

# **Canadian Approved Label**

## **PRODUCT MONOGRAPH**

**PALLADONE XL<sup>®</sup>**

**Hydromorphone Hydrochloride Controlled Release Capsules  
12, 16, 24 and 32 mg**

**OPIOID ANALGESIC**

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Control No. 074759

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## **PRODUCT MONOGRAPH**

### **NAME OF DRUG**

PALLADONE XL<sup>®</sup>

(Hydromorphone Hydrochloride Controlled Release Capsules  
12, 16, 24 and 32 mg)

### **THERAPEUTIC CLASSIFICATION**

Opioid Analgesic

### **ACTIONS**

Hydromorphone, a semi-synthetic  $\mu$  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  $\mu\text{g}/\text{kg}$ . 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.

**PALLADONE XL<sup>®</sup>** (hydromorphone controlled release capsules) administered 24 hourly provides equivalent onset and extent of analgesia to conventional release hydromorphone tablets administered every 6 hours at the same total daily dose. Administration of a single **PALLADONE XL** dose is characterized by biphasic absorption, with a relatively rapid rise to an initial peak concentration, followed by a second broader peak with therapeutic plasma concentrations maintained over the 24 hour dosing interval. A steady-state pharmacokinetic study demonstrated that the maximum plasma concentration ( $C_{\text{max}}$ ) of hydromorphone is achieved at a mean of 8.4 hours after administration of **PALLADONE XL** with a lower maximum plasma concentration ( $C_{\text{max}}$ ) and a higher minimum plasma concentration ( $C_{\text{min}}$ ) than the immediate release product. The fluctuation index, was 38%

of that observed for the immediate release product administered every 6 hours. Food had no significant effect on the absorption ( $C_{max}$ , AUC) of hydromorphone from **PALLADONE XL** and both release and absorption of hydromorphone from **PALLADONE XL** are pH independent. There is equivalent absorption of hydromorphone when **PALLADONE XL** capsules are swallowed intact or the contents sprinkled on apple sauce. Extent of absorption (AUC) and maximum concentration ( $C_{max}$ ) are proportional to dose.

### **INDICATIONS**

**PALLADONE XL<sup>®</sup>** (hydromorphone controlled release capsules) is indicated for the relief of severe pain requiring the prolonged use of an oral opioid preparation.

### **CONTRAINDICATIONS**

**PALLADONE XL<sup>®</sup>** (hydromorphone controlled release capsules) should not be given to patients with: hypersensitivity to opioid analgesics; acute asthma or other obstructive airway disease and acute respiratory depression; 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**

**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. **PALLADONE XL<sup>®</sup>** (hydromorphone controlled release capsules) 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 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 a 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 tranquillizers, sedative-hypnotics, tricyclic 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 **PALLADONE XL** 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, **PALLADONE XL** should be given to pregnant patients only when the anticipated benefits outweigh the potential risks to the fetus.

### **PRECAUTIONS**

General: 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.

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 on the respiratory centre and the respiratory depressant effects of hydromorphone may reduce respiratory drive to the point of apnea.

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.

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 patients, to patients with severely reduced hepatic or renal function, and in patients with Addison's disease, hypothyroidism, prostatic hypertrophy or urethral stricture.

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.

Drug Interactions: CNS depressants, such as other opioids, anaesthetics, sedatives, hypnotics, barbiturates, phenothiazines, chloral hydrate and glutethimide may enhance the depressant effects of hydromorphone. Monoamine oxidase inhibitors (including procarbazine hydrochloride), 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.

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

### **ADVERSE REACTIONS**

Adverse effects of **PALLADONE XL®** (hydromorphone 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 and central nervous system

depression. To a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest have occurred.

In clinical trials of patients with chronic cancer or noncancer pain, adverse effects considered possibly, probably or definitely related to **PALLADONE XL** seen in  $\geq 5\%$  of patients were headache, asthenia, abdominal pain, constipation, nausea, vomiting, dry mouth, dyspepsia, somnolence, dizziness, confusion, nervousness, pruritus 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 3 - 5 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 3 or 4 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, 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 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 less than 1% of patients in clinical trials and considered possibly related to treatment.

*General and CNS:* dysphoria, euphoria, weakness, malaise, fever, headache, agitation, tremor, uncoordinated muscle movements, alterations of mood or personality (nervousness, apprehension, depression, paranoid reaction, floating feelings, dreams), thought abnormalities, speech disorder, amnesia, muscle rigidity, hypotonia, abnormal gait, hyporeflexia, paresthesia, muscle tremor, blurred vision, nystagmus, diplopia, lacrimation disorder and miosis, transient hallucinations and disorientation, visual disturbances, tinnitus, ear pain, vertigo, insomnia, accidental injury and increased intracranial pressure.

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

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

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

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

*Musculoskeletal:* arthralgia, leg cramps, myesthesia, joint disorder, myalgia.

*Dermatologic:* pruritus, urticaria, other skin rashes and diaphoresis.

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

Withdrawal (Abstinence) Syndrome: Physical dependence with or without psychological dependence tend to occur on 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, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, nausea, trouble with sleeping, unusual increase in sweating and yawning, weakness, tachycardia and unexplained fever. 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 overdose 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, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdose, 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 a 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 dose is 12 mg every 24 hours.

Patients currently receiving other oral hydromorphone formulations may be transferred to **PALLADONE XL®** (hydromorphone controlled release capsules) at the same total daily hydromorphone dosage taken once a day.

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 taken as one **PALLADONE XL** dose every 24 hours.

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.

In patients receiving **PALLADONE XL** chronically the dose should be titrated at intervals of 48 hours to that which provides satisfactory pain relief without unmanageable side effects. **PALLADONE XL** is designed to allow 24 hourly dosing. 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.

**PALLADONE XL** capsules should be swallowed intact. The contents may be sprinkled on soft food but neither the capsules nor the beads should be crushed or chewed.

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 EQUIVALENCES<sup>1</sup>**

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

<sup>1</sup>References:

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.

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- <sup>2</sup> 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.
- <sup>3</sup> 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).
- <sup>4</sup> Based on single entity oral oxycodone in acute pain.

- <sup>5</sup> Clinical experience indicates that during chronic dosing the oral morphine/oral hydromorphone dose ratio is 5 - 7.5:1.
- <sup>6</sup> Not recommended for the management of chronic pain.
- <sup>7</sup> Extremely variable equianalgesic dose. Patients should undergo individualized titration starting at an equivalent to 1/10 of the morphine dose.
- <sup>8</sup> Mixed agonist-antagonists can precipitate withdrawal in patients on pure opioid agonists.

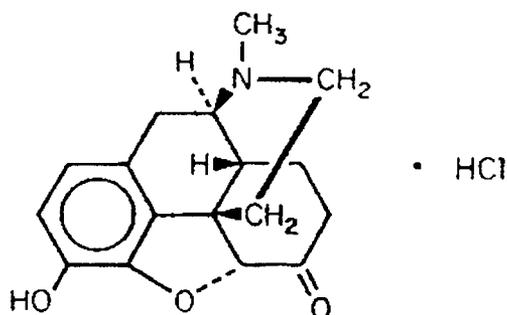
PHARMACEUTICAL INFORMATION

**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:  $C_{17}H_{19}NO_3 \cdot HCl$

Chemical Name: 4,5 $\alpha$ 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:**

*All Strengths:*

ammonio methacrylate copolymer, ethylcellulose, gelatin\*, stearyl alcohol.

*\*Capsule Shells:*

12 mg: colloidal silicon dioxide, iron oxide, sodium lauryl sulfate, titanium dioxide

16 mg: colloidal silicon dioxide, iron oxide, sodium lauryl sulfate, titanium dioxide

24 mg: colloidal silicon dioxide, FD&C blue #2, sodium lauryl sulfate, titanium dioxide

32 mg: colloidal silicon dioxide, sodium lauryl sulfate, titanium dioxide

**Storage**

**Recommendations:** Store at 15 - 30° C

**AVAILABILITY OF DOSAGE FORMS**

**PALLADONE XL<sup>®</sup>** (hydromorphone controlled release capsules) are available in strengths of 12 (cinnamon), 16 (pink), 24 (blue) and 32 (white) mg hydromorphone hydrochloride. Each capsule is imprinted with **PALLADONE XL** on the cap and a number corresponding to the strength, in mg on the body.

**PALLADONE XL** is available in opaque plastic bottles of 50 capsules.

**INFORMATION FOR THE CONSUMER**

**What is hydromorphone?**

Hydromorphone relieves pain and should help you to live more comfortably and independently.

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

**What is PALLADONE XL?**

**PALLADONE XL** is a capsule that is made in such a way as to slowly release hydromorphone over a 24 hour period, usually requiring a dose only once every 24 hours to control your pain.

**PALLADONE XL** capsules are available in four strengths: 12 (cinnamon), 16 (pink), 24 (blue) and 32 (white) mg. It may be necessary for you to take more than one capsule strength (different coloured capsules) at the same time in order to receive the total daily dosage prescribed by your doctor.

**PALLADONE XL** capsules should be swallowed intact. If directed by your physician the contents may be sprinkled on soft food, but neither the capsules nor the beads should be crushed or chewed.

**How to take your medication:**

**PALLADONE XL** capsules must be taken regularly every 24 hours (with 4 to 6 oz. of water) to prevent pain all day and night. 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

**PALLADONE XL.**

Your starting dosage of **PALLADONE XL** will be clearly labelled on the medication bottle.

Be sure to follow these directions on the label exactly; this is very important. If your dosage is changed, be sure to write it down at the time your doctor calls you or sees you. And follow the new directions exactly.

Overdose:

The most important sign of overdose is suppressed breathing (abnormally slow or weak breathing), or extreme drowsiness. If these occur, a doctor should be called immediately.

Constipation:

Hydromorphone causes constipation. This is to be expected so your doctor may order a laxative and stool softener to help relieve your constipation while you are taking **PALLADONE XL**.

Tell your doctor about the problem if it arises.

Concomitant Medications:

Your doctor should be made aware of any other medication you are taking including over-the-counter antihistamines or sleep-aids as they could affect the way you respond to hydromorphone.

Driving:

Driving or other tasks requiring full alertness should not be attempted if you experience drowsiness or sedation while taking **PALLADONE XL**.

Physical Dependence:

Patients who have taken **PALLADONE XL** for a period of time may develop physical dependence, however, this is not the same as addiction. Your doctor can advise you how to manage your physical dependence.

Reordering **PALLADONE XL**:

A new written prescription is required from your doctor each time you need more **PALLADONE XL**. Therefore, it is important to 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.

Should your pain increase, or any other complaint develop as a result of taking **PALLADONE XL**, contact your doctor immediately.

### **TOXICOLOGY**

The LD<sub>50</sub> of an intravenous (IV) and subcutaneous (SC) dose of hydromorphone in the mouse was 104 mg/kg and 84 mg/kg respectively. The LD<sub>50</sub> 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<sub>50</sub> was 51 mg/kg. Studies evaluating the carcinogenic and mutagenic potential of hydromorphone have not been conducted.

Hydromorphone has been shown to be a teratogen in the mouse and hamster. The anomalies produced resembled those produced by other opioid agonists including morphine.

### **PHARMACOLOGY**

#### **Pharmacodynamics:**

Hydromorphone and related  $\mu$ -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<sub>50</sub> 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.

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

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