PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[N]APO-HYDROmorphone

HYDROmorphone Hydrochloride Tablets

Tablets, 1 mg, 2 mg, 4 mg and 8 mg, Oral

USP

Opioid Analgesic

ATC code: N02AA03

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RECENT MAJOR LABEL CHANGES

4 DOSAGE AND **A**DMINISTRATION	04/2024
7 WARNINGS AND PRECAUTIONS	04/2024

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

APO-HYDROmorphone (HYDROmorphone hydrochloride tablets) is indicated for the relief of moderate to severe pain in adults.

1.1 Pediatrics

No data are available to Health Canada. Therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

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 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

APO-HYDROmorphone (HYDROmorphone hydrochloride tablets) is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Patients who are hypersensitive to other opioid analgesics.
- 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 (CO_2) 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 Inhibitors (MAOIs) (or within 14 days of such therapy).
- Women who are breast-feeding, pregnant, or during labour and delivery (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX and 7 WARNINGS AND PRECAUTIONS, 7.1.1 Pregnant Women and 7.1.2 Breast-feeding).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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, APO-HYDROmorphone 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 4.1 Dosing Considerations).

Addiction, Abuse, and Misuse
APO-HYDROmorphone 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 APO-HYDROmorphone, and all patients should be monitored regularly for the development of these behaviours or conditions (see 7 WARNINGS AND PRECAUTIONS, Addiction, Abuse and Misuse). APO-HYDROmorphone 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 APO-HYDROmorphone. 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 APO-HYDROmorphone or following a dose increase.

APO-HYDROmorphone tablets must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving APO-HYDROmorphone can lead to dangerous adverse events including death (see 7 WARNINGS AND PRECAUTIONS, General).

Patients must be instructed on the hazards related to taking opioids including fatal overdose.

Accidental Exposure
Accidental ingestion of even one dose of APO-HYDROmorphone, especially by children, can result in a fatal overdose of HYDROmorphone (see 11 STORAGE, STABILITY AND DISPOSAL, Disposal for instructions on proper disposal).

Neonatal Opioid Withdrawal Syndrome
Prolonged maternal use of APO-HYDROmorphone during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance, Neonatal Opioid Withdrawal Syndrome).

Interaction with Alcohol

The co-ingestion of alcohol with APO-HYDROmorphone should be avoided as it may result in dangerous additive effects, causing serious injury or death (see 7 WARNINGS AND PRECAUTIONS, Neurologic and 9.2 Drug Interactions Overview).

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 7 WARNINGS AND PRECAUTIONS, Neurologic and 9.2 Drug Interactions Overview).

- Reserve concomitant prescribing of APO-HYDROmorphone 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.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

For acute pain, it is recommended to use APO-HYDROmorphone 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) daily of APO-HYDROmorphone not be exceeded. Each patient should be assessed for their risk prior to prescribing APO-HYDROmorphone, 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 APO-HYDROmorphone (see 4.2 Recommended Dose and Dosage Adjustment, Adjustment or Reduction of Dosage).

APO-HYDROmorphone should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, or not tolerated, or would be otherwise inadequate to provide appropriate management of pain.

APO-HYDROmorphone tablets must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving APO-HYDROmorphone tablets can lead to dangerous adverse events including death (see 7 WARNINGS AND PRECAUTIONS, General).

APO-HYDROmorphone tablets should be used with caution within 12 hours pre-operatively and within the first 12 to 24 hours post-operatively (see 7 WARNINGS AND PRECAUTIONS, Peri-Operative Considerations).

APO-HYDROmorphone is not indicated for rectal administration.

4.2 Recommended Dose and Dosage Adjustment

- **Pediatrics:** Health Canada has not authorized an indication for pediatric use (see 1.1 Pediatrics).

- **Adults:** Individual dosing requirements vary considerably based on each patient's age, weight, severity and cause of pain, and medical and analgesic history.

- **Patients Not Receiving Opioids at the Time of Initiation of APO-HYDROmorphone Treatment:**
  Orally for adults, 2 to 4 mg every 4 to 6 hours as required.

- **Patients Currently Receiving Opioids:** For patients who are receiving an alternate opioid, the "oral HYDROmorphone equivalent" of the analgesic presently being used, should be determined. Having determined the total daily dosage of the present analgesic, Table 1 can be used to calculate the approximate daily oral HYDROmorphone dosage that should provide equivalent analgesia. Further dose reductions should be considered due to incomplete cross- tolerance between opioids.

- **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 to 50%** to minimize the risk of overdose. Subsequently, up-titrate the dose, as required, to reach the appropriate maintenance dose. Switching patients from parenteral HYDROmorphone to oral HYDROmorphone should be guided by the sensitivity of the individual patient. The oral starting dose should not be overestimated.

Table 1 - Opioid Conversion Table[a]

Opioids	To convert to oral morphine equivalent	To convert from oral morphine multiply by	Daily 90 mg MED[b]
Morphine	1	1	90 mg
Codeine	0.15	6.67	600 mg
HYDROmorphone	5	0.2	18 mg
Oxycodone	1.5	0.667	60 mg
Tapentadol	0.3-0.4	2.5-3.33	300 mg
Tramadol	0.1-0.2	6	***
Methadone	Morphine dose equivalence is not reliably established		

*** The maximum recommended daily dose of tramadol is 300 mg to 400 mg depending on the formulation.

[a.] Adapted from the 2017 Canadian guideline for opioids for chronic non-cancer pain. McMaster University; 2017

[b.] MED. Morphine Equivalent Dose

- **Patients with Hepatic Impairment:** Start patients on 25% to 50% of the usual APO-HYDROmorphone starting dose that would be prescribed for patients with normal hepatic function, depending on the degree of impairment. Closely monitor patients with moderate hepatic impairment for respiratory and central nervous system depression during initiation of therapy with APO-HYDROmorphone and during dose titration. Use of alternate analgesics is recommended for patients with severe hepatic impairment (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

- **Patients with Renal Impairment:** Start patients with moderate renal impairment on 50% and patients with severe renal impairment on 25% of the usual APO-HYDROmorphone starting dose that would be prescribed for patients with normal renal function. Closely monitor patients with renal impairment for respiratory and central nervous system depression during initiation of therapy with APO-HYDROmorphone and during dose titration (see 7 WARNINGS AND PRECAUTIONS, Renal).

- **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. APO-HYDROmorphone should be initiated at a low end of the dosing range and slowly titrated (see 7.1.4 Geriatrics).

- **Use with Non-Opioid Medications:** If a non-opioid analgesic is being provided, it may be continued. If the non-opioid is discontinued, consideration should be given to increasing the opioid dose to compensate for the non-opioid analgesic. APO-HYDROmorphone can be safely used concomitantly with usual doses of other non-opioid analgesics.

- **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 regular administration of the lowest dose of APO-HYDROmorphone 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 APO-HYDROmorphone. 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 moderate to 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 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance).

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.

4.4 Administration

APO-HYDROmorphone tablets may be taken with a glass of water.

4.5 Missed Dose

If the patient forgets to take one or more tablet doses, they should take their next dose at the next scheduled time and in the normal amount.

5 OVERDOSAGE

Signs and Symptoms: Serious overdosage with HYDROmorphone hydrochloride tablets are 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, toxic leukoencephalopathy (TLE), delayed post-hypoxic leukoencephalopathy (DPHL) 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.

Evacuation of gastric contents may be useful in removing unabsorbed drug, in particular when an oral formulation has been taken.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Immediate Release Tablets / 1 mg, 2 mg, 4 mg and 8 mg	Lactose anhydrous and magnesium stearate. Also contains: 1 mg: DC Yellow #10 Lake and FD&C Blue # 1 2 mg: DC Yellow #10 Lake and FD&C Yellow #6 Lake 35-42% 4 mg: DC Yellow #10 Lake

Dosage Forms:
Tablets: Each tablet contains: HYDROmorphone hydrochloride 1 mg (green), 2 mg (orange), 4 mg (yellow), or 8 mg (white, bisect). Non-medicinal ingredients: lactose anhydrous and magnesium stearate. Also contains: DC Yellow #10 Lake and FD&C Blue # 1 (for 1 mg), DC Yellow #10 Lake and FD&C Yellow #6 Lake 35-42% (for 2 mg), DC Yellow #10 Lake (for 4 mg).

APO-HYDROmorphone tablets, 1 mg:

Each round, green, flat-faced, beveled-edge tablet, engraved “APO” on one side, “H1” on the other side, contains 1 mg of HYDROmorphone hydrochloride.

APO-HYDROmorphone tablets, 2 mg:

Each round, orange, flat-faced, beveled-edge tablet, engraved “APO” on one side, “H2” on the other side, contains 2 mg of HYDROmorphone hydrochloride.

APO-HYDROmorphone tablets, 4 mg:

Each round, yellow, flat-faced, beveled-edge tablet, engraved “APO” on one side, “H4” on the other side, contains 4 mg of HYDROmorphone hydrochloride.

APO-HYDROmorphone tablets, 8 mg:

Each white, arc triangle shaped tablet, engraved “APO” on one side, “H” bisect “8” on the other side, contains 8 mg of HYDROmorphone hydrochloride.

Packaging
APO-HYDROmorphone tablets are available as green tablets of 1 mg; orange tablets of 2 mg; yellow tablets of 4 mg; or white, bisect tablets of 8 mg. APO-HYDROmorphone 1 mg, 2 mg, 4 mg and 8 mg tablets are available in bottles of 100 tablets and blister packages of 4 x 25 tablets.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

APO-HYDROmorphone is a controlled substance listed in Schedule I of the *Controlled Drugs and Substances Act* (CDSA). **Appropriate security measures should be taken to safeguard stock of HYDROmorphone against diversion.**

Patients should be instructed not to give APO-HYDROmorphone to anyone other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death. APO-HYDROmorphone should be stored securely to avoid theft or misuse.

APO-HYDROmorphone 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.

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.

Patients should be cautioned not to consume alcohol while taking APO-HYDROmorphone as it may increase the chance of experiencing serious adverse events, including death (see 9.1 Serious Drug Interactions).

Addiction, Abuse and Misuse

Like all opioids, APO-HYDROmorphone is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, APO-HYDROmorphone should be prescribed and handled with caution. This risk is increased if APO-HYDROmorphone is taken with alcohol or other CNS depressants.

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 APO-HYDROmorphone, should be used with particular care in patients with a history of mental health disorders including, but not limited to, major depression, anxiety,

alcohol, and illicit/prescription drug abuse. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

Efforts should be made to promote appropriate opioid prescribing practices that balance the uncertainties between the benefits and risks of opioid medications based on the individual needs of each patient.

APO-HYDROmorphone, tablets are intended for oral use only. The tablets should be swallowed whole, and not chewed or crushed. With parenteral abuse, the tablet excipients can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Abuse of oral dosage forms can be expected to result in serious adverse events, including death.

Cardiovascular

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 drugs such as phenothiazines and other tranquilizers, sedatives, hypnotics, tricyclic antidepressants or general anesthetics (see 9.2 Drug Interactions Overview). These patients should be monitored for signs of hypotension after initiating or titrating the dose of APO-HYDROmorphone.

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

Dependence/Tolerance

As with other opioids, tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of HYDROmorphone. APO-HYDROmorphone should therefore be prescribed and handled with the degree of caution appropriate to the use of a drug with abuse potential.

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.

Abuse or intentional misuse of HYDROmorphone may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g., major depression, anxiety and personality disorders).

Patients will require monitoring for signs of drug-seeking behaviour (e.g., too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like

benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

Patients on prolonged therapy should be withdrawn 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 8.2 Clinical Trial Adverse Reactions and 4.2 Recommended Dose and Dosage Adjustment, Adjustment or Reduction of Dosage).

Use in Drug and Alcohol Addiction: APO-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 APO-HYDROmorphone; extreme caution and awareness is warranted to mitigate the risk.

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 APO-HYDROmorphone is contraindicated in pregnant women (see 2 CONTRAINDICATIONS).

Driving and Operating Machinery

APO-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 APO-HYDROmorphone with other CNS depressants, including other opioids, phenothiazine, sedatives, hypnotics, and alcohol.

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 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

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 and is also contraindicated in patients with paralytic ileus, appendicitis, and pancreatitis. HYDROmorphone may cause spasm of the sphincter of Oddi. Monitor patients with biliary tract disease for worsening symptoms (see 2 CONTRAINDICATIONS and 8 ADVERSE REACTIONS, Nausea and Vomiting and Constipation).

Hepatic/Biliary/Pancreatic

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 (see 4.2 Recommended Dose and Dosage Adjustment, Patients with Hepatic Impairment).

Neurologic

Head Injury: The respiratory depressant effects of HYDROmorphone with carbon dioxide (CO_2) retention and the secondary elevation of cerebrospinal fluid pressure may be greatly increased in the presence of head injury, other intracranial lesions, or pre-existing increase in intracranial pressure. Opioid analgesics, including HYDROmorphone may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, APO-HYDROmorphone should not be used (see 2 CONTRAINDICATIONS).

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. When such combination therapy is contemplated, a substantial reduction in the dose of one or both agents should be considered, and patients should be carefully monitored. APO-HYDROmorphone should not be consumed

with alcohol as it may increase the chance of experiencing dangerous side effects (see 9.2 Drug Interactions Overview).

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 9.2 Drug Interactions Overview). 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 APO-HYDROmorphone 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 9.2 Drug Interactions Overview).

APO-HYDROmorphone should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see 2 CONTRAINDICATIONS and 9.1 Serious Drug Interactions).

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

Opioid-induced hyperalgesia: Opioid induced hyperalgesia (OIH) is a paradoxical response to an opioid in which there is an increase in pain perception despite stable or increased opioid exposure. It differs from tolerance, in which higher opioid doses are required to achieve the same analgesic effect or treat recurring pain. Clinically, OIH may be associated with high opioid doses, long term opioid treatment, and intraoperative opioid use. OIH may manifest as an unexplained increase in pain, more diffuse pain than pre-existing, or as pain from ordinary (i.e., non-painful) stimuli (allodynia) in the absence of disease progression. When OIH is suspected, the dose of opioid should be reduced or tapered off, if possible. It is reasonable to consider opioid rotation, or the use of a non-opioid strategy for pain control. There is currently no well-established treatment for OIH.

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

Use in Patients with Convulsive or Seizure Disorders: The HYDROmorphone in APO-HYDROmorphone may aggravate convulsions in patients with convulsive disorders and may induce or aggravate seizures in some clinical settings. Therefore, APO-HYDROmorphone should not be used in these patients (see 2 CONTRAINDICATIONS).

Serotonin Toxicity / Serotonin Syndrome: Serotonin toxicity also known as serotonin syndrome is a potentially life-threatening condition and has been reported with HYDROmorphone, including HYDROmorphone hydrochloride tablets, particularly during combined use with other serotonergic drugs (see 9.4 Drug-Drug Interactions, Serotonergic Agents).

Serotonin toxicity is characterised by neuromuscular excitation, autonomic stimulation (e.g., tachycardia, flushing) and altered mental state (e.g., anxiety, agitation, hypomania). In accordance with the Hunter Criteria, serotonin toxicity diagnosis is likely when, in the presence of at least one serotonergic agent, one of the following is observed:

- Spontaneous clonus
- Inducible clonus or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature >38°C and ocular clonus or inducible clonus.

If concomitant treatment with APO-HYDROmorphone and other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see 9 DRUG INTERACTIONS). If serotonin toxicity is suspected, discontinuation of the serotonergic agents should be considered.

Patient Counselling Information

A patient information sheet should be provided to patients when APO-HYDROmorphone is dispensed to them.

Patients receiving APO-HYDROmorphone should be given the following instructions by the physician:

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

2. Patients should be advised that APO-HYDROmorphone contains HYDROmorphone, an opioid pain medicine.

3. Patients should be advised that APO-HYDROmorphone should only be taken as directed. The dose of APO-HYDROmorphone should not be adjusted without consulting with a physician. APO-HYDROmorphone tablets must be swallowed whole (not cut, broken, chewed, dissolved, or crushed) due to the risk of fatal HYDROmorphone overdose.

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

5. Patients should be advised to consult their physician or pharmacist if other medications are being used or will be used with APO-HYDROmorphone.

6. Patients should be advised that if they have been receiving treatment with APO-HYDROmorphone and cessation of therapy is indicated, it may be appropriate to taper the APO-HYDROmorphone dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms.

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

8. Patients should be advised that APO-HYDROmorphone 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 APO-HYDROmorphone 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 APO-HYDROmorphone.

9. Patients should be advised that APO-HYDROmorphone is a potential drug of abuse. They should protect it from theft or misuse.

10. Patients should be advised that APO-HYDROmorphone should never be given to anyone other than the individual for whom it was prescribed.

11. 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 APO-HYDROmorphone. Women who are breast-feeding or pregnant should not use APO-HYDROmorphone.

Peri-Operative Considerations

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

In the case of planned chordotomy or other pain-relieving operations, patients should not be treated with APO-HYDROmorphone for at least 24 hours before the operation and APO-HYDROmorphone tablets should not be used in the immediate post-operative period.

Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. Thereafter, if APO-HYDROmorphone 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 HYDROmorphone-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.

APO-HYDROmorphone tablets should not be used in the early post-operative period (12 to 24 hours post-surgery) unless the patient is ambulatory and gastrointestinal function is normal.

Renal

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 $AUC_{0-\mu}$) is increased by 2-fold in patients with moderate (CLcr = 40 to 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). Patients with renal impairment should be closely monitored during dose titration (see 4.2 Recommended Dose and Dosage Adjustment, Patients with Renal Impairment).

Reproductive Health: Female and Male Potential

See sections 2 CONTRAINDICATIONS and 7.1.1 Pregnant Women.

- **Fertility**

Long term use of opioids may be associated with symptoms such as infertility.

- **Function**

Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido and erectile dysfunction (see 8.5 Post-Market Adverse Reactions, Androgen deficiency).

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. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. HYDROmorphone should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia, or hypercapnia (see 2 CONTRAINDICATIONS).

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of APO-HYDROmorphone, 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 APO-HYDROmorphone 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 APO-HYDROmorphone are essential (see 4.2 Recommended Dose and Dosage Adjustment, Dose Titration). Overestimating the APO-HYDROmorphone 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 4.2 Recommended Dose and Dosage Adjustment).

Sleep Apnea: Opioids can cause sleep-related breathing disorders such as sleep apnea syndromes (including central sleep apnea [CSA]) and hypoxia (including sleep-related hypoxia). Opioid use increases the risk of CSA in a dose-dependent manner. Evaluate patients on an ongoing basis for the onset of a new sleep apnea, or a worsening of an existing sleep apnea. In these patients consider decreasing the total opioid dosage or stopping the opioid treatment if appropriate, using best practices for tapering of opioids (see 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance).

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 preexisting respiratory depression for respiratory depression, particularly when initiating therapy and titrating with APO-HYDROmorphone, as in these patients, even usual therapeutic doses of APO-HYDROmorphone 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 APO-

HYDROmorphone is contraindicated in patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see 2 CONTRAINDICATIONS).

7.1 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 elderly or debilitated patients, and those with severe impairment of hepatic, pulmonary or renal function, CNS depression or coma, elevated intracranial pressure, 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.

7.1.1 Pregnant Women

Studies in humans have not been conducted. APO-HYDROmorphone crosses the placental barrier and is contraindicated in pregnant women (see 2 CONTRAINDICATIONS).

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, may be life-threatening (see 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance, Neonatal Opioid Withdrawal Syndrome and 8.5 Post-Market Adverse Reactions).

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.

7.1.2 Breast-feeding

Since opioids can cross the placental barrier and are excreted in breast milk, APO-HYDROmorphone 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 APO-HYDROmorphone is used in this population. Respiratory depression may occur in the infant if opioids are administered during labour. Therefore, APO-HYDROmorphone should not be used during or immediately prior to labour or in nursing mothers.

7.1.3 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

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 4.2 Recommended Dose and Dosage Adjustment, Geriatrics).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The adverse effects of HYDROmorphone hydrochloride tablets 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 asthenia, confusional state, constipation, light-headedness, dizziness, sedation, nausea, somnolence, 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 analgesic therapy. Stool softeners, stimulant laxatives 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.

8.2 Clinical Trial Adverse Reactions

The following adverse effects occur with opioid analgesics and include those reported in HYDROmorphone hydrochloride tablets 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 (≥ 1/10); Common (≥ 1/100 to <1/10); Uncommon (≥ 1/1,000 to <1/100); Rare (≥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, central sleep apnea syndrome

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 retention, urinary hesitancy

Reproductive System and Breast Disorders:
Uncommon: erectile dysfunction

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

8.5 Post-Market Adverse Reactions

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 7 WARNINGS AND PRECAUTIONS, Adrenal Insufficiency and 10.2 Pharmacodynamics, Endocrine System).

Anaphylaxis*:* Anaphylactic reaction has been reported with ingredients contained in APO-HYDROmorphone.

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.

There have also been post-marketing reports of Neonatal Opioid Withdrawal Syndrome (NOWS) in patients treated with HYDROmorphone (see 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance, Neonatal Opioid Withdrawal Syndrome (NOWS)).

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

- Risks from concomitant use of opioids and benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX; 7 WARNINGS AND PRECAUTIONS, Neurologic, Interactions with CNS Depressants (including benzodiazepines and alcohol))
  - Reserve concomitant prescribing of APO-HYDROmorphone and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
  - Consider dose reduction of CNS depressants in situations of concomitant prescribing.
  - Follow patients for signs and symptoms of respiratory depression and sedation.

- The concomitant use of opioids with gabapentinoids (such as gabapentin and pregabalin) and baclofen, increases the risk of opioid overdose, respiratory depression, profound sedation, coma, and death.

- Monoamine Oxidase Inhibitors (MAOIs) intensify the effects of opioid drugs which can cause anxiety,confusion, and decreased respiration. APO-HYDROmorphone is contraindicated in patients receiving MAOIs or who have used them within the previous 14 days (see 2 CONTRAINDICATIONS and 9.4 Drug-Drug Interactions, Monoamine Oxidase Inhibitors (MAOIs)).

9.2 Drug Interactions Overview

Interactions with Central Nervous System (CNS) Depressants (including benzodiazepines and alcohol): 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, gabapentin, pregabalin, baclofen, 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 7 WARNINGS AND PRECAUTIONS, Neurologic, Interactions with CNS Depressants (including benzodiazepines and alcohol) and Driving and Operating Machinery). APO-HYDROmorphone should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

9.3 Drug-Behavioural Interactions

The concomitant use of alcohol should be avoided (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX).

9.4 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.

Monoamine Oxidase Inhibitors (MAOIs): MAOIs intensify the effects of opioid drugs which can cause anxiety, confusion, and decreased respiration. APO-HYDROmorphone is contraindicated in patients receiving MAOIs or who have used them within the previous 14 days (see 2 CONTRAINDICATIONS).

HYDROmorphone may increase the anticoagulant activity of coumarin and other anticoagulants.

Serotonergic Agents: Coadministration of HYDROmorphone with a serotonergic agent, such as a selective serotonin re-uptake inhibitor (SSRI) or a serotonin norepinephrine re-uptake inhibitor (SNRI), may increase the risk of serotonin syndrome, a potentially life-threatening condition (see 7 WARNINGS AND PRECAUTIONS, Neurologic).

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

HYDROmorphone hydrochloride tablets has analgesic and antitussive activity. Small doses of HYDROmorphone produce effective and prompt relief of pain, usually with minimal nausea and vomiting.

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.

10.2 Pharmacodynamics

The onset of action of oral HYDROmorphone hydrochloride with measurable analgesia occurs approximately in 30 minutes. When sleep follows the administration of HYDROmorphone, it

is usually due to relief of pain, not to hypnosis.

In addition, HYDROmorphone is better absorbed orally than is morphine, the former approximately 20 to 25% as active orally as intramuscularly. HYDROmorphone has greater antitussive potency than codeine on a weight basis; however, its dependence liability is also greater than that of codeine.

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.

10.3 Pharmacokinetics

Absorption:
When HYDROmorphone is taken orally, it is absorbed from the gastrointestinal tract.

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:
HYDROmorphone is excreted in the urine, predominantly as the glucuronidated conjugate, with small amounts of parent drug and minor amounts of 6-hydroxy reduction metabolites. The pharmacologic activity of this and other HYDROmorphone metabolites in humans is not known.

Special Populations and Conditions

- **Pediatrics:** HYDROmorphone hydrochloride tablets has not been studied in patients less than 18 years of age and is not indicated for this population.

- **Geriatrics:** HYDROmorphone should be administered with caution, and in reduced dosages, to elderly or debilitated patients. 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 should be initiated at a low dose and slowly titrated to effect (see 7.1.4 Geriatrics).

- **Sex:** No data available.

11 STORAGE, STABILITY AND DISPOSAL

- **Storage:**
  Store APO-HYDROmorphone tablets at controlled room temperature 15°C to 30°C. Protect from light.

- **Disposal: APO-HYDROmorphone should never be disposed of in household trash.** Disposal via a pharmacy take back program is recommended. Unused or

expired APO-HYDROmorphone should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets. APO-HYDROmorphone 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.

12 SPECIAL HANDLING INSTRUCTIONS

APO-HYDROmorphone 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. APO-HYDROmorphone should not be used in front of children since they may copy these actions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

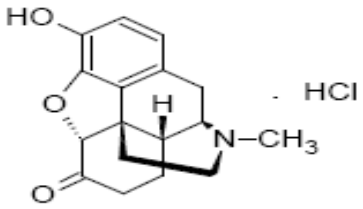
HYDROmorphone hydrochloride is a semisynthetic congener of morphine, differing structurally from morphine in the substitution of an oxygen for the 6-hydroxyl group and hydrogenation of the 7-8 double bond of the morphine molecule.

Proper name: HYDROmorphone hydrochloride

Chemical name: 4,5α-Epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride

Molecular formula and molecular mass: $C_{17}H_{19}NO_3 \cdot HCl$ / 321.8 g/mol

Structural formula:



Product Characteristics

Physical description: White or practically white powder.

pH: The solubility of HYDROmorphone hydrochloride is greater than 10 mg/mL across the physiological pH range.

Solvent Media	Final pH	Solubility (mg/mL)	Highest dose (8 mg) / Solubility (mL)
Water	5.8	>10	<0.8
0.1N HCl, pH 1.2	1.3	>10	<0.8
0.05M Phosphate Buffer (pH 2.5)	2.5	>10	<0.8
0.05M Phosphate Buffer (pH 4.5)	4.5	>10	<0.8
0.05M Phosphate Buffer (pH 6.8)	6.7	>10	<0.8

Solvent Media	Final pH	Solubility (mg/mL)	Highest dose (8 mg) / Solubility (mL)
0.05M Phosphate Buffer (pH 7.5)	7.3	>10	<0.8

Melting Point: 305°C to 310°C

pKa: 8.2 (20°C)

Solubility: Freely soluble in water; sparingly soluble in alcohol, practically insoluble in dichloromethane.

14 CLINICAL TRIALS

14.2 Comparative Bioavailability Studies

A randomized, two-way, single-dose, crossover comparative bioavailability study of APO-HYDROmorphone 8 mg tablets (Apotex Inc.) and ^{N}DILAUDID® 8 mg tablets (Abbott Laboratories Ltd.) was conducted in healthy adult male subjects under fasting conditions. Comparative bioavailability data from 18 subjects that were included in the statistical analysis are presented in the following table:

HYDROmorphone Hydrochloride (1 x 8 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (pg·h/mL)	14378.2 14547.8 (18.4)	14253.2 14481.6 (14.5)	100.9	96.2 - 105.7
AUC_I (pg·h/mL)	16596.5 16902.2 (18.2)	15518.8 15592.6 (13.1)	106.9	98.4 - 116.2
C_{max} (pg/mL)	5895.4 6489.4 (44.5)	5378.0 5814.3 (38.0)	109.6	93.4 - 128.7
T_{max}[3] (h)	0.50 (0.33 – 0.83)	0.58 (0.16 – 1.00)		
$T_{½}$[4] (h)	10.48 (32.19)	8.84 (34.48)		

1 APO-HYDROmorphone (as HYDROmorphone hydrochloride) tablets, 8 mg (Apotex Inc.)
2 ^{N}DILAUDID® (as HYDROmorphone hydrochloride) tablets, 8 mg (Abbott Laboratories Ltd.)
3 Expressed as median (range) only
4 Expressed as arithmetic mean (CV%) only

17 SUPPORTING PRODUCT MONOGRAPHS

1. ^{N}DILAUDID® (HYDROmorphone Hydrochloride Tablets 1 mg, 2 mg, 4 mg and 8 mg and HYDROmorphone Hydrochloride Sterile Solution for Injection 2 mg/mL), Submission control 273917, Product Monograph, Purdue Pharma. (AUG 29, 2023)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[N]APO-HYDROmorphone

HYDROmorphone Hydrochloride Tablets

Read this carefully before you start taking **APO-HYDROmorphone** 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 **APO-HYDROmorphone**.

Serious Warnings and Precautions

- Even if you take APO-HYDROmorphone as prescribed you are at a risk for opioid addiction, abuse, and misuse. This can lead to overdose and death. To understand your risk of opioid addiction, abuse, and misuse you should speak to your prescriber (e.g., health care professional).

- When you take APO-HYDROmorphone tablets they must be swallowed whole. Do not cut, break, crush, chew, or dissolve the tablet. This can be dangerous and can lead to death or seriously harm you.

- Life-threatening breathing problems can happen while taking APO-HYDROmorphone, especially if not take as directed. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.

- You should never give anyone your APO-HYDROmorphone. They could die from taking it. If a person has not been prescribed APO-HYDROmorphone, taking even one dose can cause a fatal overdose. This is especially true for children and for an adult who is not already taking opioids continuously.

- If you took APO-HYDROmorphone 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 APO-HYDROmorphone 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 APO-HYDROmorphone used for?

APO-HYDROmorphone is a pain medication used to control pain.

How does APO-HYDROmorphone work?

APO-HYDROmorphone contains HYDROmorphone which 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.

What are the ingredients in APO-HYDROmorphone?

Medicinal ingredient: HYDROmorphone hydrochloride

Non-medicinal ingredients in tablet: lactose anhydrous, magnesium stearate.

In addition, the tablet strengths listed below contain the following dyes:
1 mg: DC Yellow #10 Lake and FD&C Blue # 1
2 mg: DC Yellow #10 Lake and FD&C Yellow #6 Lake 35-42%
4 mg: DC Yellow #10 Lake

APO-HYDROmorphone comes in the following dosage forms:
Immediate Release Tablets: 1 mg, 2 mg, 4 mg and 8 mg.

Do not use APO-HYDROmorphone if:
- your health care professional did not prescribe it for you.
- you are allergic to HYDROmorphone, or any of the other ingredients in APO-HYDROmorphone tablets (see **What are the ingredients in APO-HYDROmorphone?**).
- 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 lung problems.
- you have any heart problems.
- you have bowel blockage or narrowing of the stomach or intestines.
- you have a condition where the bowel does not work properly (ileus) or have severe pain in your abdomen.
- you have increased pressure in your skull or have a head injury.
- you have epilepsy (seizures) or a history with epilepsy.
- you have a brain tumor.

- you suffer from alcoholism or alcohol withdrawal.
- you are taking or have taken within the past 2 weeks a Monoamine Oxidase Inhibitor (MOI) (such as phenelzine sulfate, tranylcypromine sulfate, moclobemide or selegiline).
- you are going to have a surgery or operation or have had a surgery in the last 24 hours.
- 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 APO-HYDROmorphone. 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 been told you are at risk of having heart problems or seizures.
- have heart disease.
- have low blood pressure.
- have a history of sleep apnea.
- have had problems with your mood (such as depression or anxiety), hallucinations, or other mental health problems.
- suffer from chronic or severe constipation.
- have problems with your adrenal or prostate gland.
- suffer from migraines.
- are pregnant or planning to become pregnant or are in labour.
- are breastfeeding or planning to breastfeed.
- have a sleep disorder which causes pauses in breathing or shallow breathing while sleeping (sleep apnea).
- are planning on drinking alcohol. Drinking alcohol while taking APO-HYDROmorphone may cause dangerous side effects, including death. Do NOT drink alcohol while taking APO-HYDROmorphone.
- have a condition that causes weakness or frailty.

Other warnings you should know about:

Opioid dependence and addiction: Like any opioid, APO-HYDROmorphone may cause mental and physical dependence. HYDROmorphone hydrochloride also has the potential to cause addiction. There are important differences between physical dependence and addiction. Tolerance means that, over time, a higher dose may be needed to get the same level of pain relief. It is important that you talk to your healthcare professional if you have questions or concerns about addiction, physical dependence, or tolerance. Your healthcare professional should prescribe and administer APO-HYDROmorphone with the same degree of caution appropriate to the use of other oral opioid medications. It is not recommended to use these products for a long period of time.

Pregnancy, nursing, labour, and delivery: Do not use APO-HYDROmorphone while pregnant, nursing, during labour or delivery. Opioids can be transferred to your baby through breast milk, or while still in the womb. APO-HYDROmorphone can then cause life-threatening breathing problems in your unborn baby or nursing infant. Your healthcare professional will determine if the benefits of using APO-HYDROmorphone outweigh the risks to your unborn baby or breastfeeding infant.

If you are pregnant and are taking APO-HYDROmorphone**,** 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 health care professional will monitor and guide you on how to slowly stop taking APO-HYDROmorphone**.** 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 APO-HYDROmorphone. APO-HYDROmorphone 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 health care professional may do tests, give you another medication, and slowly take you off APO-HYDROmorphone**.**

Serotonin toxicity (also known as serotonin syndrome): APO-HYDROmorphone can cause serotonin toxicity, 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 toxicity if you take APO-HYDROmorphone with certain anti-depressants, migraine medications or muscle relaxants medications.

Serotonin toxicity 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.

Sleep Apnea: Opioids can cause a problem called sleep apnea (stopping breathing from time to time while sleeping). Tell your health care professional if you have a history of sleep apnea or if anyone notices that you stop breathing from time to time while sleeping.

Worsened pain**:** Taking opioids for pain can sometimes have the unintended effect of making your pain feel worse (opioid-induced hyperalgesia) even though your opioid dose has been unchanged or increased. This can also include feeling pain in new places in your body, or feeling pain from something that would not normally hurt, for example, feeling pain from clothing touching your skin. Tell your healthcare professional if you notice a change like this in your pain while you are taking APO-HYDROmorphone.

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

Serious Drug Interactions

Taking APO-HYDROmorphone with the following medicines can cause serious side effects, including breathing problems that can lead to death:

- alcohol, including prescription and non-prescription medications that contain alcohol. Do NOT drink alcohol while you are taking APO-HYDROmorphone. It can lead to:
  - drowsiness,
  - unusually slow or weak breathing,
  - serious side effects or,
  - a fatal overdose.
- Monoamine Oxidase Inhibitors (MAOi), used to treat depression. Do NOT take APO-HYDROmorphone with MAOi's or if you have taken an MAOi in the last 14 days.
- benzodiazepines, medicines used to help you sleep or that help reduce anxiety (e.g., diazepam, lorazepam, alprazolam).
- antiepileptics, used to treat and prevent seizures (e.g., gabapentin, carbamazepine, phenytoin, oxcarbazepine, phenobarbital).
- drugs used to treat nerve pain (e.g., pregabalin)
- drugs used to prevent and control seizures in the treatment of epilepsy (e.g., gapapentin)
- other sedative drugs which may enhance the drowsiness caused by APO-HYDROmorphone.

The following may interact with APO-HYDROmorphone:

- alcohol. This includes prescription and non-prescription medications that contain alcohol. **Do not** drink alcohol while you are taking APO-HYDROmorphone. 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 APO-HYDROmorphone
- general anesthetics (medicines used during surgery)
- drugs used to treat serious mental or emotional disorders, such as schizophrenia
- antihistamines, medicines used to treat allergies
- anti-emetics (for the prevention of vomiting)
- muscle relaxants drugs used to treat muscle spasms and back pain (e.g., baclofen).
- anticoagulants (blood thinners)
- some heart medications (such as beta blockers)
- drugs used to treat migraines (e.g. triptans)
- St. John's Wort

How to take APO-HYDROmorphone:

Take APO-HYDROmorphone tablets:
- usually every 4 to 6 hours, or as directed by your health care professional
- with a full glass of water

APO-HYDROmorphone tablets**:**
Swallow whole. Do not cut, break, crush, chew or dissolve the tablet. This can be dangerous and can lead to death or seriously harm you.

Usual Dose:
Your dose is tailored/personalized just for you. Be sure to follow your health care professional's dosing instructions exactly. Do not increase or decrease your dose without consulting your health care professional.

Your health care professional will prescribe the lowest dose that works to control your pain. It is recommended that you only take APO-HYDROmorphone for up to 7 days. If you need to take APO-HYDROmorphone for longer, your health care professional 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 health care professional to determine if you still need APO-HYDROmorphone**.** Be sure to use APO-HYDROmorphone only for the condition for which it was prescribed.

If your pain increases or you develop any side effect as a result of taking APO-HYDROmorphone, tell your health care professional immediately.

Stopping your Medication:
If you have been taking APO-HYDROmorphone for more than a few days, you should not stop taking it all of a sudden. Your health care professional will monitor and guide you on how to slowly stop taking APO-HYDROmorphone. 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 APO-HYDROmorphone.

Refilling your Prescription for APO-HYDROmorphone:

A new written prescription is required from your health care professional each time you need more APO-HYDROmorphone**.** Therefore, it is important that you contact your health care professional before your current supply runs out.

Only obtain prescriptions for this medication from the health care professional in charge of your treatment. Do not seek prescriptions from other health care professionals unless you switch to another health care professional for your pain management.

Overdose:

If you think you, or a person you are caring for, have taken too much APO-HYDROmorphone, contact a 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:

If you miss one dose, take it as soon as possible. However, if it is almost time for your next dose, then skip the missed dose. Do not take two doses at once. If you miss several doses in a row, talk to your health care professional before restarting your medication.

What are possible side effects from using APO-HYDROmorphone?

These are not all the possible side effects you may feel when taking APO-HYDROmorphone. 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
- low sex drive, impotence (erectile dysfunction), infertility

Talk with your health care professional or pharmacist about ways to prevent constipation when

you start using APO-HYDROmorphone.

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 toxicity *(also known as 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, tell 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 APO-HYDROmorphone in a secure place to prevent theft, misuse, or accidental exposure**.
- Store tablets at room temperature (15° to 30°C). Protect from light.
- **Keep APO-HYDROmorphone 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 APO-HYDROmorphone, get emergency help right away.**

Disposal:

APO-HYDROmorphone 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 APO-HYDROmorphone:

- Talk to your healthcare professional.
- Find the full product monograph 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); the manufacturer's website (http://www.apotex.ca/products), or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9

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