

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

^NAPO-HYDROmorphone CR

HYDROmorphone* Hydrochloride Controlled Release Capsules

Capsules, 3 mg, 4.5 mg, 6 mg, 9 mg, 12 mg, 18 mg, 24 mg and 30 mg, Oral

Opioid Analgesic

ATC code: N02AA03

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*HYDROmorphone is the name of the active chemical ingredient (hydromorphone) and is not a brandname/tradename.

RECENT MAJOR LABEL CHANGES

4 DOSAGE AND ADMINISTRATION	09/2024
7 WARNINGS AND PRECAUTIONS	09/2024

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

RECENT MAJOR LABEL CHANGES	2
TABLE OF CONTENTS	2
PART I: HEALTH PROFESSIONAL INFORMATION	4
1 INDICATIONS	4
1.1 Pediatrics	4
1.2 Geriatrics	4
2 CONTRAINDICATIONS	4
3 SERIOUS WARNINGS AND PRECAUTIONS BOX	5
4 DOSAGE AND ADMINISTRATION	6
4.1 Dosing Considerations	6
4.2 Recommended Dose and Dosage Adjustment.....	7
4.4 Administration	10
4.5 Missed Dose.....	10
5 OVERDOSAGE	11
6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING	12
7 WARNINGS AND PRECAUTIONS	13
7.1 Special Populations	23
7.1.1 Pregnant Women.....	24
7.1.2 Breast-feeding	24
7.1.3 Pediatrics	24
7.1.4 Geriatrics	24
8 ADVERSE REACTIONS	25
8.1 Adverse Reaction Overview	25
8.2 Clinical Trial Adverse Reactions	26

8.5	Post-Market Adverse Reactions	27
9	DRUG INTERACTIONS	28
9.1	Serious Drug Interactions.....	28
9.2	Drug Interactions Overview	29
9.3	Drug-Behavioural Interactions	29
9.4	Drug-Drug Interactions	29
9.5	Drug-Food Interactions	30
9.6	Drug-Herb Interactions	30
9.7	Drug-Laboratory Test Interactions	30
10	CLINICAL PHARMACOLOGY	30
10.1	Mechanism of Action	30
10.2	Pharmacodynamics.....	30
10.3	Pharmacokinetics.....	32
11	STORAGE, STABILITY AND DISPOSAL	34
12	SPECIAL HANDLING INSTRUCTIONS	34
PART II: SCIENTIFIC INFORMATION		35
13	PHARMACEUTICAL INFORMATION	35
14	CLINICAL TRIALS.....	35
14.3	Comparative Bioavailability Studies.....	35
16	NON-CLINICAL TOXICOLOGY	38
17	SUPPORTING PRODUCT MONOGRAPHS	39
PATIENT MEDICATION INFORMATION		40

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

APO-HYDROmorphone CR (HYDROmorphone hydrochloride controlled release capsules) is indicated for the management of pain in adults severe enough to require daily, continuous, long-term opioid treatment, and:

- that is opioid-responsive; and
- for which alternative options are inadequate.

APO-HYDROmorphone CR is not indicated as an as-needed (prn) analgesic.

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, 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 CR (HYDROmorphone hydrochloride controlled release capsules) 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, intermittent or short duration pain that can be managed with other pain medications.
- The management of acute pain, including use in outpatient or day surgeries.

- The management of peri-operative pain.
- Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus.
- Patients with acute respiratory depression, elevated carbon dioxide (CO₂) 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 greater risks of overdose and death with controlled release opioid formulations, APO-HYDROmorphone CR (HYDROmorphone hydrochloride controlled release capsules) 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 CR 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 CR, 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 CR 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 CR. 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

CR or following a dose increase.

Instruct patients to swallow APO-HYDROmorphone CR capsules whole or to sprinkle the contents of the capsule on applesauce or custard and swallow immediately without chewing. Cutting, breaking, crushing, chewing, or dissolving APO-HYDROmorphone CR capsules can lead to rapid release and absorption of a potentially fatal dose of HYDROmorphone (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 CR capsules 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 CR 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 \(NOWS\)](#)).

Interaction with Alcohol

The co-ingestion of alcohol with APO-HYDROmorphone CR should be avoided as it may result in dangerous additive effects, causing serious injury or death (see [7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance, Use in Drug and Alcohol Addiction](#) 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](#)).

Reserve concomitant prescribing of APO-HYDROmorphone CR 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

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 CR not be exceeded. Each patient should be assessed for their risk prior to prescribing APO-

HYDROmorphone CR, 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 CR (see [4.2 Recommended Dose and Dosage Adjustment, Adjustment or Reduction of Dosage](#)).

APO-HYDROmorphone CR 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 CR capsules must be swallowed whole or opened and the contents sprinkled onto a tablespoonful of warm or cold (4°C to 40°C) applesauce or room temperature custard. The entire contents of the tablespoonful of food and HYDROmorphone mixture should be swallowed as soon as possible after sprinkling and should be discarded if not consumed. The food/drug mixture should not be chewed, and the ingestion should be followed by rinsing the mouth with fluid to ensure that the entire contents are swallowed. Taking broken, chewed, dissolved or crushed capsules can lead to the rapid release and absorption of a potentially fatal dose of HYDROmorphone (see [7 WARNINGS AND PRECAUTIONS, General](#)).

Despite data demonstrating the bioequivalence of HYDROmorphone hydrochloride controlled release capsules after sprinkling capsule contents on selected soft foods for up to 30 minutes (see [7 WARNINGS AND PRECAUTIONS, General](#)), sprinkled doses should be ingested as soon as possible to avoid errors from the loss of product identification features after removal of beads from the capsule shell. After sprinkling, if unsure of the elapsed time or which food sample contains the mixture, discard all implicated food samples.

Capsule strengths of 18 mg and higher, or a single dose greater than 12 mg, are for opioid tolerant patients only, requiring HYDROmorphone equivalent dosages of 36 mg or more per day. A single dose greater than 12 mg, or total daily dose greater than 24 mg, may lead to severe medical consequences including fatal respiratory depression in patients not previously exposed to similar doses of opioids (see [7 WARNINGS AND PRECAUTIONS, General](#) and [4.1 Dosing Considerations](#)).

APO-HYDROmorphone CR 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 CR Treatment:** Patients who are opioid naïve or receiving low, intermittent doses of weak opioid analgesics may be initiated on APO-HYDROmorphone CR capsules 3 mg every 12 hours.
- **Patients Currently Receiving Opioids:** Patients currently receiving other oral HYDROmorphone formulations may be transferred to APO-HYDROmorphone CR at the same total daily HYDROmorphone dosage, equally divided into two 12 hourly APO-HYDROmorphone CR doses.

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. This total daily oral HYDROmorphone dose should then be equally divided into two 12 hourly APO-HYDROmorphone CR doses. 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 (for oral bioavailability see section [14.3 Comparative Bioavailability Studies](#))

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 – 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 with moderate hepatic impairment on

25% of the APO-HYDROmorphone CR dose that would be prescribed for patients with normal hepatic function. Closely monitor patients with moderate hepatic impairment for respiratory and central nervous system depression during initiation of therapy with APO-HYDROmorphone CR 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 APO-HYDROmorphone CR 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 CR 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 CR should be initiated at a low end of the dosing range and slowly titrated (see [7.1.4 Geriatrics](#)).
- **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 regular administration of the lowest dose of controlled release HYDROmorphone (APO-HYDROmorphone CR) 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.

In patients receiving APO-HYDROmorphone CR chronically, the dose should be titrated at intervals of 48 hours to that which provides satisfactory pain relief without unmanageable side effects. APO-HYDROmorphone CR is designed to allow 12 hourly dosing.

If pain repeatedly occurs at the end of the dosing interval it is generally an indication for a dosage increase rather than more frequent administration of controlled release HYDROmorphone (APO-HYDROmorphone CR).

- **Adjustment or Reduction of Dosage:** Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including APO-HYDROmorphone CR. 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 [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, post-herpetic 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.

- **Management of Patients Requiring Rescue Medication:** Some patients taking APO-HYDROmorphone CR according to a fixed time schedule may require immediate-release analgesics as "rescue" medication for pain. Selection of rescue medication should be based on individual patient conditions. APO-HYDROmorphone CR is a controlled release formulation and therefore is not intended for use as rescue medication.

4.4 Administration

APO-HYDROmorphone CR capsules may be swallowed whole or administered by carefully opening the capsules and sprinkling the contents onto a tablespoonful of warm or cold (4°C to 40°C), applesauce or room temperature custard. Applesauce (pH 3.56) is among the most acidic of soft foods and custard (pH 6.95) is among the least acidic. The entire contents of the tablespoon should be swallowed as soon as possible after sprinkling and should be discarded if not consumed. The food/drug mixture must not be chewed and the ingestion should be followed by rinsing the mouth with fluid to ensure that the entire contents are swallowed (see [7 WARNINGS AND PRECAUTIONS, General](#)).

4.5 Missed Dose

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

5 OVERDOSAGE

Signs and Symptoms: Serious overdose with APO-HYDROmorphone CR 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, miotic pupils, toxic leukoencephalopathy (TLE), delayed post-hypoxic leukoencephalopathy (DPHL) and sometimes bradycardia and hypotension. In severe overdose, apnea, circulatory collapse, cardiac arrest, and death may occur.

Treatment: In the treatment of overdose, primary attention should be given to the establishment of adequate respiratory exchange through the 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 overdose, 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, particularly sustained release formulations, 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, particularly when a controlled release 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	Controlled Release Capsules / 3, 4.5, 6, 9, 12, 18, 24 and 30 mg	<p>Anhydrous lactose, colloidal silicon dioxide, dibutyl sebacate, ethyl cellulose, magnesium stearate and povidone.</p> <p>Capsule Shells: gelatin, talc and titanium dioxide. Additional capsule shell ingredients specific to each strength are as follows:</p> <p>3 mg: D&C Yellow No.10, FD&C Green No.3</p> <p>4.5 mg: FD&C Blue No.1, FD&C Red No.3</p> <p>6 mg: D&C Red No.28, FD&C Blue No.1, FD&C Red No.40</p> <p>9 mg: FD&C Blue No.1</p> <p>12 mg: D&C Red No.28, D&C Yellow No.10, FD&C Blue No.1, FD&C Red No.40</p> <p>18 mg: iron oxide yellow</p> <p>24 mg: iron oxide black</p> <p>30 mg: iron oxide red, iron oxide yellow</p> <p>Imprinting Ink: ammonium hydroxide, ferrousferic oxide, propylene glycol and shellac glaze.</p>

Dosage Forms

3 mg: Hard gelatin capsules with light green opaque body and light green opaque cap. Imprinted "APO HM3" in black ink. Filled with white to off-white, round, biconvex controlled release coated tablet(s) (each about 2.4 mm).

4.5 mg: Hard gelatin capsules with blue violet opaque body and blue violet opaque cap. Imprinted "APO HM4.5" in black ink. Filled with white to off-white, round, biconvex controlled release coated tablet(s) (each about 2.4 mm).

6 mg: Hard gelatin capsules with pink opaque body and pink opaque cap. Imprinted "APO HM6" in black ink. Filled with white to off-white, round, biconvex controlled release coated tablet(s) (each about 2.4 mm).

9 mg: Hard gelatin capsules with light blue opaque body and light blue opaque cap. Imprinted "APO HM9" in black ink. Filled with white to off-white, round, biconvex controlled release coated tablet(s) (each about 2.4 mm).

12 mg: Hard gelatin capsules with medium orange opaque body and medium orange opaque cap. Imprinted "APO HM12" in black ink. Filled with white to off-white, round, biconvex controlled release coated tablet(s) (each about 2.4 mm).

18 mg: Hard gelatin capsules with EEC yellow opaque body and EEC yellow opaque cap. Imprinted "APO HM18" in black ink. Filled with white to off-white, round, biconvex controlled release coated tablet(s) (each about 2.4 mm).

24 mg: Hard gelatin capsules with dark gray opaque body and dark gray opaque cap. Imprinted "APO HM24" in black ink. Filled with white to off-white, round, biconvex controlled release coated tablet(s) (each about 2.4 mm).

30 mg: Hard gelatin capsules with swedish orange opaque body and swedish orange opaque cap. Imprinted "APO HM30" in black ink. Filled with white to off-white, round, biconvex controlled release coated tablet(s) (each about 2.4 mm).

Packaging

APO-HYDROmorphone CR is supplied in opaque plastic bottles of 60 and 100 capsules.

7 WARNINGS AND PRECAUTIONS

Please see [3 SERIOUS WARNINGS AND PRECAUTIONS BOX](#)

General

APO-HYDROmorphone CR must be swallowed whole, or opened and the entire contents

sprinkled onto a tablespoonful of applesauce or custard (see [4.1 Dosing Considerations](#)). The entire contents of the tablespoon of food and HYDROmorphone mixture should be swallowed as soon as possible after sprinkling and should be discarded if not consumed. The food/drug mixture should not be chewed, and the ingestion should be followed by rinsing the mouth with fluids to ensure that the entire contents are swallowed. Taking broken, chewed, dissolved or crushed capsules, or their contents, could lead to the rapid release and absorption of a potentially fatal dose of HYDROmorphone.

Despite data demonstrating the bioequivalence of HYDROmorphone hydrochloride controlled release capsules after sprinkling capsule contents on selected soft foods for up to 30 minutes (see [10.3 Pharmacokinetics](#)), sprinkled doses should be ingested as soon as possible to avoid errors from the loss of product identification features after removal of beads from the capsule shell. After sprinkling, if unsure of the elapsed time or which food sample contains the mixture, discard all implicated food samples.

APO-HYDROmorphone CR 18 mg, 24 mg and 30 mg capsules, or a single dose greater than 12 mg are for use in opioid tolerant patients only (see also [4.1 Dosing Considerations](#)). A single dose greater than 12 mg, or total daily doses greater than 24 mg of APO-HYDROmorphone CR, may cause fatal respiratory depression when administered to patients who are not tolerant to the respiratory depressant effects of opioids. Care should be taken in the prescribing of these capsule strengths (see [7 WARNINGS AND PRECAUTIONS, General](#) and [9.1 Serious Drug Interactions](#)).

HYDROmorphone hydrochloride controlled release capsules 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 CR capsules to anyone other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death. APO-HYDROmorphone CR capsules should be stored securely to avoid theft or misuse.

APO-HYDROmorphone CR should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain, the management of patients receiving potent opioids, and 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 CR, 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 CR is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, APO-HYDROmorphone CR 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 APO-HYDROmorphone CR, should be used with particular care in patients with a history of alcohol and illicit/prescription drug abuse and other mental health disorders including, but not limited to, major depression and anxiety. 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.

With parenteral abuse, the capsule excipients can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury.

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 the concurrent administration of drugs such as phenothiazines and other tranquilizers, sedatives, hypnotics, tricyclic antidepressants or certain 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 CR.

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

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 CR 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 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 [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 CR 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 CR; 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 NOWS. 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 NOWS 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 CR is contraindicated in pregnant women (see [2 CONTRAINDICATIONS](#)).

Driving and Operating Machinery

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, phenothiazines, sedatives, hypnotics and alcohol.

Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Endocrine and Metabolism

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

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 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 [8.1 Adverse Reaction Overview, Nausea and Vomiting](#) and [Constipation](#)).

Hepatic/Biliary/Pancreatic

After oral administration of HYDROMorphone at a single 4 mg dose (2 mg HYDROMorphone tablets), mean exposure to HYDROMorphone (C_{max} and $AUC_{0-\infty}$) is increased 4-fold in patients with moderate (Child-Pugh Group B) hepatic impairment compared with subjects with normal hepatic function. Due to increased exposure of HYDROMorphone, patients with moderate hepatic impairment should be started at a lower dose and closely monitored during dose titration. Pharmacokinetics of HYDROMorphone in severe hepatic impairment patients has not been studied. Further increase in C_{max} and AUC of HYDROMorphone in this group is expected. As such, starting dose should be even more conservative (see [4.2 Recommended Dose and Dosage Adjustment, Patients with Hepatic Impairment](#)).

Neurologic

Head Injury: The respiratory depressant effects of HYDROmorphone with carbon dioxide (CO₂) retention and 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, HYDROmorphone Hydrochloride Controlled Release Capsules should not be used (see [2 CONTRAINDICATIONS](#)).

Interactions with CNS Depressants (including benzodiazepines and alcohol): APO-HYDROmorphone CR 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, 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 CR 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 CR 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 CR 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 HYDROmorphine may occur particularly at high doses. A HYDROmorphine dose reduction or change in opioid may be required.

Use in Patients with Convulsive or Seizure Disorders: The HYDROmorphine in APO-HYDROmorphine CR may aggravate convulsions in patients with convulsive disorders and may induce or aggravate seizures in some clinical settings. Therefore, APO-HYDROmorphine CR 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 HYDROmorphine, including HYDROmorphine hydrochloride controlled release capsules, 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-HYDROmorphine CR and other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see [9.4 Drug-Drug Interactions, Serotonergic Agents](#)). 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 CR capsules are dispensed to them.

Patients receiving APO-HYDROmorphone CR 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 CR should be kept under lock and out of sight and out of reach of children.
2. Patients should be advised that APO-HYDROmorphone CR contains HYDROmorphone, an opioid pain medicine.
3. Patients should be advised that APO-HYDROmorphone CR should only be taken as directed. The dose of APO-HYDROmorphone CR should not be adjusted without consulting with a physician.
4. APO-HYDROmorphone CR capsules should not be broken, chewed, dissolved or crushed, due to the risk of fatal HYDROmorphone overdose.
5. APO-HYDROmorphone CR should be swallowed whole or opened and the contents sprinkled onto a tablespoonful of warm or cold (4° to 40°C) applesauce or room temperature custard. The entire contents of the tablespoon of food and HYDROmorphone mixture should be swallowed as soon as possible after sprinkling and should be discarded if not consumed. The food/drug mixture should not be chewed, and the ingestion should be followed rinsing the mouth with fluids to ensure that the entire contents are swallowed.
6. Patients should be advised to report episodes of pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
7. Patients should not combine APO-HYDROmorphone CR with alcohol or other central nervous system depressants (sleep aids, tranquilizers) because dangerous additive effects may occur, resulting in serious injury or death.
8. Patients should be advised to consult their physician or pharmacist if other medications are being used or will be used with APO-HYDROmorphone CR.
9. Patients should be advised that if they have been receiving treatment with

APO-HYDROmorphine CR and cessation of therapy is indicated, it may be appropriate to taper APO-HYDROmorphine CR dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms.

10. Patients should be advised of the most common adverse reactions that may occur while taking APO-HYDROmorphine CR: asthenia, confusion, constipation, dizziness, light-headedness, nausea, sedation, somnolence, hyperhidrosis, and vomiting. If symptoms worsen, seek immediate medical attention.
11. Patients should be advised that APO-HYDROmorphine CR 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-HYDROmorphine CR 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-HYDROmorphine CR.
12. Patients should be advised that APO-HYDROmorphine CR is a potential drug of abuse. They should protect it from theft or misuse.
13. Patients should be advised that APO-HYDROmorphine CR should never be given to anyone other than the individual for whom it was prescribed.
14. Patients should be advised that APO-HYDROmorphine CR doses of 12 mg or more are for use only in individuals tolerant to the effect of opioids.
15. 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-HYDROmorphine CR. Women who are breast-feeding or pregnant should not use APO-HYDROmorphine CR.

Peri-Operative Considerations

APO-HYDROmorphine CR is contraindicated for peri-operative pain relief unless gastrointestinal function is normal. In the case of planned cordotomy or other pain-relieving operations, patients should not be treated with APO-HYDROmorphine CR for at least 48 hours before the operation and APO-HYDROmorphine CR should not be used within the first 24 hours post-operatively. Thereafter, if APO-HYDROmorphine CR 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) (see [2 CONTRAINDICATIONS](#)).

Renal

After oral administration of HYDROmorphone at a single 4 mg dose (2 mg HYDROmorphone tablets), exposure to HYDROmorphone (C_{max} and AUC_{0-48}) is increased in patients with impaired renal function by 2-fold in moderate ($CLCr = 40$ to 60 mL/min) and 3-fold in 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 longer terminal elimination half-life (40 hr) compared to patients with normal renal function (15 hr). Patients with moderate renal impairment should be started on a lower dose. Starting doses for patients with severe renal impairment should be even lower. 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 CR, 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 CR and following dose increases.

To reduce the risk of respiratory depression, proper dosing and titration of APO-HYDROmorphone CR are essential (see [4.2 Recommended Dose and Dosage Adjustment, Dose Titration](#)). Overestimating the APO-HYDROmorphone CR dose when converting patients from

another opioid product can result in fatal overdose with the first dose.

Respiratory depression occurs most frequently in overdose, the elderly, in the debilitated, and in those suffering from conditions accompanied by hypoxia or hypercapnia, when even moderate therapeutic doses may dangerously decrease pulmonary ventilation. This effect may be lessened by careful dose titration as severe pain can antagonize the respiratory depressant action of HYDROmorphone.

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](#) and [4.2 Recommended Dose and Dosage Adjustment , Adjustment or Reduction of Dosage](#)).

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 APO-HYDROmorphone CR, as in these patients, even usual therapeutic doses of APO-HYDROmorphone CR 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 CR 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 and the initial dose should be reduced for the elderly or debilitated, and those with severe impairment of hepatic, pulmonary or renal function; myxedema or hypothyroidism; adrenocortical insufficiency (i.e. Addison's disease); CNS depression or coma; elevated intracranial pressure; toxic psychosis; prostatic hypertrophy or urethral stricture; gallbladder disease; acute alcoholism; delirium tremens; or kyphoscoliosis.

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

APO-HYDROmorphone CR is contraindicated during labour, delivery, pregnancy and in nursing mothers. Animal studies with both morphine and HYDROmorphone, have indicated the possibility of teratogenic effects. In humans, it has not conclusively been established whether HYDROmorphone can cause fetal harm when administered during pregnancy or can affect reproductive capacity, therefore APO-HYDROmorphone CR is contraindicated in patients who are pregnant (see [2 CONTRAINDICATIONS](#)).

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 (see [7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance, Neonatal Opioids Withdraw Symptoms \(NOWS\)](#) 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

APO-HYDROmorphone CR is contraindicated in nursing mothers. HYDROmorphone can cross the placental barrier and is also excreted in breast milk. Life-threatening respiratory depression may 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 CR is used in this population. Respiratory depression may occur in the infant if opioids are administered during labour. Therefore, APO-HYDROmorphone CR 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, 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 APO-HYDROmorphine CR are similar to those of other opioid analgesics, and represent an extension of pharmacological effects of the drug class. The major hazards of HYDROmorphine 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, dizziness, hyperhidrosis, light headedness, nausea, sedation, somnolence, and vomiting.

Sedation: Some degree of sedation is experienced by most patients upon initiation of therapy. This may be at least 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. If nausea and vomiting become troublesome during prolonged therapy with APO-HYDROmorphine CR for chronic pain, a prescription for an antiemetic medication may be considered. In the cancer patient, investigation of nausea should include such causes as constipation, bowel obstruction, uremia, hypercalcemia, hepatomegaly, tumour 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 decreased appetite, early satiety, vomiting and abdominal fullness. These symptoms may 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 controlled release capsules 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

Rare: lethargy

Not known: convulsions, dyskinesia, hyperalgesia, syncope, increased intracranial pressure, nystagmus, central sleep apnea syndrome

Eye Disorders:

Uncommon: visual impairment

Not known: miosis, diplopia

Cardiac Disorders:

Rare: bradycardia, palpitations, tachycardia

Vascular Disorders:

Uncommon: hypotension

Not known: flushing, hypertension

Respiratory, Thoracic and Mediastinal Disorders:

Uncommon: dyspnea

Rare: respiratory depression
Not known: bronchospasm, 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:

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
Uncommon: drug withdrawal syndrome, fatigue, malaise, peripheral edema
Not known: drug tolerance, drug withdrawal syndrome neonatal, chills, disorientation, 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, Endocrine and Metabolism](#)) and [10.2 Pharmacodynamics, Endocrine System](#).

Anaphylaxis: Anaphylactic reaction has been reported with ingredients contained in HYDROmorphone hydrochloride controlled release capsules.

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids. 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, Opioids Withdraw Symptoms \(NOWS\)](#)).

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 CR 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 CR 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): APO-HYDROmorphone CR (HYDROmorphone hydrochloride controlled release capsules) should be dosed with caution in patients who are currently taking other CNS depressants or other drugs that may cause respiratory depression, hypotension, profound sedations, or may potentially result in coma. Such agents include antidepressants, antihistamines, antipsychotics, anxiolytics, barbiturates, benzodiazepines, centrally acting antiemetics, gabapentin, pregabalin, baclofen, chloral hydrate, clonidine and related substances, general anesthetics, some heart medications (e.g. beta-blockers), neuroleptics, other opioid derivatives (analgesic and antitussive) phenothiazines and sedatives or hypnotics. When such combined therapy is contemplated, a substantial reduction in the dose of one or both agents should be considered, and patients carefully monitored. Patients should also be warned that these combinations increase central nervous system depression and can make driving vehicles and operating machinery hazardous (see [7 WARNINGS AND PRECAUTIONS, Driving and Operating Machinery](#)). APO-HYDROmorphone CR should not be consumed with alcohol as it may increase chance of experiencing dangerous side effects.

***In Vitro* Dissolution Studies of Interaction with Alcohol:** Increasing concentrations of alcohol in the dissolution medium resulted in a decrease in the rate of release of HYDROmorphone from APO-HYDROmorphone CR capsules at lower alcohol concentrations (up to 20%) and more rapid release, only at the highest alcohol concentrations (35 to 40%). The clinical significance of these findings is unknown.

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 CR 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, a semi-synthetic μ opioid agonist, is a hydrogenated ketone of morphine and shares the pharmacologic properties typical of opioid analgesics.

HYDROmorphone and related opioids produce their major effects on the central nervous system and gastrointestinal tract. These include analgesia, drowsiness, mental clouding, changes in mood, euphoric mood or dysphoria, respiratory depression, cough suppression, decreased gastrointestinal motility, nausea, vomiting, increased cerebrospinal fluid pressure, increased biliary pressure, pinpoint constriction of the pupils, 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

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.

The relationship between plasma concentration of HYDROmorphine and analgesic effect has not been well established. In patients with chronic pain, HYDROmorphine 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 HYDROmorphine; like morphine, 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: The primary effect of HYDROmorphine on the cardiovascular system is peripheral vasodilation which may be at least partially due to release of histamine. In the supine patient, therapeutic doses of HYDROmorphine have no major effect on blood pressure or cardiac rate and rhythm but orthostatic hypotension may result on standing.

Central Nervous System: HYDROmorphine depresses respiration. The respiratory depression is discernible even with doses too small to disturb consciousness and increases progressively as the dose is increased. The primary mechanism of respiration depression involves a reduction in responsiveness of the brainstem respiratory centers to carbon dioxide (CO₂). In a study in healthy volunteers the relative potency of HYDROmorphine and morphine for suppression of the ventilatory response to carbon dioxide was 8:1, a value consistent with the relative analgesic potency of the two drugs.

HYDROmorphine 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. HYDROmorphine 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 HYDROmorphine 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: HYDROmorphine 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.

Concentration – Efficacy Relationships: No clear relationship has been demonstrated between plasma concentration of HYDROmorphone and analgesic effect although one study in patients with chronic pain suggests that concentrations less than 4 ng/mL are associated with lower degrees of pain relief.

Concentration – Adverse Reaction Relationship: It is generally accepted that in patients with chronic pain, opioid analgesics should be titrated to the dose required to adequately relieve pain without unmanageable side effects. In three Canadian studies of HYDROmorphone administered by continuous subcutaneous infusion, the mean maximum daily dose was 310 mg and 578 mg in two of the studies, and the highest dose received by individual patients in the three studies was 3,360 mg, 4,024 mg and 4,320 mg.

In a crossover study involving 45 cancer patients, the efficacy and safety of HYDROmorphone hydrochloride controlled release capsules given 12 hourly was compared with immediate release HYDROmorphone tablets given 4 hourly. Assessment of pain, nausea and sedation four times per day for seven days indicated that HYDROmorphone hydrochloride controlled release capsules provided an equivalent degree of pain control to immediate release HYDROmorphone tablets and was associated with an equivalent incidence of typical opioid side effects.

HYDROmorphone and related μ -agonist opioids produce their major effects on the CNS and the bowel. The effects include analgesia, drowsiness, changes in mood, respiratory depression, cough suppression, decreased gastrointestinal motility, nausea, vomiting, and alterations of the endocrine and autonomic nervous systems.

In animal studies the relative potency of single doses of HYDROmorphone and morphine for a variety of pharmacologic effects were: analgesia 4.1:1; LD₅₀ 6.32:1; convulsant activity 7.92:1; general depression 7.67:1; excitatory effect 3.35:1; emetic activity 2.75:1; respiratory depression 13.63:1. In acute pain studies in man, relative analgesic potency ranged from 6.7:1 to 11.1:1 and in chronic dosing in patients with cancer pain the ratio of morphine to HYDROmorphone doses producing equivalent analgesia was 7.5:1. Clinical experience suggests that the oral potency ratio of HYDROmorphone to morphine ranges from 4:1 to 7.5:1.

10.3 Pharmacokinetics

HYDROmorphone hydrochloride controlled release capsules administered 12 hourly provides equivalent analgesia to conventional release HYDROmorphone tablets administered every 4 hours in patients with cancer pain. Steady-state pharmacokinetic studies demonstrate that maximum plasma concentration (C_{max}) of HYDROmorphone is achieved at a mean of 4.8 hours after administration of HYDROmorphone hydrochloride controlled release capsules, with

maximum and minimum concentrations equivalent to those obtained with 4 hourly administration of the immediate release tablets.

Absorption

The rate and extent of absorption of HYDROmorphine from HYDROmorphine hydrochloride controlled release capsules were studied when sprinkled on one tablespoon (15 mL) of soft foods under the following conditions: warm ($40^{\circ} \pm 2^{\circ}\text{C}$) applesauce (pH 3.56), cold ($4^{\circ} \pm 1^{\circ}\text{C}$) applesauce (pH 3.62), and room temperature ($23^{\circ} \pm 2^{\circ}\text{C}$) custard (pH 6.95). All three studies concluded that bioequivalence was demonstrated when HYDROmorphine was administered as an intact capsule vs. administration of capsule contents sprinkled on these foods in healthy subjects under fasting conditions. For the conditions under study, the HYDROmorphine bioavailability was not affected by the pH of the soft foods or temperatures, with a contact time at 30 minutes.

Food Effects: The extent of absorption of HYDROmorphine from APO-HYDROmorphine CR is equivalent to that from conventional tablets (HYDROmorphine tablets) and is not significantly influenced when administered in the presence of food. In patients with chronic cancer pain receiving doses of APO-HYDROmorphine CR ranging from 6 mg to 216 mg/day there was a linear relationship between area under the plasma concentration-time curve (AUC) and dose.

Distribution:

The terminal elimination half-life after intravenous administration in humans is approximately 2.5 to 3.0 hours. The pharmacokinetics of HYDROmorphine have been shown to be linear over a range of intravenous doses from 10 to 40 mcg/kg.

Metabolism:

After oral administration of conventional release HYDROmorphine tablets, the drug is rapidly absorbed and, like morphine, undergoes presystemic elimination (approximately 50%), presumably as a result of metabolism in the liver.

Elimination:

The principal mode of elimination is by excretion in the urine as HYDROmorphine- 3-glucuronide, which, at steady-state is present in plasma at concentrations approximately 26 times those of the parent drug. The pharmacologic activity of this and other HYDROmorphine metabolites in humans is not known.

In three separate studies, the elimination half-life following intravenous administration of HYDROmorphine in man was 2.6, 2.4 and 3.1 hours. Following oral administration, in two of the studies, the elimination half-life was 2.5 to 4.1 hours and absolute bioavailability was 51 to 62%, indicating substantial presystemic elimination.

In a study in which bolus intravenous, 10, 20 or 40 mcg/kg doses of HYDROmorphine were administered to healthy human subjects, there was a linear relationship between area under the plasma HYDROmorphine concentration-time curve and dose. The plasma concentration-

time data was fitted best by a triexponential function, the coefficients of which were also linearly related to dose, indicating dose independent pharmacokinetics.

In urinary excretion studies, 36.8% of a 4 mg dose was recovered over 48 hours as glucuronide conjugate of the parent drug with only 5.6% present as unchanged drug. The metabolites dihydromorphine and dihydroisomorphine were present as glucuronide conjugates in amounts representing 0.1% and 1% of the administered dose, respectively.

Special Populations and Conditions

- **Pediatrics:** APO-HYDROmorphine CR has not been studied in patients less than 18 years of age and is not indicated for this population.
- **Geriatrics:** HYDROmorphine 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. HYDROmorphine 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 at room temperature (15°C to 30°C). Keep in a dry place.
- **Disposal:** APO-HYDROmorphine CR should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired APO-HYDROmorphine CR should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets. APO-HYDROmorphine CR 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-HYDROmorphine CR 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-HYDROmorphine CR should not be used in front of children, since they may copy these actions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

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

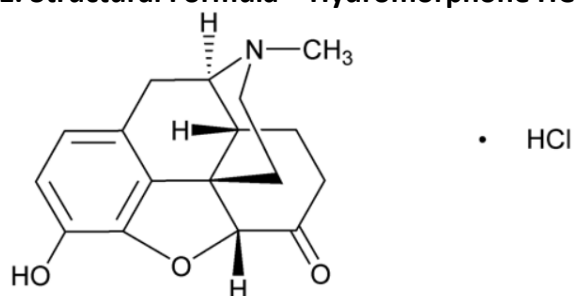
Proper name: Hydromorphone Hydrochloride

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

Molecular formula and molecular mass: C₁₇H₁₉NO₃ HCl / 321.8 g/mol

Structural formula:

Figure 1. Structural Formula – Hydromorphone HCl



Product Characteristics

Physicochemical

properties: Hydromorphone hydrochloride is a hydrogenated ketone of morphine.

Appearance: White or almost white, crystalline powder.

Solubility: Freely soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

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

14 CLINICAL TRIALS

14.3 Comparative Bioavailability Studies

A randomized, single dose, double-blinded, 2-way crossover comparative bioavailability study,

conducted under fasting conditions, was performed on healthy male and female volunteers. The results obtained from 16 volunteers who completed the study are summarized in the following table. The rate and extent of absorption of hydromorphone was measured and compared following a single oral dose (1 x 30 mg capsule) of Apo-Hydromorphone CR (hydromorphone hydrochloride) 30 mg Controlled-Release Capsules (Apotex Inc.) and HYDROMORPH CONTIN[®] (hydromorphone hydrochloride) 30 mg Capsules (Purdue Pharma).

Hydromorphone (1 x 30 mg) From Measured Data Geometric Mean [#] Arithmetic Mean (CV%)				
Parameter	Test*	Reference [†]	Ratio of Geometric Means (%)	90% Confidence Interval (%)
AUC _t (pg h/mL)	63156.9 67921.6 (43)	59456.9 63129.9 (39)	106.2	97.0 - 116.3
AUC _{inf} (pg h/mL)	69032.8 75039.2 (45)	63699.6 67183.1 (43)	108.4	97.4 - 120.6
C _{max} (pg/mL)	4279.6 4549.5 (38)	4760.9 5255.7 (45)	89.9	76.9 - 105.1
T _{max} [§] (h)	3.44 (52)	3.41 (34)		
T _{half} [§] (h)	14.65 (39)	11.57 (26)		
* Apo-Hydromorphone CR (hydromorphone hydrochloride) 30 mg Capsules (Apotex Inc.) [†] HYDROMORPH CONTIN [®] (hydromorphone hydrochloride) 30 mg Capsules (Purdue Pharma) was purchased in Canada. [#] Based on Geometric Least Squares Means. [§] Expressed as arithmetic means (CV%) only.				

A randomized, single dose, double-blinded, 2-way crossover comparative bioavailability study, conducted under fed conditions, was performed on healthy male and female volunteers. The results obtained from 25 volunteers who completed the study are summarized in the following table. The rate and extent of absorption of hydromorphone was measured and compared following a single oral dose (1 x 30 mg capsule) of Apo-Hydromorphone CR (hydromorphone hydrochloride) 30 mg Controlled-Release Capsules (Apotex Inc.) and HYDROMORPH CONTIN[®] (hydromorphone hydrochloride) 30 mg Capsules (Purdue Pharma).

Hydromorphone (1 x 30 mg) From Measured Data Geometric Mean [#] Arithmetic Mean (CV%)				
Parameter	Test*	Reference [†]	Ratio of Geometric Means (%)	90% Confidence Interval (%)
AUC _t (pg h/mL)	56484.7 58776.7 (29)	56965.9 60352.1 (35)	99.2	92.3 - 106.5
AUC _{inf} (pg h/mL)	59188.6 61510.4 (29)	59610.7 63371.7 (35)	99.3	92.2 - 107.0
C _{max} (pg/mL)	3681.2 4219.2 (57)	3049.9 3586.1 (59)	120.7	101.4 - 143.7
T _{max} [§] (h)	5.28 (138)	6.76 (68)		
T _{half} [§] (h)	10.36 (42)	10.72 (42)		
[*] Apo-Hydromorphone CR (hydromorphone hydrochloride) 30 mg Capsules (Apotex Inc.) [†] HYDROMORPH CONTIN [®] (hydromorphone hydrochloride) 30 mg Capsules (Purdue Pharma) was purchased in Canada. [#] Based on Geometric Least Squares Means. [§] Expressed as arithmetic means (CV%) only.				

In a single dose bioavailability study, the controlled release characteristics of HYDROmorphone hydrochloride controlled release capsules were demonstrated with reference to immediate release HYDROmorphone tablets. Following 4 mg doses of both formulations, the time of attainment of maximum plasma concentration (T_{max}) was 4.0 hours with HYDROmorphone hydrochloride controlled release capsules and 1.0 hour with the immediate release HYDROmorphone tablets. The maximum plasma concentration was reduced while the extent of absorption of the immediate release HYDROmorphone tablets with HYDROmorphone hydrochloride controlled release capsules was equivalent to that of the immediate release HYDROmorphone tablets. In the same study, administration of HYDROmorphone hydrochloride controlled release capsules together with a high protein, high fat meal, did not result in a significant increase in the extent of absorption of HYDROmorphone, compared with the fasting state.

In three separate pharmacokinetic studies, the rate and extent of absorption of HYDROmorphone with HYDROmorphone hydrochloride controlled release capsules was studied when sprinkled on one tablespoon (15 mL) of soft foods under the following conditions: warm (40°C ± 2°C) applesauce (pH 3.56), cold (4°C ± 1°C) applesauce (pH 3.62), and room temperature (23°C ± 2°C) custard (pH 6.95). All three studies concluded that bioequivalence was demonstrated when HYDROmorphone was administered as an intact capsule vs. administration of capsule contents sprinkled on these foods in healthy subjects under fasting conditions. For the conditions under study, the HYDROmorphone bioavailability was not affected by the pH of the soft foods or temperature, with a contact time at 30 minutes.

In a multiple dose pharmacokinetic study in patients with cancer pain, 12 hourly administration of HYDROmorphone hydrochloride controlled release capsules demonstrated bioequivalence to immediate release HYDROmorphone tablets administered 4 hourly, with respect to extent of absorption (AUC), and maximum and minimum plasma concentrations (C_{max} , C_{min}), with a significant delay in mean time of maximum plasma concentration, from 1.5 to 4.8 hours (Table 3).

Table 3 - Multiple Dose Pharmacokinetic Study Comparing Immediate Release HYDROmorphone Tablets with HYDROmorphone Hydrochloride Controlled Release Capsules

Pharmacokinetic Parameter (n = 18)	Immediate Release HYDROmorphone Tablets	HYDROmorphone Hydrochloride Controlled Release Capsules	Ratio, % (90% Confidence Interval)*
AUC ₀₋₁₂ ng hr mL ⁻¹	119.0	123.1	102 (92-113)
C _{max} ng mL ⁻¹	19.7	17.8	97 (85-111)
C _{min} ng mL ⁻¹	5.3	6.0	111 (96-124)
T _{max} (hr)	1.5	4.8	-

* Derived from ln transformed data.

In the same study, the relationship between dose of HYDROmorphone hydrochloride controlled release capsules and area under the plasma concentration-time curve of HYDROmorphone was linear over a range of daily doses from 6 mg to 216 mg.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: The LD₅₀ of an intravenous (IV) and subcutaneous (SC) dose of HYDROmorphone in the mouse was 104 mg/kg and 84 mg/kg, respectively. The LD₅₀ of an IV and SC dose of HYDROmorphone HCl in the mouse was 55 mg/kg and 120 mg/kg respectively. In the rat the SC LD₅₀ was 51 mg/kg.

Carcinogenicity: The carcinogenic effects of HYDROmorphone are unknown.

Genotoxicity: HYDROmorphone was non-genotoxic in the Ames test and the *in vivo* mouse micronucleus assay, but positive in the mouse lymphoma assay with metabolic activation. Similar findings have been reported with other opioid analgesics like codeine and oxycodone, although codeine was negative in rodent carcinogenicity studies.

Reproductive and Development Toxicology: No effects have been observed on male or female fertility or sperm parameters.

- **Teratology and Peri/Post-Natal Reproductive Toxicity:**

Teratogenic Effects - Human: There are no well-controlled studies of HYDROmorphine in pregnant women.

Evidence of a teratogenic effect was reported in the literature in mice and hamsters, but was not in GLP rat and rabbit studies. The anomalies produced resembled those produced by other opioid agonists, including morphine.

No effects on long-term reproductive performance of the F1 generation in rats were observed.

17 SUPPORTING PRODUCT MONOGRAPHS

1. HYDROMORPH CONTIN® (HYDROmorphine hydrochloride Controlled Release Capsules 3 mg, 4.5 mg, 6 mg, 9 mg, 10 mg, 12 mg, 18 mg, 20 mg, 24 mg and 30 mg), submission control 273931, Product Monograph Purdue Pharma (AUG 25, 2023)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

^NAPO-HYDROmorphone CR

HYDROmorphone Hydrochloride Controlled Release Capsules

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

Serious Warnings and Precautions

- Even if you take APO-HYDROmorphone CR as prescribed you are at 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 health care professional.
- Life-threatening breathing problems can happen while taking APO-HYDROmorphone CR, especially if not taken 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 CR. They could die from taking it. If a person has not been prescribed APO-HYDROmorphone CR, 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 CR 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 feverSeek immediate medical help for your baby.
- Taking APO-HYDROmorphone CR 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-HYDROmorphine CR used for?

APO-HYDROmorphine CR is used for the long-term management of pain, when:

- the pain is severe enough to require daily, around-the-clock pain medication
- the health care professional determines that other treatment options are not able to effectively manage your pain

APO-HYDROmorphine CR is NOT used (“as needed”) to treat pain that you only have once in a while.

How does APO-HYDROmorphine CR work?

APO-HYDROmorphine CR is an oral controlled release capsule that slowly releases HYDROmorphine over a 12 hour period.

APO-HYDROmorphine CR contains HYDROmorphine which is a pain medication belonging to the class of medicines 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-HYDROmorphine CR?

Medicinal ingredient: HYDROmorphine hydrochloride

Non-medicinal ingredients: Anhydrous lactose, colloidal silicon dioxide, dibutyl sebacate, ethyl cellulose, magnesium stearate and povidone.

In addition, the capsule shells contain the following ingredients:

All capsules: gelatin, talc and titanium dioxide.

3 mg:	D&C Yellow No.10, FD&C Green No.3
4.5 mg:	FD&C Blue No.1, FD&C Red No.3
6 mg:	D&C Red No.28, FD&C Blue No.1, FD&C Red No.40
9 mg:	FD&C Blue No.1
12 mg:	D&C Red No.28, D&C Yellow No.10, FD&C Blue No.1, FD&C Red No.40
18 mg:	iron oxide yellow
24 mg:	iron oxide black
30 mg:	iron oxide red, iron oxide yellow

Imprinting ink: ammonium hydroxide, ferrosferric oxide, propylene glycol and shellac glaze.

APO-HYDROmorphine CR comes in the following dosage forms:

Controlled Release Capsules: 3 mg, 4.5 mg, 6 mg, 9 mg, 12 mg, 18 mg, 24 mg and 30 mg

Do not use APO-HYDROmorphone CR if:

- your health care professional did not prescribe it for you.
- you are allergic to HYDROmorphone, other opioids, or any of the other ingredients of APO-HYDROmorphone CR (see [What are the ingredients in APO-HYDROmorphone CR?](#)).
- you have mild or short term pain that can be controlled by the occasional use of pain medications, including those available without a prescription.
- you have severe asthma, trouble breathing, or other lung problems.
- you have any heart problems.
- you have a 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 Inhibitors (MAOIs) medication (e.g., phenelzine sulfate, tranylcypromine sulfate, moclobemide or selegiline).
- you are pregnant or plan to become pregnant or you are in labour.
- you are breastfeeding.
- you are under 18 years of age.
- you are going to have a surgery or operation or have had a surgery in the last 24 hours.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APO-HYDROmorphone CR. 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.
- have problems with your thyroid, adrenal or prostate gland.
- suffer from chronic or severe constipation.
- 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-HYDROmorphine CR may cause dangerous side effects, including death. Do NOT drink alcohol while taking APO-HYDROmorphine CR.
- have a condition that causes weakness or frailty.

Other warnings you should know about:

Opioid dependence and addiction: Like any opioid, APO-HYDROmorphine CR 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-HYDROmorphine CR 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-HYDROmorphine CR while pregnant, nursing, during labour or delivery. Opioids can be transferred to your baby through breast milk, or while still in the womb. APO-HYDROmorphine CR can then cause life-threatening breathing problems in your unborn baby or nursing infant.

If you are pregnant and are taking APO-HYDROmorphine CR, 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-HYDROmorphine CR. 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-HYDROmorphine CR. APO-HYDROmorphine CR can cause:

- drowsiness
- dizziness
- 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 healthcare professional may do tests, give you another medication, and slowly take you off APO-HYDROmorphine CR.

Serotonin Toxicity (also known as Serotonin Syndrome): APO-HYDROmorphine CR 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 Syndrome if you take APO-HYDROmorphine CR 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 healthcare 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-HYDROmorphine CR.

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-HYDROmorphine CR 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-HYDROmorphine CR. It can lead to:
 - drowsiness
 - unusually slow or weak breathing,

- serious side effects or,
- a fatal overdose.
- Monoamine Oxidase Inhibitors (MAOIs), used to treat depression. Do NOT take APO-HYDROmorphine CR with MAOIs or if you have taken an MAOIs 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. gabapentin)
- other sedative drugs which may enhance the drowsiness caused by APO-HYDROmorphine CR.

The following may interact with APO-HYDROmorphine CR:

- alcohol, including prescription and non-prescription medications containing alcohol. **Do not** drink alcohol while taking APO-HYDROmorphine CR. 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-HYDROmorphine CR.
- other opioid analgesics, medicines used to treat pain (e.g. butorphanol, nalbuphine, pentazocine, buprenorphine).
- 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 medication (such as beta blockers).
- drugs used to treat migraines (e.g. triptans).
- St. John's Wort.

How to take APO-HYDROmorphine CR:

Take APO-HYDROmorphine CR:

- exactly as prescribed
- every 12 hours

APO-HYDROmorphine CR can be swallowed whole or sprinkled on applesauce or custard.

Swallowed:

- swallow the capsule whole
- take the capsule with a full glass of water
- **do not** cut, break, chew, dissolve or crush the capsule - this can be dangerous and life threatening

Sprinkled:

- measure a tablespoon of warm or cold (4° to 40°C) applesauce or room temperature custard
- open the capsule
- sprinkle contents onto the tablespoon
- ensure the capsule is emptied of all contents
- take the entire tablespoon as soon as possible
- **do not** chew the contents (beads)
- rinse your mouth and swallow the water
- **do not** keep any of the food/medicine mixture for another dose

If you do not remember when you sprinkled the medicine on the applesauce or custard, or which food you sprinkled the medicine on, throw out the food/medicine mixture.

Do not take a single dose greater than 12 mg of APO-HYDROmorphine CR every 12 hours unless you are “opioid tolerant”. Your healthcare professional will tell you when you are “opioid tolerant” to a certain dose of APO-HYDROmorphine CR.

Usual Dose:

Dosage is individualized. Be sure to follow your healthcare professional’s dosing instructions exactly. Do not increase or decrease your dose without consulting your healthcare professional. Taking higher doses can lead to more side effects and greater chance of overdose.

Review your pain regularly with your healthcare professional to determine if you still need APO-HYDROmorphine CR. Be sure to use APO-HYDROmorphine CR only for the condition for which it was prescribed.

Should your pain increase or any other complaint develop as a result of taking APO-HYDROmorphine CR, tell your healthcare professional immediately.

Stopping your Medication:

You should not stop taking APO-HYDROmorphine CR all at once if you have been taking it for more than a few days. Your healthcare professional will monitor and guide you on how to slowly stop taking APO-HYDROmorphine CR. 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 with 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-HYDROmorphine CR.

Refilling your Prescription for APO-HYDROmorphine CR:

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

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

Overdose:

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

It is important that you do not miss any doses. If you miss a dose, take your next dose at your usual time. You should always try to get back on track with your regular dosing schedule (e.g., 8 o'clock in the morning and 8 o'clock in the evening). If you miss several doses in a row, talk to your healthcare professional before restarting your medication.

What are possible side effects from using APO-HYDROmorphine CR?

These are not all the possible side effects you may feel when taking APO-HYDROmorphine CR. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- confusion
- constipation
- dizziness
- drowsiness
- light-headedness
- nausea, vomiting, or poor appetite
- lack of muscle strength
- sleepiness
- sweating
- low sex drive, impotence (erectile dysfunction), infertility
- itching
- dry mouth
- insomnia
- abdominal pain
- headache
- anxiety
- problems with vision
- weakness, uncoordinated muscle movement

Talk with your healthcare professional or pharmacist about ways to prevent constipation when you start using APO-HYDROmorphine CR.

If nausea and vomiting become troublesome during prolonged therapy with APO-HYDROmorphine CR, talk to your healthcare professional or pharmacist.

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, 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 APO-HYDROmorphine CR capsules in a secure place to prevent theft, misuse or accidental exposure.**
- Store at room temperature (15°C to 30°C). Keep in a dry place.
- **Keep APO-HYDROmorphine CR capsules 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-HYDROmorphine CR capsules, get emergency help right away.**

Disposal:

APO-HYDROmorphine CR capsules 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-HYDROmorphine CR capsules:

- 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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