

PRODUCT MONOGRAPH

^NHydromorph•IR[®]

**Hydromorphone Hydrochloride Tablets
2, 4 and 8 mg**

**Purdue Pharma Std.
Opioid Analgesic
ATC: N02AA03**

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PRODUCT MONOGRAPH

NAME OF DRUG

^NHydromorph•IR[®]

Hydromorphone Hydrochloride Tablets
2, 4 and 8 mg

THERAPEUTIC CLASSIFICATION

Opioid Analgesic

ACTIONS

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, euphoria 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.

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.

Pharmacokinetics: After oral administration of conventional release hydromorphone tablets, the drug is rapidly absorbed and, like morphine, undergoes pre-systemic elimination (approximately 50%), presumably as a result of metabolism in the liver. The terminal elimination half-life after intravenous administration is approximately 2.5 - 3.0 hours. The pharmacokinetics of hydromorphone have been shown to be linear over a range of intravenous doses from 10 - 40 µg/kg. 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.

Hydromorph•IR[®] (hydromorphone hydrochloride tablets) administered every four hours is bioequivalent to Dilaudid[®] tablets administered every 4 hours.

Dilaudid[®] is a product of Abbott Laboratories, Limited.

INDICATIONS

Hydromorph•IR[®] (hydromorphone hydrochloride tablets) is indicated for the relief of moderate to severe pain.

CONTRAINDICATIONS

Hydromorph•IR[®] (hydromorphone hydrochloride tablets) should not be given to patients with: hypersensitivity to opioid analgesics, hydromorphone, or any other component of the product; acute asthma or other obstructive airway disease and acute respiratory depression; elevated carbon dioxide levels in the blood; cor pulmonale; acute alcoholism; delirium tremens; severe CNS depression; convulsive disorders; increased cerebrospinal or intracranial pressure; head injury; suspected surgical abdomen; concomitant MAO inhibitors (or within 14 days of such therapy).

WARNINGS

Abuse of Opioid Formulations: **Hydromorph•IR[®]** (hydromorphone hydrochloride tablets) are intended for oral use only. Abuse can lead to overdose and death. This risk is increased if **Hydromorph•IR** is taken with alcohol or other CNS depressants. With parenteral abuse, the tablet excipients, especially talc, can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury.

Patients should be instructed not to give Hydromorph•IR to anyone other than for whom it was prescribed, as such, inappropriate use may have severe medical consequences, including death.

Patients should be cautioned not to consume alcohol while taking **Hydromorph•IR**, as it may increase the chance of experiencing dangerous side effects.

Hydromorph•IR should be used with caution preoperatively and within the first 24 hours postoperatively.

Drug Dependence: As with other opioids, tolerance and physical dependence tend to develop upon repeated administration of hydromorphone and there is a potential for development of psychological dependence. **Hydromorph•IR[®]** should therefore be prescribed and handled with the degree of caution appropriate to the use of a drug with abuse potential. Drug abuse is not usually a problem in patients with severe pain in which hydromorphone is appropriately indicated. Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist. Therefore, patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control.

CNS Depression: Hydromorphone should be used only with caution and in reduced dosage during concomitant administration of other opioid analgesics, general anaesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, antidepressants and other CNS depressants, including alcohol. Respiratory depression, hypotension and profound sedation or coma may result.

Severe pain antagonizes the subjective and respiratory depressant actions of hydromorphone. Should pain suddenly subside, these effects may rapidly become manifest. Patients who are

scheduled for cordotomy or other interruption of pain transmission pathways should not receive **Hydromorph•IR** within 24 hours of the procedure.

Use in Pregnancy: Animal studies with both morphine and hydromorphone have indicated the possibility of teratogenic effects. While experience in humans has not identified this as a risk, **Hydromorph•IR** should be given to pregnant patients only when the anticipated benefits outweigh the potential risks to the fetus.

PRECAUTIONS

Respiratory Depression: Hydromorphone should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia. Such patients are often less sensitive to the stimulatory effects of carbon dioxide (CO₂) on the respiratory centre and the respiratory depressant effects of hydromorphone may reduce respiratory drive to the point of apnea.

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

Hypotension: Hydromorphone administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of such drugs as phenothiazines or certain anaesthetics.

Acute Abdominal Conditions: 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.

Special Risk Groups: Hydromorphone should be administered with caution, and in reduced dosages, to elderly or debilitated, to patients with severely impaired pulmonary, hepatic or renal function, and in patients with adrenocortical insufficiency (e.g., Addison's disease), delirium tremens, hypothyroidism, pancreatitis, prostatic hypertrophy, toxic psychosis or urethral stricture.

Hydromorphone should not be used where there is the possibility of paralytic ileus occurring.

Use during Labour/Delivery and in Nursing Mothers: In view of the potential for opioids to cross the placental barrier and to be excreted in breast milk, hydromorphone should be used with caution during labour or in nursing mothers. Physical dependence or respiratory depression may occur in the infant.

Driving and Operating Dangerous 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, sedative/hypnotics and alcohol.

Drug Interactions: CNS depressants, such as other opioids, anaesthetics, sedatives, antidepressants, hypnotics, barbiturates, phenothiazines, (centrally acting) antiemetics, chloral hydrate and glutethimide may enhance the depressant effect of hydromorphone. Monoamine oxidase inhibitors (including procarbazine hydrochloride) should not be taken within two weeks of use. Pyrazolidone antihistamines, beta-blockers and alcohol may also enhance the depressant effect of hydromorphone. When combined therapy is contemplated, the dose of one or both agents should be reduced.

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.

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

ADVERSE REACTIONS

Adverse effects of **Hydromorph•IR[®]** (hydromorphone hydrochloride tablets) are similar to those of other opioid analgesics, and represent an extension of pharmacological effects of the drug class. The major hazards of hydromorphone include respiratory and central nervous system depression. To a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest have occurred.

The most frequently observed adverse effects are sedation, nausea, vomiting, constipation, asthenia, lightheadedness, dizziness, confusion and sweating.

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. When instituting prolonged therapy with an opioid for chronic pain, the routine prescription of an antiemetic should be considered. In the cancer patient, investigation of nausea should include such causes as constipation, bowel obstruction, uremia, hypercalcemia, hepatomegaly, tumor invasion of celiac plexus and concurrent use of drugs with emetogenic properties. Persistent nausea which does not respond to dosage reduction may be caused by opioid-induced gastric stasis and may be accompanied by other symptoms including anorexia, early satiety, vomiting and abdominal fullness. These symptoms respond to chronic treatment with gastrointestinal prokinetic agents.

Constipation: Practically all patients become constipated while taking opioids on a persistent basis. In some patients, particularly the elderly or bedridden, fecal impaction may result. It is essential to caution the patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged opioid analgesic therapy. Stool softeners, stimulant laxatives and other appropriate measures should be used as required.

Less Frequently Observed with Opioid Analgesics: The following adverse effects occur less frequently with opioids and include those occurring in less than 1% of patients in clinical trials and considered possibly related to treatment.

General and CNS: abnormal gait, accidental injury, agitation, alterations of mood or personality
(nervousness, apprehension, depression, paranoid reaction, floating feelings,

dreams), amnesia, blurred vision, convulsions, diplopia, dysphoria, ear pain, euphoria, fever, headache, hyporeflexia, hypotonia, increased intracranial pressure, insomnia, lacrimation disorder and miosis, malaise, muscle rigidity, muscle tremor, nystagmus, paresthesia, speech disorder, thought abnormalities, tinnitus, transient hallucinations and disorientation, tremor, uncoordinated muscle movements, vertigo, visual disturbances and weakness

Cardiovascular: bradycardia, chest pain, chills, faintness, flushing of the face, hypertension, hypotension, migraine, palpitation, peripheral edema, syncope and tachycardia

Respiratory: bronchospasm, cough, dyspnea, hiccup, laryngospasm, rhinitis and voice alteration

Gastrointestinal: anorexia, biliary tract spasm, cramps, diarrhea, dry mouth, dysphagia, gastritis, paralytic ileus, stomatitis and taste alterations

Genitourinary: antidiuretic effects, dysuria, hesitancy or incontinence, impotence, menstrual disorder, polyuria and urinary retention

Musculoskeletal: arthralgia, joint disorder, leg cramps, myalgia and myasthenia

Dermatologic: diaphoresis, pruritus and other skin rashes and urticaria

Other: dehydration, hyponatremia, increased SGOT (AST) or SGPT (ALT), leukopenia and weight loss

Withdrawal (Abstinence) Syndrome: Physical dependence with or without psychological dependence tends to occur with chronic administration. An abstinence syndrome may be precipitated when opioid administration is discontinued or opioid antagonists administered. The following withdrawal symptoms may be observed after opioids are discontinued: 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, unexplained fever, weakness and yawning. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal from the drug, these symptoms are usually mild.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms: Serious overdosage with hydromorphone may be characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, miotic pupils, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Treatment: Primary attention should be given to the establishment of adequate respiratory exchange through the provision of a patent airway and controlled or assisted ventilation. The opioid antagonist naloxone hydrochloride is a specific antidote against respiratory depression due to overdose or as a result of unusual sensitivity to hydromorphone. An appropriate dose of the antagonist should therefore be administered, preferably by the intravenous route. The usual initial i.v. adult dose of naloxone is 0.4 mg or higher. Concomitant efforts at respiratory resuscitation should be carried out. Since the duration of action of hydromorphone, particularly sustained release formulations, may exceed that of the antagonist, the patient should be under continued surveillance and doses of the antagonist should be repeated as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated.

In individuals physically dependent on opioids, the administration of the usual dose of opioid antagonist will precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of antagonist administered. The use of opioid antagonists in such individuals should be avoided if possible. If an opioid antagonist must be used to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care by using dosage titration, commencing with 10 to 20% of the usual recommended initial dose.

Evacuation of gastric contents may be useful in removing unabsorbed drug, particularly when a sustained release formulation has been taken.

DOSAGE AND ADMINISTRATION

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

The usual initial adult dose of **Hydromorph•IR[®]** (hydromorphone hydrochloride tablets) is 2 to 4 mg every 4 to 6 hours.

Patients Currently Receiving Opioids: For patients who are receiving an alternate opioid, the "oral hydromorphone equivalent" of the analgesic presently being used should be determined. Having determined the total daily dosage of the present analgesic, Table 1 can be used to calculate the approximate daily oral hydromorphone dosage that should provide equivalent analgesia.

Dose Titration: Dose titration is the key to success with opioid analgesic therapy. **Proper optimization of doses scaled to the relief of the individual's pain should aim at the regular administration of the lowest dose which will maintain the patient free of pain at all times. Dosage adjustments should be based on the patient's clinical response.**

If breakthrough pain repeatedly occurs at the end of the dosing interval it is generally an indication for a dosage increase rather than more frequent administration.

Adjustment or Reduction of Dosage: 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. If treatment discontinuation is required, the dose of opioid may be decreased as follows: one-half of the previous daily dose given q6h for the first two days, followed thereafter by a 25% reduction every two days.

Opioid analgesics may only be partially effective in relieving dysesthetic pain, postherpetic neuralgia, stabbing pains, activity-related pain and some forms of headache. That is not to say that patients with advanced cancer suffering from some of these forms of pain should not be given an adequate trial of opioid analgesics, but it may be necessary to refer such patients at an early time to other forms of pain therapy.

TABLE 1
OPIOID ANALGESICS: APPROXIMATE ANALGESIC EQUIVALENCES¹

| Drug | Equivalent Dose (mg) ² (compared to morphine 10 mg IM) | | Duration of Action (hours) |
|---|--|------------------|-------------------------------|
| | Parenteral | Oral | |
| Strong Opioid Agonists: | | | |
| Morphine | 10 | 60 ³ | 3-4 |
| Oxycodone | 15 | 30 ⁴ | 2-4 |
| Hydromorphone | 1.5 | 7.5 ⁵ | 2-4 |
| Anileridine | 25 | 75 | 2-3 |
| Levorphanol | 2 | 4 | 4-8 |
| Meperidine ⁶ | 75 | 300 | 1-3 |
| Oxymorphone | 1.5 | 5 (rectal) | 3-4 |
| Methadone ⁷ | - | - | - |
| Heroin | 5-8 | 10-15 | 3-4 |
| Weak Opioid Agonists: | | | |
| Codeine | 120 | 200 | 3-4 |
| Propoxyphene | 50 | 100 | 2-4 |
| Mixed Agonist-Antagonists⁸: | | | |
| Pentazocine ⁶ | 60 | 180 | 3-4 |
| Nalbuphine | 10 | - | 3-6 |
| Butorphanol | 2 | - | 3-4 |

References:

¹ Expert Advisory Committee on the Management of Severe Chronic Pain in Cancer Patients, Health and Welfare Canada. Cancer pain: A monograph on the management of cancer pain. Ministry of Supplies and Services Canada, 1987. Cat. No. H42-2/5-1984E.

Foley KM. The treatment of cancer pain. N Engl J Med 1985;313(2):84-95.

Aronoff GM, Evans WO. Pharmacological management of chronic pain: A review. In: Aronoff GM, editor. Evaluation and treatment of chronic pain. 2nd ed. Baltimore (MD): Williams and Wilkins; 1992. p. 359-68.

Cherny NI, Portenoy RK. Practical issues in the management of cancer pain. In: Wall PD, Melzack R, editors. Textbook of pain. 3rd ed. New York: Churchill Livingstone; 1994. p. 1437-67.

² **Most of this data was derived from single-dose, acute pain studies and should be considered an approximation for selection of doses when treating chronic pain.**

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

⁴ Based on single entity oral oxycodone in acute pain.

⁵ Clinical experience indicates that during chronic dosing the oral morphine/oral hydromorphone dose ratio is 5 - 7.5:1.

⁶ Not recommended for the management of chronic pain.

⁷ Extremely variable equianalgesic dose. Patients should undergo individualized titration starting at an equivalent to 1/10 of the morphine dose.

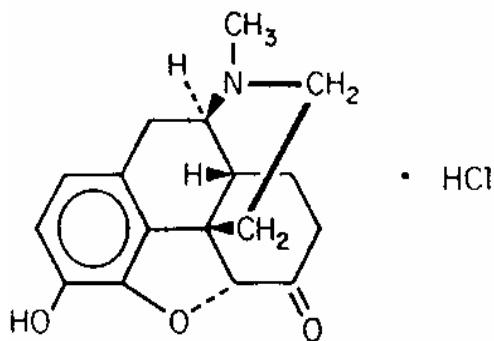
⁸ Mixed agonist-antagonists can precipitate withdrawal in patients on pure opioid agonists.

PHARMACEUTICAL INFORMATION

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

Proper Name: Hydromorphone Hydrochloride

Structure:



Molecular Formula: C₁₇H₁₉NO₃ • HCl

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

Molecular Weight: 321.8

Appearance: Fine, white, or practically white, crystalline powder.

Solubility: Soluble 1:3 in water and 1:100 in alcohol (90%); practically insoluble in chloroform and ether.

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

Composition:

Active Ingredient(s): Hydromorphone Hydrochloride

Non-medicinal Ingredients (all strengths): Croscarmellose sodium, lactose, magnesium stearate, microcrystalline cellulose, starch and talc

Stability and Storage Recommendations:

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

AVAILABILITY OF DOSAGE FORMS

Hydromorph•IR[®] (hydromorphone hydrochloride tablets) are scored, white tablets available in strengths of 2, 4 and 8 mg of hydromorphone hydrochloride. Each tablet is engraved with P IR on one side and a number corresponding to the mg strength on the other.

Hydromorph•IR is supplied in opaque plastic bottles of 50 tablets.

INFORMATION FOR THE CONSUMER

Read this information carefully before you take Hydromorph•IR[®] tablets. Also read the information you get with your prescription refills, since there may be something new. This information does not take the place of talking with your doctor about your medical condition or your treatment. Only you and your doctor can decide if **Hydromorph•IR** is right for you. Share the information in this leaflet with members of your household.

What is hydromorphone?

Hydromorphone is a medicine used to treat moderate to severe pain and should help you live more comfortably and independently. Hydromorphone belongs to a class of drugs which is commonly referred to as opiates, opioids or narcotics, and also includes codeine, fentanyl, morphine and oxycodone.

Your pain may increase or decrease from time to time and your doctor may need to change the amount of hydromorphone you take daily (daily dosage).

What is Hydromorph•IR?

Hydromorph•IR is an immediate release tablet containing the medicine hydromorphone, used to treat moderate to severe pain. **Hydromorph•IR** is made to release hydromorphone promptly, usually requiring dosing every 4 to 6 hours to control pain.

Hydromorph•IR is available in three strengths: 2, 4 and 8 mg as white tablets. It may be necessary for you to take more than one tablet strength at the same time in order to receive the total daily dosage prescribed by your doctor.

Before you take Hydromorph•IR:

Your doctor should know about all of your medical conditions before deciding if **Hydromorph•IR** is right for you and what daily dosage is best. Tell your doctor about all of your medical problems, especially the following ones: trouble breathing or lung problems; head injury; liver or kidney problems; gastrointestinal problems; low blood pressure; prostate problems; urethral stricture (unusual narrowing of the urethra); adrenal gland problems, such as Addison's disease; convulsions or seizures; alcoholism; hallucinations or other severe mental problems; past or present substance abuse or drug addiction.

You should also tell your doctor if you are pregnant, breast-feeding, or intend to become pregnant while receiving **Hydromorph•IR** as this drug may not be right for you in these circumstances.

Hydromorph•IR should not be used if:

- your doctor did not prescribe it for you;
- your pain is mild;
- you have severe asthma or severe lung problems;
- you have experienced severe allergic reactions (e.g., severe rash, hives, breathing problems, swelling of the mouth, tongue, face, or other areas or dizziness) while taking any opioid,

hydromorphone, or any of the non-medicinal ingredients, in the past;

- you suffer from alcoholism;
- you have a head injury;
- you suffer from seizures.

How to take Hydromorph•IR:

You should not consume alcohol while taking Hydromorph•IR, as it may increase the chance of experiencing dangerous side effects.

Follow your doctor's directions exactly. **Hydromorph•IR** tablets must be taken regularly, usually every 4 to 6 hours (with 4 to 6 oz. of water) or as directed by your doctor. If your pain worsens, making you uncomfortable, contact your doctor immediately and she/he may decide that it is necessary to adjust your daily dosage of **Hydromorph•IR**.

Your daily dosage of **Hydromorph•IR** will be clearly labelled on the medication bottle. Be sure to follow these directions exactly; this is very important. Do not increase or decrease your daily dosage without consulting your doctor. If your daily dosage is changed by your doctor, be sure to write it down at the time your doctor calls you or sees you and follow the new directions exactly. Regularly discuss your pain control and any side effects with your doctor, to determine if you still need **Hydromorph•IR**. Be sure to use **Hydromorph•IR** only for the condition for which it was prescribed.

Stopping Hydromorph•IR:

Consult your doctor for instructions on how to discontinue taking **Hydromorph•IR**. You should not stop taking **Hydromorph•IR** all at once if you have been taking it for more than a few days, since this may lead to uncomfortable symptoms.

After you stop taking **Hydromorph•IR**, you should take the unused tablets to your pharmacist to be destroyed.

Side effects you may have while taking Hydromorph•IR:

The most common side effects you may experience are constipation, nausea, drowsiness, dizziness, vomiting, itching, headache, dry mouth, confusion, weakness and sweating. Tell your doctor about these problems if they arise. Your doctor may prescribe a laxative and/or stool softener to help relieve constipation while you are taking **Hydromorph•IR**.

If you experience any symptoms related to difficulty in breathing, such as tight chest or wheezing, fainting, or rapid heartbeat, tell your doctor or pharmacist immediately.

Overdose:

The most important signs of overdose are suppressed breathing (abnormally slow or weak breathing), dizziness, confusion or extreme drowsiness. In case of suspected overdose, or if any of these symptoms occur, call your doctor and/or your local emergency number immediately.

Taking Hydromorph•IR with other medications:

You should not take **Hydromorph•IR** if you are currently taking (or recently stopped taking) one of the medicines known as monoamine oxidase inhibitors (e.g. Nardil[®], Parnate[®]).

Tell your doctor about all medicines that you are taking. Your doctor should decide whether you can take **Hydromorph•IR** with other medicines. These include:

- other opioids, anaesthetics, sedatives, hypnotics, barbiturates, phenothiazines, antidepressants, some heart medications (e.g., beta-blockers), blood-thinners (coumarin or other anticoagulants), some antiemetics (medications to stop vomiting or nausea), chloral hydrate and glutethimide (not available in Canada);
- antihistamines or sleep aids (these medicines could depress your breathing or your level of consciousness);
- medicines that you buy yourself without a prescription;
- any herbal remedies that you may be taking.

Driving/Other Activities:

Driving, operating hazardous machinery, or other tasks requiring full alertness should not be attempted for the first few days of taking **Hydromorph•IR**, or after your daily dosage is changed, since you may experience drowsiness or sedation. If drowsiness or sedation occurs, do not undertake such activities until you have talked with your doctor.

Abuse, Addiction and Physical Dependence:

There is a risk of abuse or addiction with all opioids. Some patients, particularly those who may have abused drugs in the past, may have a higher risk of abusing or developing an addiction while taking opioids, such as **Hydromorph•IR**.

Patients who have taken **Hydromorph•IR** for a period of time may develop physical dependence, and should not abruptly stop taking it. However, physical dependence is not the same as addiction.

If you have concerns about abuse, addiction or physical dependence, please tell your doctor.

Reordering Hydromorph•IR:

A new written prescription is required from your doctor each time you need more **Hydromorph•IR**. Therefore, it is important that you contact your doctor at least three working days before your current supply runs out.

It is very important that you do not miss any doses. If you miss one dose, take it as soon as possible, but if it is almost time for your next dose, then skip the missed dose. Do not take two doses at once, unless your doctor tells you to. If you miss several doses in succession, talk to your doctor before restarting.

Do not seek additional prescriptions for **Hydromorph•IR** from any other doctor - unless responsibility for your pain management has been transferred to another doctor.

Should your pain increase or any other complaint develop as a result of taking **Hydromorph•IR**, tell your doctor immediately.

Storage of Hydromorph•IR:

Hydromorph•IR contains an opioid medicine and must be stored in a secure place to prevent theft and misuse. Do not give **Hydromorph•IR** to anyone other than the person for whom it was prescribed since it may seriously harm them. Keep **Hydromorph•IR** out of the reach of children. Accidental overdose by a child is dangerous and may result in death. Keep **Hydromorph•IR** in a cool, dry place, between 15 and 30°C.

This leaflet summarizes important information about **Hydromorph•IR**. If you would like more information, talk with your doctor and/or pharmacist or contact the manufacturer, Purdue Pharma, at 1-800-387-5349.

PHARMACOLOGY

Pharmacodynamics: 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.

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 symptoms may be manifest from these hormonal changes.

In vitro and animal studies indicate various effects of natural opioids, such as morphine, on components of the immune system; the clinical significance of these findings is unknown. Whether hydromorphone, a semi-synthetic opioid, has immunological effects similar to morphine is unknown.

In animal studies the relative potency of single doses of hydromorphone and morphine for a variety of pharmacologic effects were: analgesia 4.1:1; LD₅₀ 6.32:1; convulsant activity 7.92:1; general depression 7.67:1; excitatory effect 3.35:1; emetic activity 2.75:1; respiratory depression 13.63:1.

In acute pain studies in man, relative analgesic potency ranged from 6.7:1 to 11.1:1 and in chronic dosing in patients with cancer pain the ratio of morphine to hydromorphone doses producing

equivalent analgesia was 7.5:1. Clinical experience suggests that the oral potency ratio of hydromorphone to morphine ranges from 4:1 to 7.5:1.

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. 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 3360 mg, 4024 mg and 4320 mg.

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. 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.

In the gastrointestinal tract, hydromorphone usually decreases the secretion of hydrochloric acid in the stomach, diminishes biliary, pancreatic and intestinal secretion, and delays digestion of food in the small intestine, and diminishes or abolishes propulsive peristaltic waves in the colon.

Hydromorphone causes constriction of the pupil due to excitatory action on the autonomic segment of the nucleus of the oculomotor nerve.

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.

Pharmacokinetics: 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 µg/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

dihydromorphone and dihydroisomorphine were present as glucuronide conjugates in amounts representing 0.1% and 1% of the administered dose, respectively.

TOXICOLOGY

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

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.

Carcinogenicity: The carcinogenic effects of hydromorphone are unknown.

Impairment of Fertility: 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.

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