PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[N]APO-HYDROmorphone CR

HYDROmorphone* Hydrochloride Controlled Release Capsules
3 mg, 4.5 mg, 6 mg, 9 mg, 12 mg, 18 mg, 24 mg and 30 mg

Opioid Analgesic

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

RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome (NOWS), April 2021

7 WARNINGS AND PRECAUTIONS, Respiratory, Sleep Apnea, April 2021

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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

Pediatrics (<18 years of age): The safety and efficacy of HYDROmorphone hydrochloride controlled release capsules has not been studied in the pediatric population. Therefore the use of APO-HYDROmorphone CR is not recommended in patients under 18 years of age.

1.2 Geriatrics

Geriatrics (>65 years of age): In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, concomitant disease or other drug therapy (see WARNINGS AND PRECAUTIONS, Special Populations, 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 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 (CO_2) levels in the blood and cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).
- Women who are breast-feeding, pregnant, or during labour and delivery (see SERIOUS WARNINGS AND PRECAUTIONS BOX and WARNINGS AND PRECAUTIONS).

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 DOSAGE AND ADMINISTRATION).

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 WARNINGS AND PRECAUTIONS). 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 WARNINGS AND PRECAUTIONS). Further, instruct patients of 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 STORAGE, STABILITY AND 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 WARNINGS AND PRECAUTIONS).

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 WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

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

- Reserve concomitant prescribing of 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 (HYDROmorphone hydrochloride controlled release capsules) 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 DOSAGE AND ADMINISTRATION, 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 (4ºC to 40ºC) 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 WARNINGS AND PRECAUTIONS**).

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 ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics), sprinkled doses should be ingested as soon as possible to avoid errors from the loss of product identification features after removal of mini-tablets 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 WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

APO-HYDROmorphone CR is not indicated for rectal administration.

4.2 Recommended Dose and Dosage Adjustment

Pediatrics (<18 years of age): Health Canada has not authorized an indication for pediatric use (see INDICATIONS).

Adults (≥18 years of age): 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.

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 WARNINGS AND PRECAUTIONS, Special Populations, Hepatic Impairment).

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 WARNINGS AND PRECAUTIONS, Special Populations, Renal Impairment).

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 WARNINGS AND PRECAUTIONS).

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 WARNINGS AND PRECAUTIONS). Tapering should be individualized and carried out under medical supervision.

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

Opioid analgesics may only be partially effective in relieving dysesthetic pain, 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.

4.3 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 WARNINGS AND PRECAUTIONS).

4.4 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

Symptoms

Serious overdosage with APO-HYDROmorphone CR (HYDROmorphone hydrochloride) is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), dizziness, confusion, extreme somnolence progressing to stupor or coma, pneumonia aspiration, skeletal muscle flaccidity, cold and clammy skin, miotic pupils, toxic leukoencephalopathy, delayed post-hypoxic leukoencephalopathy and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Treatment

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

Since the duration of action of HYDROmorphone, 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 immediately.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	All Non-medicinal Ingredients
Oral	Controlled Release Capsules / 3, 4.5, 6, 9, 12, 18, 24 and 30 mg	anhydrous lactose, colloidal silicon dioxide, dibutyl sebacate, ethyl cellulose, magnesium stearate and povidone. Capsule Shells: gelatin, talc and titanium dioxide. Additional capsule shell ingredients specific to each strength are as follows: 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, ferrosoferric

		oxide, propylene glycol and shellac glaze.

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).

Composition

Active Ingredient:
Hydromorphone Hydrochloride

Non-medicinal Ingredients (all strengths):
anhydrous lactose, colloidal silicon dioxide, dibutyl sebacate, ethyl cellulose, magnesium stearate and povidone.

Capsule Shells: gelatin, talc and titanium dioxide. Additional capsule shell ingredients specific to each strength are as follows:

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, ferrosoferric oxide, propylene glycol and shellac glaze.

Packaging

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

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

General

APO-HYDROmorphone CR must be swallowed whole, or opened and the entire contents sprinkled onto a tablespoonful of applesauce or custard (see DOSAGE AND ADMINISTRATION). 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 ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics), sprinkled doses should be ingested as soon as possible to avoid errors from the loss of product identification features after removal of mini-tablets 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 DOSAGE AND ADMINISTRATION). 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 WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

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.

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 DRUG INTERACTIONS).

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

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. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

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, 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 also DRUG INTERACTIONS). 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 and physical dependence may develop upon repeated administration of HYDROmorphone and there is a potential for development of psychological dependence. 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.

Patients on prolonged therapy should be tapered gradually from the drug if it is no longer required for

pain control. Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist. Some of the symptoms that may be associated with abrupt withdrawal of an opioid analgesic include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, anxiety, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning (see ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION, 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.

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.

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 CONTRAINDICATIONS and ADVERSE REACTIONS, Nausea and Vomiting and Constipation).

Neonatal Opioid Withdrawal Syndrome (NOWS)

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

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration,

and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

Use of APO-HYDROmorphone CR capsules are contraindicated in pregnant women (see CONTRAINDICATIONS).

Neurologic

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 DRUG INTERACTIONS).

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

Advise both patients and caregivers about the risks of respiratory depression and sedation when 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 DRUG INTERACTIONS).

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

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

Use in Patients with Convulsive or Seizure Disorders

The HYDROmorphone in APO-HYDROmorphone CR may aggravate convulsions in patients with convulsive disorders and may induce or aggravate seizures in some clinical settings. Therefore, APO-HYDROmorphone CR should not be used in these patients (see CONTRAINDICATIONS).

Serotonin Toxicity / Serotonin Syndrome

Serotonin toxicity also known as serotonin syndrome is a potentially life-threatening condition and has

been reported with HYDROmorphone, including HYDROmorphone hydrochloride controlled release capsules, particularly during combined use with other serotonergic drugs (see DRUG INTERACTIONS).
Serotonin toxicity is characterised by neuromuscular excitation, autonomic stimulation (e.g. tachycardia, flushing) and altered mental state (e.g. anxiety, agitation, hypomania). In accordance with the Hunter Criteria, serotonin toxicity diagnosis is likely when, in the presence of at least one serotonergic agent, one of the following is observed:

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

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

Head Injury
The respiratory depressant effects of HYDROmorphone with carbon dioxide (CO_2) 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 should not be used (see CONTRAINDICATIONS).

Peri-Operative Considerations
APO-HYDROmorphone 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-HYDROmorphone CR for at least 48 hours before the operation and APO-HYDROmorphone CR should not be used within the first 24 hours post-operatively. Thereafter, if APO-HYDROmorphone 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 CONTRAINDICATIONS).

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. APO-HYDROmorphone CR should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia (see CONTRAINDICATIONS).

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of

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 DOSAGE AND ADMINISTRATION). 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.

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

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 fashion. 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 reducing or stopping the opioid treatment if appropriate, using best practices for tapering of opioids (see WARNINGS AND PRECAUTIONS, Dependence/Tolerance; DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage).

Sexual Function

Reproduction

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

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 (4ºC to 40ºC) 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-HYDROmorphone CR and cessation of therapy is indicated, it may be appropriate to taper APO-HYDROmorphone 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-HYDROmorphone 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-HYDROmorphone 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-HYDROmorphone 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-HYDROmorphone CR.

12. Patients should be advised that APO-HYDROmorphone CR is a potential drug of abuse.

They should protect it from theft or misuse.

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

14. Patients should be advised that APO-HYDROmorphone 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-HYDROmorphone CR. Women who are breast-feeding or pregnant should not use APO-HYDROmorphone CR.

7.1 Special Populations

Special Risk Groups
In general, opioids should be given 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 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 WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome and ADVERSE REACTIONS, 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 (< 18 years of age)

The safety and efficacy of HYDROmorphone hydrochloride controlled release capsules has not been studied in the pediatric population. Therefore the use of APO-HYDROmorphone CR is not recommended in patients under 18 years of age.

7.1.4 Geriatrics (> 65 years of age)

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

7.1.5 Hepatic Impairment

After oral administration of HYDROmorphone at a single 4 mg dose (2 mg HYDROmorphone tablets), mean exposure to HYDROmorphone (C_{max} and AUC_{∞}) is increased 4-fold in patients with moderate (Child-Pugh Group B) hepatic impairment compared with subjects with normal hepatic function. 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 DOSAGE AND ADMINISTRATION).

7.1.6 Renal Impairment

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 - 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 DOSAGE AND ADMINISTRATION).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The adverse effects of APO-HYDROmorphone CR (HYDROmorphone hydrochloride controlled release capsules) are similar to those of other opioid analgesics, and represent an extension of pharmacological effects of the drug class. The major hazards of HYDROmorphone 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-HYDROmorphone 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 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 (≥ 1/10); Common (≥ 1/100 to <1/10); Uncommon (≥ 1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (< 1/10,000), Not known (cannot be estimated from the available data).

Immune System Disorders:
Not known: anaphylactic reactions, hypersensitivity reactions (including oropharyngeal swelling)

Metabolism and Nutrition Disorders:
Common: decreased appetite

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

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

8.3 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 WARNINGS AND PRECAUTIONS, Endocrine and ACTION AND CLINICAL PHARMACOLOGY).

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 WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome (NOWS)).

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions Box

- 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 WARNINGS AND PRECAUTIONS)
  - 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
- MAO inhibitors intensify the effects of opioid drugs which can cause anxiety, confusion and decreased respiration. APO-HYDROmorphone CR is contraindicated in patients receiving MAO inhibitors or who have used them within the previous 14 days.

9.2 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, 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 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 - 40%). The clinical significance of these findings is unknown.

9.3 Drug-Drug Interactions

Administration with Mixed Activity Agonist/Antagonist Opioids

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

MAO Inhibitors
MAO inhibitors intensify the effects of opioid drugs which can cause anxiety, confusion and decreased respiration. APO-HYDROmorphone CR is contraindicated in patients receiving MAO inhibitors or who have used them within the previous 14 days (see 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 WARNINGS AND PRECAUTIONS, Neurologic).

9.4 Drug-Food Interactions

Interactions with food have not been established.

9.5 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.6 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

9.7 Drug-Lifestyle Interactions

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

10 ACTION AND 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 HYDROmorphone and analgesic effect has not been well established. In patients with chronic pain, HYDROmorphone should be titrated to the dose required to adequately relieve pain without unmanageable side effects.

There is no intrinsic limit to the analgesic effect of HYDROmorphone; 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 HYDROmorphone 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 HYDROmorphone have no major effect on blood pressure or cardiac rate and rhythm but orthostatic hypotension may result on standing.

Central Nervous System
HYDROmorphone 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 (CO_2). In a study in healthy volunteers the relative potency of HYDROmorphone 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.

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

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

Gastrointestinal Tract and Other Smooth Muscle
HYDROmorphone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation.

Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

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

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; LD_{50} 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

APO-HYDROmorphone CR (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 HYDROmorphone from HYDROmorphone hydrochloride controlled release capsules were studied when sprinkled on one tablespoon (15 mL) of soft foods under the following conditions: warm (40° ± 2°C) applesauce (pH 3.56), cold (4° ± 1°C) applesauce (pH 3.62), and room temperature (23° ± 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 temperatures, with a contact time at 30 minutes.

Food Effects: The extent of absorption of HYDROmorphone from APO-HYDROmorphone CR is equivalent to that from conventional tablets and is not significantly influenced when administered in the presence of food. In patients with chronic cancer pain receiving doses of APO-HYDROmorphone 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 HYDROmorphone 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 HYDROmorphone 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 HYDROmorphone-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 HYDROmorphone metabolites in humans is not known.

In three separate studies, the elimination half-life following intravenous administration of HYDROmorphone 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 - 4.1 hours and absolute bioavailability was 51 - 62%, indicating substantial presystemic elimination.

In a study in which bolus intravenous, 10, 20 or 40 mcg/kg doses of HYDROmorphone were administered to healthy human subjects, there was a linear relationship between area under the plasma HYDROmorphone 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 (<18 years of age): Individuals under 18 years of age should not take APO-HYDROmorphone CR.

Geriatrics (>65 years of age): HYDROmorphone should be administered with caution, and in reduced dosages, to elderly or debilitated patients. Respiratory depression has occurred in the elderly following administration of large initial doses of opioids to patients who were not opioid-tolerant or when opioids were co-administered with other agents that can depress respiration. HYDROmorphone should be initiated at a low dose and slowly titrated to effect (see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics).

Sex: No data available.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15°C to 30° C).

Disposal
APO-HYDROmorphone CR should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired APO-HYDROmorphone 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-HYDROmorphone 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-HYDROmorphone 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-HYDROmorphone CR should not be used in front of children, since they may copy these actions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

HYDROmorphone 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 7-8 double bond of the morphine molecule.

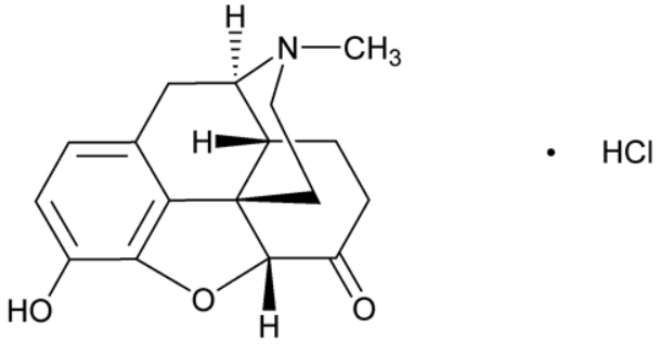
Proper name: Hydromorphone Hydrochloride

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

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

Structural formula:

Figure 1. Structural Formula – Hydromorphone HCl



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

14.1 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.

Bioavailability

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.

15 NON-CLINICAL TOXICOLOGY

General Toxicology

The LD_{50} of an intravenous (IV) and subcutaneous (SC) dose of HYDROmorphone in the mouse was 104 mg/kg and 84 mg/kg, respectively. The LD_{50} 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 LD_{50} 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 HYDROmorphone 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.

16 SUPPORTING PRODUCT MONOGRAPHS

1. Product Monograph - HYDROMORPH CONTIN® (HYDROmorphone* Hydrochloride Controlled Release Capsules) 3, 4.5, 6, 9, 10, 12, 18, 20, 24 and 30 mg. Purdue Pharma. Control No.: 237700. Date of Revision: July 30, 2020.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

^{N}APO-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 that can lead to overdose and death. To understand your risk of opioid addiction, abuse, and misuse you should speak to your prescriber (e.g., doctor).
- 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.
- 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.
- 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 fever

  Seek 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-HYDROmorphone CR used for?

APO-HYDROmorphone 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 doctor determines that other treatment options are not able to effectively manage your pain

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

How does APO-HYDROmorphone CR work?

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

APO-HYDROmorphone CR contains HYDROmorphone 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-HYDROmorphone CR?

Medicinal ingredient: HYDROmorphone 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. Additional capsule shell ingredients specific to each strength are as follows:

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, ferrosoferric oxide, propylene glycol and shellac glaze.

APO-HYDROmorphone 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 doctor 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 breathing problems
- you have any heart problems
- you have a bowel blockage or narrowing of the stomach or intestines
- you have severe pain in your abdomen
- you have a head injury
- if you are at risk for seizures
- you have a brain tumor
- you suffer from alcoholism
- you are taking or have taken within the past 2 weeks a Monoamine Oxidase Inhibitor (MAO inhibitor) 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, or recently had, a planned surgery

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 heart disease
- have low blood pressure
- have a history of sleep apnea
- have past or current depression
- have problems with your thyroid, adrenal or prostate gland
- suffer from chronic or severe constipation
- have, or had in the past, hallucinations or other severe mental problems
- suffer from migraines
- are pregnant or planning to become pregnant

Other warnings you should know about:

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

Pregnancy, nursing, labour and delivery
Do not use APO-HYDROmorphone 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-HYDROmorphone CR can then cause life-threatening breathing problems in your unborn baby or nursing infant.

Driving and using machines
Before you do tasks which may require special attention, you should wait until you know how you react to APO-HYDROmorphone CR. APO-HYDROmorphone 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 doctor may do tests, give you another medication, and slowly take you off APO-HYDROmorphone CR.

Serotonin Syndrome
APO-HYDROmorphone CR can cause Serotonin Syndrome, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop

Serotonin Syndrome if you take APO-HYDROmorphone CR with certain anti-depressants or migraine medications.

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

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

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

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

The following may interact with APO-HYDROmorphone CR:

- alcohol, including prescription and non-prescription medications containing alcohol. **Do not** drink alcohol while taking APO-HYDROmorphone 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-HYDROmorphone CR
- other opioid analgesics (for pain)
- general anesthetics (used during surgery)
- drugs used to help you sleep or to reduce anxiety (benzodiazepines)
- antidepressants (for depression and mood disorders). **Do not** take APO-HYDROmorphone CR with monoamine oxidase (MAO) inhibitors or if you have taken MAO inhibitors in the last 14 days before treatment with APO-HYDROmorphone CR
- drugs used to treat serious mental or emotional disorders, such as schizophrenia
- antihistamines (for allergies)
- anti-emetics (for the prevention of vomiting)
- drugs used to treat muscle spasms and back pain
- 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-HYDROmorphone CR:

Take APO-HYDROmorphone CR
- exactly as prescribed
- every 12 hours

APO-HYDROmorphone CR Capsules 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°C 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 (mini-tablets)
- 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-HYDROmorphone CR every 12 hours unless you are "opioid tolerant". Your doctor will tell you when you are "opioid tolerant" to a certain dose of APO-HYDROmorphone CR.

APO-HYDROmorphone CR is not recommended for rectal administration.

Usual Adult Starting Dose:

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

Review your pain regularly with your doctor to determine if you still need **APO-HYDROmorphone CR**. Be sure to use **APO-HYDROmorphone 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-HYDROmorphone CR**, tell your doctor immediately.

Stopping your Medication:

You should not stop taking **APO-HYDROmorphone CR** all at once if you have been taking it for more than a few days.

Your doctor will monitor and guide you on how to slowly stop taking **APO-HYDROmorphone 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-HYDROmorphone CR**.

Refilling your Prescription for APO-HYDROmorphone CR:

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

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

Overdose:

If you think you, or a person you are caring for, have taken too much **APO-HYDROmorphone 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 doctor before restarting your medication.

What are possible side effects from using APO-HYDROmorphone CR?
These are not all the possible side effects you may feel when taking **APO-HYDROmorphone 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 doctor or pharmacist about ways to prevent constipation when you start using APO-HYDROmorphone CR.

If nausea and vomiting become troublesome during prolonged therapy with APO-HYDROmorphone CR, talk to your doctor 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 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-HYDROmorphone 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-HYDROmorphone 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-HYDROmorphone CR capsules, get emergency help right away.**

Disposal:

APO-HYDROmorphone 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-HYDROmorphone 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://health-products.canada.ca/dpd-bdpp/index-eng.jsp). Find the Patient Medication Information on the manufacturer's website http://www.apotex.ca/products, or by calling 1-800-667-4708.

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