: Anaphylactic reactions, 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

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) and 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 consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

Drug-Drug Interactions

Administration with Mixed Activity Agonist/Antagonist Opioids: 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.

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

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 18 mg (90 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).

Dosing Considerations

HYDROmorphone Hydrochloride Injection USP is a high dose solution of HYDROmorphone hydrochloride. It should be used only in opioid tolerant patients requiring high doses of opioid agonists. Do not confuse HYDROmorphone Hydrochloride Injection USP with the lower dose of HYDROmorphone since overdose and death could result.
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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**).

HYDROmorphone Hydrochloride Injection USP sterile solution for injection 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. Once opened, any unused portion should be discarded.

Recommended Dose and Dosage Adjustment

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.

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

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

Opioid Rotation: 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-Antagonists^g:			
Pentazocine ^f	60	180	3 - 4
Nalbuphine	10	-	3 - 6
Butorphanol	2	-	3 - 4

Footnotes:

a References:

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- b **Most of the 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 becomes 2 to 3:1 (i.e., 20 to 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: 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:

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 individualised and carried out under medical supervision.

Patient 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.

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, 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.

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.

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**).

Disposal

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.

Symptoms: Serious overdose with HYDROmorphone 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 overdose, particularly following intravenous injection, apnea, circulatory collapse, cardiac arrest and death may occur.

Treatment: In the treatment of overdose, 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 CO₂ 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 $t_{1/2}$ 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 between 15°C and 25°C. Protect from light and freezing. Do not use beyond the expiry date indicated on the label.

HYDROmorphone Hydrochloride Injection USP is for single use only. Discard any unused portion.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms and Composition

HYDROmorphone Hydrochloride Injection USP: Each 1 mL of sterile solution contains 0.4 mg of HYDROmorphone hydrochloride, 0.104 mg of citric acid (as anhydrous), 0.137 mg of sodium citrate (as dihydrate) and sodium chloride 0.9% in water for injection; no added preservative. HYDROmorphone Hydrochloride Injection USP is supplied in latex-free containers.

Packaging:

HYDROmorphone Hydrochloride Injection USP is available in:

- 50 mL single-use flexible plastic containers, overwrapped with an opaque film.
- 100 mL single-use flexible plastic containers, overwrapped with an opaque film.

NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. A slight yellowish discoloration may develop in HYDROmorphone solutions. This yellowish colouration is proportional to HYDROmorphone concentration and has a tendency to increase over time. The colouration is of an esthetic nature and not a result of chemical degradation. No loss of potency has been demonstrated. Also, note that HYDROmorphone Hydrochloride Injection USP does not contain any preservatives; therefore, unused portions of the remaining drug in the flexible plastic container should be discarded.

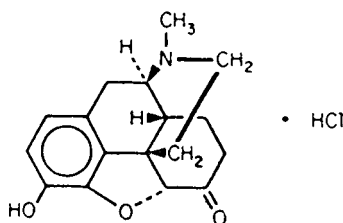
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

HYDROmorphine is a semisynthetic congener of morphine, differing structurally from morphine in the substitution of an oxygen for the 6-hydroxyl group and hydrogenation of the 7-8 double bond of the morphine molecule.

Proper Name:	HYDROmorphine Hydrochloride
Chemical Name:	4,5 α -Epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride
Molecular Formula:	C ₁₇ H ₁₉ NO ₃ •HCl
Molecular Weight:	321.8 g/mol
Structural Formula:	



Physicochemical Properties:	HYDROmorphine hydrochloride is a hydrogenated ketone of morphine.
Appearance:	Fine, white, or practically white, crystalline powder.
Solubility:	Soluble 1:3 in water and 1:100 in alcohol (90%); practically insoluble in chloroform and ether.
Melting Point:	Decomposes at 305° to 315°C.
pH:	0.5 mg/mL solution in water has a pH of 5.4.
pKa:	8.2 (20°C)

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION HYDROmorphone Hydrochloride Injection USP

(0.4 mg/mL Sterile Solution for Injection)

Read this carefully before you start taking HYDROmorphone Hydrochloride Injection USP and each time you get a refill. 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

- **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.**

What is HYDROmorphone Hydrochloride Injection USP used for?

HYDROmorphone Hydrochloride Injection USP is an injection containing HYDROmorphone (an opioid analgesic) used to control pain.

How does HYDROmorphone Hydrochloride Injection USP work?

HYDROmorphone Hydrochloride Injection USP is a pain medication belonging to the class of drugs known as opioids, which includes codeine, fentanyl, morphine and oxycodone. It relieves pain by acting on specific nerve cells of the spinal cord and brain.

HYDROmorphone Hydrochloride Injection USP is used to treat severe pain in patients who need an opioid administered by injection. This is given into the vein in doses or concentrations that are higher than those usually needed.

What are the ingredients in HYDROmorphone Hydrochloride Injection USP?

Medicinal ingredient: HYDROmorphone Hydrochloride

Non-medicinal ingredients: citric acid, sodium citrate and sodium chloride.

HYDROmorphone Hydrochloride Injection USP comes in the following dosage forms:

Solution for injection: 50 mL and 100 mL single-use flexible plastic containers.

Do not use HYDROmorphone Hydrochloride Injection USP if:

- your doctor did not prescribe it for you
- you are allergic to HYDROmorphone, other opioids, or any of the other ingredients in HYDROmorphone Hydrochloride Injection USP (see **What the non-medicinal ingredients are:**);
- 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 MAOI (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

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, 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
- are pregnant or planning to become pregnant

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

HYDROmorphone Hydrochloride Injection USP is a high dose solution of HYDROmorphone hydrochloride. It should be used only in opioid tolerant patients requiring high doses of opioid agonists. Do not confuse HYDROmorphone Hydrochloride Injection USP with the lower dose of HYDROmorphone since overdosage and death could result.

Usual Adult Starting Dose:

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 consulting your doctor.

Your doctor will prescribe the lowest dose that works to control your pain. It is recommended that you only take HYDROmorphone Hydrochloride Injection USP for up to 7 days. If you need to take HYDROmorphone Hydrochloride Injection USP for longer, your doctor will determine the best dose for you to lower the risk of side effects and overdose. Higher doses can lead to more side effects and a greater chance of overdose.

Review your pain regularly with your doctor to determine if you still need HYDROmorphone Hydrochloride Injection USP. Be sure to use HYDROmorphone Hydrochloride Injection USP only for the condition for which it was prescribed.

If your pain increases or you develop any side effect as a result of taking HYDROmorphone Hydrochloride Injection USP, tell your doctor immediately.

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 do it slowly to avoid uncomfortable symptoms such as having:

- 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.

Refilling your Prescription for HYDROmorphone Hydrochloride Injection USP:

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 medication 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.

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 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
- Light headedness
- Sweating
- Constipation
- Confusion
- Anxiety
- 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 HYDROmorphone Hydrochloride Injection USP.

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, sweating.		√	
	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.**
- Store at room temperature between 15°C and 25°C. Protect from light and freezing. Do not use beyond the expiry date indicated on the label.
- **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.**

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

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://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>) or by contacting the sponsor at www.sterinova.com, or by calling 1-844-329-2939.

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