Doctor Leaflet

Palladone SR Capsules

Narcotic prescription required

Composition
Each capsule contains: Hydromorphone hydrochloride 4, 8, or 24 mg incorporated in a controlled-release system

Action
Hydromorphone is a semisynthetic opioid agonist analgesic that acts primarily at the mu opiate receptor. Opiate receptors in the central nervous system mediate analgesic activity. Opioid agonists occupy the same receptors as endogenous opioid peptides (enkephalins or endorphins), and both may alter the central release of neurotransmitters from afferent nerves sensitive to noxious stimuli. Opioid antagonists block the opiate receptor, inhibit the pharmacological activity of the agonist and will precipitate withdrawal in dependent patients.

Hydromorphone has similar pharmacological and pharmacokinetic properties to morphine to which it is chemically related. However, it is approximately 7.5 times more potent on a mg for mg basis when administered orally. Hydromorphone is recognized by the World Health Organization as an alternative opioid to morphine for cancer pain. This is important since one of the cornerstones of cancer pain management is opioid rotation. Opioid rotation consists of switching a patient from one opioid to another in order to achieve adequate analgesia with few side effects. In particular, hydromorphone may have a better side effect profile than morphine in some individuals, producing less severe constipation and vomiting.

Palladone SR capsules incorporate hydromorphone in a controlled-release system which allows the patient to take the preparation on a 12-hourly basis. The hydromorphone is gradually released and absorbed with controlled bioavailability. Analgesics for severe cancer pain should be administered around-the-clock (and not on an as-needed basis). Thus, Palladone SR capsules have a significant advantage compared with other, conventional forms of hydromorphone in the relief of severe cancer pain, for those patients who are able to take an oral preparation.

Indications
Palladone SR capsules are indicated for the relief of severe pain in cancer.

Contraindications
Hydromorphone is contraindicated in patients with known hypersensitivity to its effect. It is contraindicated in respiratory depression, coma, diarrhea caused by poisoning or associated with pseudomembranous colitis caused by cephalosporins, lincomycins or

penicillins. Hydromorphone is not recommended for use in obstetric analgesia and in pediatrics.

Warnings

Drug Dependence

Hydromorphone, like all opioid analgesics, may cause physical dependence whereby the body adapts itself to the drug. This involves physiological changes which explain two phenomena frequently seen with long-term opioid treatment: tolerance and the withdrawal syndrome.

Tolerance is defined as the need to administer a higher dose of the opioid to maintain the same level of analgesia. For most patients, the first indication of tolerance is a decrease in the duration of analgesia for a given dose and the appearance of breakthrough pain. Tolerance may be confused with an increase in the pain intensity of the disease itself (which is the most common reason an increase in dosage is indicated). Irrespective of the underlying cause, it is recommended that the dose be increased and the patient re-titrated until the pain is again controlled.

Withdrawal symptoms, sometimes called the opioid abstinence syndrome, are those manifested by a patient upon cessation of treatment or rapid reduction of dosage.

If a reduction in dosage is required, the opioid abstinence syndrome can usually be avoided by gradually decreasing the dosage in the following fashion. Half the prior daily dosage should be given for the first 2 days. This should be reduced by 25% every 2 days thereafter, until the total dosage is 30 mg/day in oral morphine equivalents. The drug may be discontinued after 2 days at this dosage level.

Physical dependence does not imply psychological dependence. Psychological dependence is a pattern of compulsive drug use characterized by a craving for an opioid and the need to use the opioid for effects other than pain relief. This type of dependence is extremely rare in patients taking opioids for the relief of severe pain. This must not be confused with the behavior of patients whose pain is inadequately treated, who will also manifest drug-seeking behavior. For these patients titration to pain-controlling dosage is required.

Head Injury

Because of the tendency of hydromorphone to produce respiratory depression and its capacity to elevate cerebrospinal fluid pressure, it should be used with extreme caution, if at all, in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure since both of these adverse reactions may be markedly exaggerated. Opioid agonists like hydromorphone may interfere with evaluation of CNS functions, especially relative to consciousness levels, pupillary changes, and respiratory depression, thereby masking the clinical course of patients with head injuries. In such cases, hydromorphone must be used with extreme caution and only when it is absolutely essential.

Paralytic Ileus
Palladone SR capsules should not be used where there is the possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, Palladone SR capsules should be discontinued immediately.

Cordotomy
Patients about to undergo cordotomy or other pain-relieving surgical procedures should be transferred to immediate release hydromorphone prior to surgery. If further treatment with Palladone SR capsules is indicated then the dosage should be adjusted to the new post-operative requirement.

Asthma and other Respiratory Conditions
Hydromorphone should be used with extreme caution, if at all, in patients with acute asthma, chronic obstructive pulmonary disease or cor-pulmonale, a decreased respiratory reserve (as in emphysema, kyphoscoliosis or severe obesity), hypoxia or hypercapnia. Even therapeutic doses of opioids may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.

Cardiovascular Effects
Opioids may produce orthostatic hypotension in ambulatory patients. Opioids may also cause severe hypotension in individuals whose ability to maintain their blood pressure has already been compromised by depleted blood volume or concurrent administration of other drugs such as phenothiazines or certain anesthetics.

Use in Pregnancy and Labor
Hydromorphone crosses the placental barrier. Because of possible adverse effects on fetal development, hydromorphone is not recommended for use during pregnancy. Use during labor is not recommended (see Contraindications). It may lead to respiratory depression, especially in the premature neonate.

Use in Breastfeeding
It is not known whether hydromorphone is excreted in human milk. However, because many drugs are excreted in human milk and because of the potential for adverse effects in infants, nursing should be discontinued if hydromorphone is absolutely indicated.

Use in Pediatrics
Hydromorphone is not recommended for use in children under 12 years.

Use in the Elderly
Hydromorphone should be used with caution in the elderly. The elderly may require a lower dosage than adults to achieve adequate analgesia. Some elderly patients may be sensitive to the respiratory depressant effect of hydromorphone and should be monitored closely during therapy initiation and any subsequent dosage increase.

Adverse Reactions

The most serious adverse reactions to hydromorphone are respiratory depression and, to a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest.
The most frequent adverse reactions include lightheadedness, dizziness, miosis, drowsiness, sedation, constipation, nausea, vomiting and sweating. Other adverse reactions include mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, euphoria, confusion, dysphoria, psychic dependence, mood changes, weakness, dry mouth, biliary tract spasm, ureteral spasm, spasm of vesical sphincters and urinary retention, hesitancy oliguria, decreased libido, pruritus and urticaria. In some individuals, hydromorphone may cause less constipation or emesis than morphine preparations. When nausea and vomiting or constipation are troublesome, Palladone SR capsules can be readily combined with anti-emetics or laxatives.

Precautions
Use with caution in patients with Addison's disease, cardiac arrhythmia, cardiovascular disease, cerebral arteriosclerosis, history of drug abuse or dependence, ulcerative colitis, gall bladder and hepato-renal impairment, prostatic hypertrophy, urethral stricture, respiratory disease, hypothyroidism, convulsive disorders, and acute alcoholism. The administration of opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Palladone SR capsules are not recommended in the first 24 hours post-operatively. After this time, they should be used with caution particularly following abdominal surgery. Opioid agonist-induced increase in intraluminal pressure may endanger surgical anastomosis.

Persons who perform potentially hazardous tasks requiring mental alertness and/or physical coordination should be warned about possible CNS adverse effects (e.g. driving may be affected). As with all opioids, a reduction in dosage may be advisable in the elderly and in debilitated patients (see Warnings).

Drug Interactions
Because of potential adverse interactions, hydromorphone should be used with extreme caution in individuals who are concurrently receiving other narcotic analgesics, general anesthetics, phenothiazines, tranquilizers, antihistamines, sedative hypnotics, tricyclic antidepressants and other CNS depressants including alcohol, anticholinergics and neuromuscular blocking agents. Respiratory depression, hypotension, profound sedation, coma, severe constipation, or urinary retention may result.

Caution should be exercised if hydromorphone is to be used concurrently with monoamine oxidase inhibitors (e.g., phenelzine), and within two weeks of their discontinuation, since severe reactions have been reported with other opioid analgesics, especially pethidine. In such patients, it is recommended that a small test dose of hydromorphone (25% of the usual dose) or several small incremental test doses over a period of several hours should be administered first, to permit observation of any interaction.

Administration of a mixed agonist/antagonist opioid analgesic (e.g., pentazocine, buprenorphine) to a patient receiving therapy with a pure agonist opioid such as hydromorphone may reduce the analgesic effect, or precipitate withdrawal.

Similarly, administration of an opioid antagonist like naltrexone can precipitate withdrawal in patients receiving hydromorphone.

Laboratory and Diagnostic Interference
Plasma amylase and lipase concentrations may be increased in the presence of hydromorphone. Because of the induction by hydromorphone of spasms of the sphincter of Oddi and increased biliary tract pressure, determinations of these enzymes may remain unreliable 24 hours post-medication.

Dosage and Administration
A. General Recommendations
For the correct and effective use of hydromorphone it is critical to adjust the dosing regimen for each patient individually. The following dosage recommendations are, therefore, only suggested approaches to what is actually a series of clinical decisions in the management of the pain of an individual patient. The dosage of hydromorphone is individualized according to the patient's pain, metabolism, previous history of analgesic therapy, and response to hydromorphone.

Palladone SR 4, 8, and 24 mg capsules should be taken on a regular 12-hourly schedule, at the minimum dose required to achieve acceptable analgesia. Palladone SR capsules should be swallowed whole or may be opened and their contents sprinkled onto cold, soft food. Palladone SR capsules are available in three dosage strengths that can be combined to obtain the precise dose for each individual. Four mg of oral hydromorphone has an analgesic efficacy equivalent to 30 mg morphine sulphate given orally.

B. Initial Dosage
Opioid-Naive Patients
In opioid-naive patients, for ease of titration, the initial daily dosage of hydromorphone can be established using hydromorphone immediate-release capsules, using a 4-hourly schedule. The total daily dose should then be divided in two and administered as Palladone SR capsules 12-hourly.

Alternatively, opioid-naive patients can be started directly on Palladone SR capsule therapy. These patients should initially receive a conservative dose of 4 mg 12-hourly, in order to avoid overdosage. The majority of patients will then require an upward titration. (Appropriate use of the 24 mg capsules must be decided by careful evaluation of each clinical situation.)

Conversion From Other Opioid Analgesics
If a patient has been receiving opioid-containing medications prior to Palladone SR capsules, standard conversion ratio estimates (see below) should be used to convert the previous 24-hour opioid use to an oral hydromorphone equivalent. Calculate the total daily

dosage of each opioid (mg). Multiply the daily dose of each prior opioid by the appropriate multiplication factor from the table for oral and/or parenteral forms, adding the results to obtain the equivalent total daily hydromorphone oral dose. Then, divide by 2 to compute the hydromorphone q12h dose. Round to a dose that is appropriate for the Palladone SR capsule strengths/combinations available.

For example, in a patient taking 120mg oral morphine daily (60 mg MCR twice daily) who is being switched to hydromorphone:

120 X 0.13 = 15.6 mg daily oral hydromorphone

15.6 ÷ 2 = 7.8 mg q12 hours.

The patient should receive an 8 mg Palladone SR capsule twice daily.

Patients receiving immediate release hydromorphone on a regular basis will find it more convenient to continue treatment with Palladone SR capsules, which are administered at 12-hourly intervals. Note: When converting between immediate release and slow release hydromorphone, the total daily dosage of hydromorphone remains the same.

Multiplication Factors for Converting from Other Opioids to Oral Hydromorphone
(mg/day prior opioid x factor = mg/day oral hydromorphone)

Prior Opioid	Oral	Parenteral
morphine	0.13	0.4
methadone	0.2	0.4
pethidine	0.013	0.05
pentazocine	0.02	0.06
codeine	0.02	-
oxycodone	0.13	-
buprenorphine	4.67 (sublingual)	-
fentanyl	*	40

*Transdermal fentanyl: Eighteen hours following the removal of the transdermal fentanyl patch, treatment with Palladone SR capsules can be initiated. Although there has been no systematic assessment of such conversion, a conservative dose of 4 mg q12 hours should be initially substituted for each 25 ug fentanyl transdermal patch. The patient should be closely monitored for early titration as there is limited clinical experience with this conversion.

The conversion table is only meant to serve as a guide. It should be noted that the above table is based on a hydromorphone:morphine ratio of 7.5:1. However, recent studies have indicated that during chronic morphine dosing, the ratio may approximate 4:1. Therefore, the above table presents a conservative starting dose, and consideration should be given to early upward titration in a significant portion of patients. In the rare patient receiving very large opioid doses, consideration should be given to the potential for incomplete cross tolerance. When converting these patients to hydromorphone therapy, the starting dose estimated by the conversion ratio may need to be decreased. In all circumstances, the patient's response following conversion from other opioids must be carefully monitored

and the dosage of Palladone SR capsules adjusted accordingly. (Note: The table should not be used for converting patients from hydromorphone to other opioids.)

C. Titration to Pain Control

Adjustments of the initial dosage should be made to obtain an appropriate balance between pain relief and opioid adverse experiences. The optimal dose is that which maintains adequate analgesia for 12 hours with no or controllable side effects. If the initial dose provides inadequate analgesia, patients should be assessed following incremental increases in dosage. As a guideline the total daily hydromorphone dose can be increased by 25% to 50% of the current dose. As there is no upper limit to the amount of hydromorphone that may be given in intractable oncologic pain, the quantity administered should be that which produces adequate analgesia. Adequate analgesia is generally considered to be mild or no pain with the regular use of no more than two doses of supplemental analgesia per 24 hours. Rescue medication should be available (see Supplemental Analgesia).

If significant adverse events occur before the therapeutic goal of mild or no pain is achieved, the events should be treated aggressively. Once adverse events are under control, upward titration can continue to an acceptable level of pain control. If the adverse experiences cannot be controlled or tolerated, opioid rotation should be considered.

D. Supplemental Analgesia

Most cancer patients given around-the-clock therapy with controlled-release oral opioids will need to have immediate-release medication available for "rescue" from breakthrough pain or to prevent incident pain (the latter occurs predictably during certain patient activities). The most logical rescue medication is immediate release hydromorphone. The supplemental analgesic should be prescribed at 1/4 to 1/3 of the 12-hour Palladone SR dose. The rescue medication is dosed every 4 hours as needed for breakthrough pain and administered one hour before anticipated incident pain. If more than two doses of rescue medication are needed within 24 hours, the dose of Palladone SR should be titrated upward.

E. Maintenance of Therapy

During the course of treatment the patient may experience a recurrence of pain due to an increase in the level of pain because of disease progression or due to the development of tolerance. Regardless of the reason, the hydromorphone dose should be increased and the patient re-titrated as outlined above in order to re-establish pain control.

Patients about to undergo any pain-relieving surgical procedure should be transferred to immediate release hydromorphone prior to surgery. Following surgery if further treatment with Palladone SR capsules is indicated, the dosage should be adjusted to the new post-operative requirement.

F. Cessation of Therapy

Dose Tapering

When the patient no longer requires chronic therapy with Palladone SR capsules, the dosage should be slowly tapered, as described above (see Drug Dependence, Warnings). If

signs of withdrawal appear, tapering should be stopped. The dose should be slightly increased until the signs and symptoms disappear. Tapering should then begin again but with longer periods of time between each dose reduction.

Conversion from Palladone SR to Parenteral Opioids
A 1:5 ratio of oral to parenteral hydromorphone equivalence is suggested. To avoid overdose, initiate treatment with ½ of the estimated equianalgesic dose of parenteral opioid and titrate the dose based upon the patient's response.

Overdosage
Manifestations
Hydromorphone overdosage is initially characterized by sedation, confusion and delirium. If such symptoms become apparent, Palladone SR capsules should be withdrawn and the patient monitored. Later manifestations of serious hydromorphone overdosage include pin-point pupils, CNS depression ranging from extreme somnolence progressing to stupor or coma, respiratory depression which may progress to Cheyne-Stokes respiration and/or cyanosis, cold, clammy skin and/or hypothermia, flaccid skeletal muscles, and sometimes bradycardia and hypotension. In severe cases, circulatory failure, cardiac arrest and death may occur.

Treatment
The treatment of overdosage consists of induced emesis or gastric lavage (in the conscious patient) and establishment of adequate respiration through the provision of a patent airway and institution of assisted or controlled ventilation. If depressed respiration is associated with muscular rigidity, an I.V. neuromuscular blocking agent may be required.

If necessary, administer an opioid antagonist, preferably naloxone (0.4 mg in 10 ml saline using small bolus injections that are titrated against the respiratory rate). Because the duration of action of hydromorphone exceeds that of the administered naloxone, the patient should be kept under observation in order to ascertain whether additional doses of the antagonist are required. An antagonist should not be administered in the absence of significant respiratory or cardiovascular depression.

Note: In individuals who are physically dependent upon hydromorphone, the administration of the usual dose of naloxone will precipitate an acute withdrawal syndrome. The severity of the syndrome is dependent upon the degree of physical dependence and the dose of naloxone given. If at all possible, avoid the use of an antagonist in such individuals. If, however, absolutely necessary, administer the naloxone with extreme caution, using only 10-20% of the usual initial dose given.

Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as required.
A 0.02% aqueous solution of potassium permanganate may be used for lavage.
Observe the patient for a rise in temperature or pulmonary complications that may require antibiotic therapy.

Pharmaceutical Precautions
Store at or below 25^{o} C.

Presentation
Palladone SR 4 mg 14 pale blue-capped capsules
Palladone SR 8 mg 14 pink-capped capsules
Palladone SR 24 mg 14 blue-capped capsules

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