

ATTACHMENT 2

Hydromorphone Hydrochloride Tablets

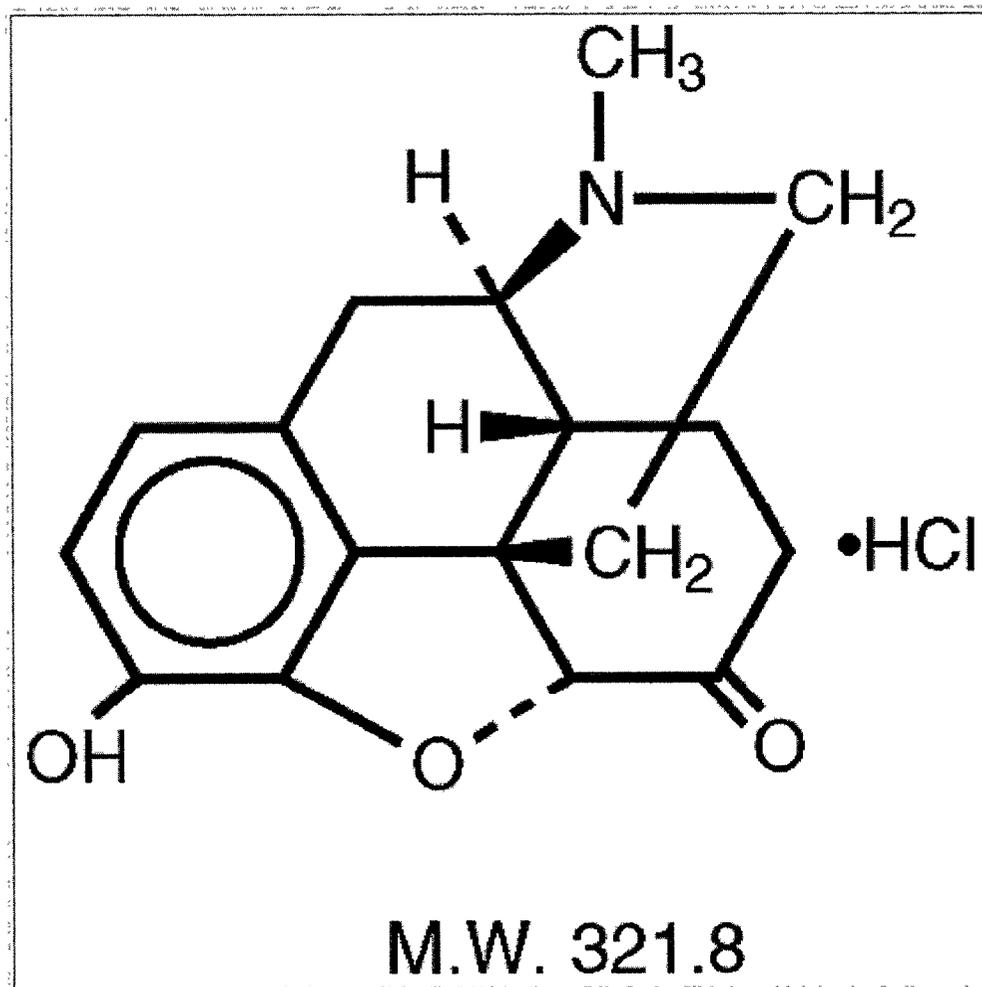
2 mg, 4 mg

Rx only

DESCRIPTION

Hydromorphone Hydrochloride Tablets, a hydrogenated ketone of morphine, are an opioid analgesic.

The chemical name of Hydromorphone Hydrochloride Tablets is 4,5(α)-epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride. The structural formula is:



Each Hydromorphone Hydrochloride 2 mg and 4 mg Tablet contains 2 mg or 4 mg hydromorphone hydrochloride. The inactive ingredients will be furnished when the ANDA is submitted, since this is proprietary information. The inactive ingredients are GRAS ingredients at the appropriate levels.



CLINICAL PHARMACOLOGY

Many of the effects described below are common to this class of mu-opioid agonist analgesics. In some instances, data may not exist to distinguish the effects of Hydromorphone Hydrochloride Tablets from those observed with other opioid analgesics. However, in the absence of data to the contrary, it is assumed that Hydromorphone Hydrochloride Tablets would possess all the actions of mu-agonist opioids.

Central Nervous System: Opioid analgesics exert their primary effects on the central nervous system and organs containing smooth muscle. The principal actions of therapeutic value are analgesia and sedation. A significant feature of the analgesia is that it can occur without loss of consciousness. Opioid analgesics also suppress the cough reflex and may cause respiratory depression, mood changes, mental clouding, euphoria, dysphoria, nausea, vomiting and electroencephalographic changes.

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.

Opioids depress the cough reflex by direct effect on the cough center in the medulla.

Opioids depress the respiratory reflex by a direct effect on brain stem respiratory centers. The mechanism of respiratory depression also involves a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension.

Opioids cause miosis. Pinpoint pupils are a common sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings) and marked mydriasis occurs with asphyxia.

Gastrointestinal Tract and Other Smooth Muscle: Gastric, biliary and pancreatic secretions are decreased by opioids. Opioids cause a reduction in motility associated with an increase in tone in the gastric antrum and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, and tone may be increased to the point of spasm. The end result is constipation. Opioids can cause a marked increase in biliary tract pressure as a result of spasm of the sphincter of Oddi.

Cardiovascular System: Certain opioids produce peripheral vasodilation which may result in orthostatic hypotension. Release of histamine may occur with opioids and may contribute to drug-induced hypotension. Other manifestations of histamine release may include pruritus, flushing, and red eyes.

The dosage of opioid analgesics like Hydromorphone Hydrochloride Tablets should be individualized for any given patient, since adverse events can occur at doses that may not provide complete freedom from pain (see **INDIVIDUALIZATION OF DOSAGE**).



PHARMACOKINETICS:

The analgesic activity of Hydromorphone Hydrochloride Tablets is due to the parent drug, hydromorphone. Hydromorphone is rapidly absorbed from the gastrointestinal tract after oral administration and undergoes extensive first-pass metabolism. In vivo bioavailability following single-dose administration of an 8 mg hydromorphone hydrochloride tablet is approximately 24% (coefficient of variation 21%). Bioequivalence between a Hydromorphone Hydrochloride 8 mg Tablet and an equivalent dose of Hydromorphone Hydrochloride Oral Liquid has been demonstrated. Dose proportionality between a Hydromorphone Hydrochloride 8 mg Tablet and other strength Hydromorphone Hydrochloride Tablets has not been established.

Absorption: After oral administration of a Hydromorphone Hydrochloride 8 mg Tablet or liquid, peak plasma hydromorphone concentrations are generally attained within 1/2 to 1-hour.

Mean (%cv)				
Dosage Form	C _{max} (ng)	T _{max} (hrs)	AUC (ng*hr/mL)	T _{1/2} (hrs)
8 mg Tablet	5.5 (33%)	0.74 (34%)	23.7 (28%)	2.6 (18%)
8 mg Oral Liquid	5.7 (31%)	0.73 (71%)	24.6 (29%)	2.8 (20%)

Food effects: The effect on the rate and extent of absorption of Hydromorphone Hydrochloride Tablets when given with food has not been studied.

Distribution: At therapeutic plasma levels, hydromorphone is approximately 8-19% bound to plasma proteins. After an intravenous bolus dose, the steady state of volume distribution [mean (%cv)] is 302.9 (32%) liters.

Metabolism: Hydromorphone is extensively metabolized via glucuronidation in the liver, with greater than 95% of the dose metabolized to hydromorphone-3-glucuronide along with minor amounts of 6-hydroxy reduction metabolites.

Elimination: Only a small amount of the hydromorphone dose is excreted unchanged in the urine. Most of the dose is excreted as hydromorphone-3-glucuronide along with minor amounts of 6-hydroxy reduction metabolites. The systemic clearance is approximately 1.96 (20%) liters/minute. The terminal elimination half-life of hydromorphone after an intravenous dose is about 2.3 hours.

Special Populations: Pediatrics: Pharmacokinetics of hydromorphone have not been evaluated in children.



Hepatic and renal impairment: The effects of hepatic and renal disease on the clearance of hydromorphone are unknown but caution should be taken to guard against possible accumulation if hepatic and/or renal functions are seriously impaired.

Pregnancy and nursing mothers: Hydromorphone crosses the placenta. Hydromorphone is also found in low levels in breast milk, and may cause respiratory compromise in newborns when administered during labor or delivery.

CLINICAL TRIALS

Analgesic effects of single doses of Hydromorphone Hydrochloride Oral Liquid administered to patients with post-surgical pain have been studied in double-blind controlled trials. In one study with 61 patients, both 5 mg and 10 mg of Hydromorphone Hydrochloride Oral Liquid provided significantly more analgesia than placebo. In another trial with 80 patients, 5 mg and 10 mg of Hydromorphone Hydrochloride Oral Liquid were compared to 30 mg and 60 mg of morphine sulfate oral liquid. The pain relief provided by 5 mg and 10 mg Hydromorphone Hydrochloride Oral Liquid was comparable to 30 mg and 60 mg oral morphine sulfate, respectively.

INDIVIDUALIZATION OF DOSAGE:

Safe and effective administration of opioid analgesics to patients with acute or chronic pain depends upon a comprehensive assessment of the patient. The nature of the pain (severity, frequency, etiology, and pathophysiology) as well as the concurrent medical status of the patient will affect selection of the starting dosage.

In non-opioid-tolerant patients, therapy with hydromorphone is typically initiated at an oral dose of 2-4 mg every four hours, but elderly patients may require lower doses (see **PRECAUTIONS - Geriatric Use**).

In patients receiving opioids, both the dose and duration of analgesia will vary substantially depending on the patient's opioid tolerance. The dose should be selected and adjusted so that at least 3-4 hours of pain relief may be achieved. In patients taking opioid analgesics, the starting dose of Hydromorphone Hydrochloride Tablets should be based on prior opioid usage. This should be done by converting the total daily usage of the previous opioid to an equivalent total daily dosage of oral Hydromorphone Hydrochloride Tablets using an equianalgesic table (see below). For opioids not in the table, first estimate the equivalent total daily usage of oral morphine, then use the table to find the equivalent total daily dosage of Hydromorphone Hydrochloride Tablets.

Once the total daily dosage of Hydromorphone Hydrochloride Tablets has been estimated, it should be divided into the desired number of doses. Since there is individual variation in response to different opioid drugs, only 1/2 to 2/3 of the estimated dose of Hydromorphone Hydrochloride Tablets calculated from equivalence tables should be given for the first few doses, then increased as needed according to the patient's response.



In chronic pain, doses should be administered around-the-clock. A supplemental dose of 5-15% of the total daily usage may be administered every two hours on an "as-needed" basis.

Periodic reassessment after the initial dosing is always required. If pain management is not satisfactory and in the absence of significant opioid-induced adverse events, the hydromorphone dose may be increased gradually. If excessive opioid side effects are observed early in the dosing interval, the hydromorphone dose should be reduced. If this results in breakthrough pain at the end of the dosing interval, the dosing interval may need to be shortened. Dose titration should be guided more by the need for analgesia than the absolute dose of opioid employed.

OPIOID ANALGESIC EQUIVALENTS WITH APPROXIMATELY EQUIANALGESIC POTENCY *		
Nonproprietary (Trade) Name	IM or SC Dose	ORAL Dose
Morphine sulfate	10mg	40-60mg
Hydromorphone HCL	1.3-2mg	6.5-7.5mg
Oxymorphone HCl (Numorphan)	1-1.1mg	6.6mg
Levorphanol tartrate (Levo-Dromoran)	2-2.3mg	4 mg
Meperidine, pethidine HCl (Demerol)	75-100mg	300-400 mg
Methadone HCl (Dolophine)	10mg	10-20mg
*Dosages, and ranges of dosages represented, are a compilation of estimated equipotent dosages from published references comparing opioid analgesics in cancer and severe pain.		

INDICATIONS AND USAGE

Hydromorphone Hydrochloride Tablets are indicated for the management of pain in patients where an opioid analgesic is appropriate.

CONTRAINDICATIONS

Hydromorphone Hydrochloride Tablets are contraindicated in: patients with known hypersensitivity to hydromorphone, patients with respiratory depression in the absence of resuscitative equipment, and in patients with status asthmaticus. Hydromorphone Hydrochloride Tablets are also contraindicated for use in obstetrical analgesia.



WARNINGS

Impaired Respiration: Respiratory depression is the chief hazard of Hydromorphone Hydrochloride Tablets. Respiratory depression occurs most frequently in overdose situations, in 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.

Hydromorphone Hydrochloride Tablets should be used with extreme caution in patients with chronic obstructive pulmonary disease or cor pulmonale, patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or in patients with preexisting respiratory depression. In such patients even usual therapeutic doses of opioid analgesics may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.

Drug Dependence: Hydromorphone Hydrochloride Tablets are a Schedule II narcotic. Hydromorphone Hydrochloride Tablets can produce drug dependence of the morphine type and therefore have the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of Hydromorphone Hydrochloride Tablets, which should be prescribed and administered with the degree of caution appropriate to the use of morphine. Abrupt discontinuance in the administration of Hydromorphone Hydrochloride Tablets in patients who are physically dependent on opioids is likely to result in a withdrawal syndrome (see **DRUG ABUSE AND DEPENDENCE**).

Neonatal Withdrawal Syndrome: Infants born to mothers physically dependent on Hydromorphone Hydrochloride Tablets will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms. (see **DRUG ABUSE AND DEPENDENCE**).

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of Hydromorphone Hydrochloride Tablets with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or preexisting increase in intracranial pressure. Opioid analgesics including Hydromorphone Hydrochloride Tablets may produce effects which can obscure the clinical course and neurologic signs of further increase in intracranial pressure in patients with head injuries.

Hypotensive Effect: Opioid analgesics, including Hydromorphone Hydrochloride Tablets, may cause severe hypotension in an individual whose ability to maintain blood pressure has already been compromised by a depleted blood volume, or a concurrent administration of drugs such as phenothiazines or general anesthetics (see **PRECAUTIONS - Drug Interactions**). Therefore, Hydromorphone Hydrochloride Tablets should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.



Sulfites: Contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

PRECAUTIONS

Special Risk Patients: In general, opioids should be given with caution and the initial dose should be reduced in the elderly or debilitated and those with severe impairment of hepatic, pulmonary or renal functions; myxedema or hypothyroidism; adrenocortical insufficiency (e.g., Addison's Disease); CNS depression or coma; toxic psychoses; prostatic hypertrophy or urethral stricture; gall bladder disease; acute alcoholism; delirium tremens; kyphoscoliosis or following gastrointestinal surgery.

The administration of opioid analgesics including Hydromorphone Hydrochloride Tablets may obscure the diagnoses or clinical course in patients with acute abdominal conditions and may aggravate preexisting convulsions in patients with convulsive disorders.

Reports of mild to severe seizures and myoclonus have been reported in severely compromised patients, administered high doses of parenteral hydromorphone, for cancer and severe pain. Opioid administration at very high doses is associated with seizures and myoclonus in a variety of diseases where pain control is the primary focus.

Use in Ambulatory Patients: Hydromorphone Hydrochloride Tablets may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g. driving, operating machinery). Patients should be cautioned accordingly. Hydromorphone Hydrochloride Tablets may produce orthostatic hypotension in ambulatory patients. The addition of other CNS depressants to Hydromorphone Hydrochloride Tablet therapy may produce additive depressant effects, and Hydromorphone Hydrochloride Tablets should not be taken with alcohol.

Use in Biliary Surgery: Opioid analgesics, including Hydromorphone Hydrochloride Tablets, 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.

Use in Drug and Alcohol Dependent Patients: Hydromorphone Hydrochloride Tablets should be used with caution in patients with alcoholism and other drug dependencies due to the increased frequency of opioid tolerance, dependence, and the risk of addiction observed in these patient populations. Abuse of Hydromorphone Hydrochloride Tablets in combination with other CNS depressant drugs can result in serious risk to the patient.

Drug Interactions: The concomitant use of other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers and alcohol may produce additive depressant effects. Respiratory depression, hypotension and profound sedation or coma may occur. When such combined therapy is contemplated, the



dose of one or both agents should be reduced. Opioid analgesics, including Hydromorphone Hydrochloride Tablets, may enhance the action of neuromuscular blocking agents and produce an excessive degree of respiratory depression.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Animal carcinogenicity studies have not been performed with Hydromorphone Hydrochloride Tablets.

Hydromorphone Hydrochloride Tablets were not mutagenic in the in vitro Ames reverse mutation assay, in the in vitro chromosome aberration assay in human lymphocytes, or in the in vivo mouse bone marrow micronucleus test.

Fertility in male or female rats was not affected after daily oral administration at doses up to 7 mg/kg/day (41 mg/m²). Hydromorphone Hydrochloride Tablets were dosed from 4 weeks prior to mating in males and 2 weeks prior to mating in females.

Pregnancy-Pregnancy Category C: Neither embryo-fetal toxicity nor teratogenic effects were observed following administration of Hydromorphone Hydrochloride Tablets at oral doses up to 7 mg/kg/day (41 mg/m²) in rats from day 6 to day 17 of gestation and up to 25 mg/kg/day (315 mg/m²) in rabbits from day 6 to day 20 of gestation.

Literature reports of hydromorphone hydrochloride administration to pregnant Syrian hamsters show that Hydromorphone Hydrochloride Tablets are teratogenic at a dose of 20 mg/kg which is 600 times the human dose. A maximal teratogenic effect (50% of fetuses affected) in the Syrian hamster was observed at a dose of 25 mg/kg (738 mg/m²).

There are no well-controlled studies in women. Hydromorphone is known to cross placental membranes. Hydromorphone Hydrochloride Tablets should be used in pregnant women only if the potential benefit justifies the potential risk to the fetus (see **Labor and Delivery** and **DRUG ABUSE AND DEPENDENCE**).

Nonteratogenic effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal. Approaches to the treatment of this syndrome have included supportive care and, when indicated, drugs such as paregoric or phenobarbital.

Labor and Delivery: Hydromorphone Hydrochloride Tablets are contraindicated in Labor and Delivery (see **CONTRAINDICATIONS**).

Nursing Mothers: Low levels of opioid analgesics have been detected in human milk. As a general rule, nursing should not be undertaken while a patient is receiving Hydromorphone Hydrochloride Tablets since it, and other drugs in this class, may be excreted in the milk.



Pediatric Use: Safety and effectiveness in children have not been established.

Geriatric Use: Clinical studies of Hydromorphone Hydrochloride Tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. 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, and of concomitant disease or other drug therapy (see **INDIVIDUALIZATION OF DOSAGES** and **PRECAUTIONS**).

ADVERSE REACTIONS

The adverse effects of Hydromorphone Hydrochloride Tablets are similar to those of other opioid agonist analgesics, and represent established pharmacological effects of the drug class. The major hazards include respiratory depression and apnea. To a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest have occurred.

The most frequently observed adverse effects are light-headedness, dizziness, sedation, nausea, vomiting, sweating, flushing, dysphoria, euphoria, dry mouth, and pruritus. These effects seem to be more prominent in ambulatory patients and in those not experiencing severe pain. Syncopal reactions and related symptoms in ambulatory patients may be alleviated if the patient lies down.

Less Frequently Observed with Opioid Analgesics:

General and CNS: Weakness, headache, agitation, tremor, uncoordinated muscle movements, alterations of mood (nervousness, apprehension, depression, floating feelings, dreams), muscle rigidity, paresthesia, muscle tremor, blurred vision, nystagmus, diplopia and miosis, transient hallucinations and disorientation, visual disturbances, insomnia and increased intracranial pressure may occur.

Cardiovascular: Chills, tachycardia, bradycardia, palpitation, faintness, syncope, hypotension and hypertension have been reported.

Respiratory: Bronchospasm and laryngospasm have been known to occur.

Gastrointestinal: Constipation, biliary tract spasm, ileus, anorexia, diarrhea, cramps and taste alteration have been reported.

Genitourinary: Urinary retention or hesitancy, and antidiuretic effects have been reported.

Dermatologic: Urticaria, other skin rashes, and diaphoresis.



DRUG ABUSE AND DEPENDENCE

Hydromorphone Hydrochloride Tablets are a Schedule II narcotic, similar to morphine. Opioid analgesics may cause psychological and physical dependence (see **WARNINGS**). Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug. Withdrawal symptoms also may be precipitated in the patient with physical dependence by the administration of a drug with opioid antagonist activity, e.g., naloxone (see **OVERDOSAGE**).

Physical dependence usually does not occur to a clinically significant degree until after several weeks of continued opioid usage, but it may become clinically detectable after as little as a week. Tolerance, in which increasingly larger doses are required in order to produce the same degree of analgesia, is initially manifested by a shortened duration of analgesic effect, and subsequently, by decreases in the intensity of analgesia. In chronic pain patients, and in opioid-tolerant cancer patients, the dose of Hydromorphone Hydrochloride Tablets should be guided by the degree of tolerance manifested.

In chronic pain patients in whom opioid analgesics including Hydromorphone Hydrochloride Tablets are abruptly discontinued, a severe abstinence syndrome should be anticipated. This may be similar to the abstinence syndrome noted in patients who withdraw from heroin. The latter abstinence syndrome may be characterized by restlessness, lacrimation, rhinorrhea, yawning, perspiration, gooseflesh, restless sleep or "y'en" and mydriasis during the first 24 hours. These symptoms may increase in severity and over the next 72 hours may be accompanied by increasing irritability, anxiety, weakness, twitching and spasms of muscles, kicking movements, severe backache, abdominal and leg pains, abdominal and muscle cramps, hot and cold flashes, insomnia, nausea, anorexia, vomiting, intestinal spasm, diarrhea, coryza and repetitive sneezing, increase in body temperature, blood pressure, respiratory rate and heart rate.

Because of excessive loss of fluids through sweating, or vomiting and diarrhea, patients experiencing the syndrome usually exhibit marked weight loss, dehydration, ketosis, and disturbances in acid-base balance. Cardiovascular collapse can occur. Without treatment, most observable symptoms disappear in 5-14 days; however, there appears to be a phase of secondary or chronic abstinence which may last for 2-6 months characterized by insomnia, irritability, muscular aches, and autonomic instability.

In the treatment of physical dependence on Hydromorphone Hydrochloride Tablets, the patient may be detoxified by gradual reduction of the dosage, although this is unlikely to be necessary in the terminal cancer patient. If abstinence symptoms become severe, the patient may be detoxified with methadone. Temporary administration of tranquilizers and sedatives may aid in reducing patient anxiety. Gastrointestinal disturbances or dehydration should be treated accordingly.



OVERDOSAGE

Serious overdosage with Hydromorphone Hydrochloride Tablets is characterized by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and sometimes bradycardia and hypotension. In serious overdosage, particularly following intravenous injection, apnea, circulatory collapse, cardiac arrest and death may occur.

In the treatment of overdosage, primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. A potentially serious oral ingestion, if recent, should be managed with gut decontamination. In unconscious patients with a secure airway, instill activated charcoal (30-100 g in adults, 1-2 g/kg in infants) via a nasogastric tube. A saline cathartic or sorbital may be added to the first dose of activated charcoal.

Opioid-Tolerant Patient: Since tolerance to the respiratory and CNS depressant effects of opioids develops concomitantly with tolerance to their analgesic effects, serious respiratory depression due to an acute overdose is unlikely to be seen in opioid-tolerant patients receiving the usual therapeutic dosage of Hydromorphone Hydrochloride Tablets for chronic pain.

NOTE: In such an individual who is physically dependent on opioids, administration of the usual dose of an 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 should be reserved for cases where such treatment is clearly needed. If necessary to treat serious respiratory depression in the physically-dependent patient, the opioid antagonist should be administered with extreme care and by titration, using fractional (one fifth to one tenth) doses of the antagonist.

Non-Tolerant Patient: The opioid antagonist, naloxone, is a specific antidote against respiratory depression which may result from overdosage, or unusual sensitivity to Hydromorphone Hydrochloride Tablets. A dose of naloxone (usually given as a test dose of 0.4 mg, followed by up to 2.0 mg if needed) 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 circulatory depression. Naloxone should be administered cautiously to persons who are known, or suspected to be physically dependent on Hydromorphone Hydrochloride Tablets (see **Opioid-Tolerant Patient**). In such cases, an abrupt or complete reversal of narcotic effects may precipitate an acute abstinence syndrome. Since the duration of action of Hydromorphone Hydrochloride Tablets 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. Apply other supportive measures when indicated.



Supportive measures (including oxygen, vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massages or defibrillation.

DOSAGE AND ADMINISTRATION

Hydromorphone Hydrochloride Tablets: The usual starting dose for Hydromorphone Hydrochloride Tablets is 2 mg to 4 mg, orally, every 4 to 6 hours.

A gradual increase in dose may be required if analgesia is inadequate, as tolerance develops, or if pain severity increases. The first sign of tolerance is usually a reduced duration of effect.

SAFETY AND HANDLING INSTRUCTIONS:

Hydromorphone Hydrochloride Tablets pose little risk of direct exposure to health care personnel and should be handled and disposed of prudently in accordance with hospital or institutional policy. Patients and their families should be instructed to flush any Hydromorphone Hydrochloride Tablets that are no longer needed.

Access to abusable drugs such as Hydromorphone Hydrochloride Tablets presents an occupational hazard for addiction in the health care industry. Routine procedures for handling controlled substances developed to protect the public may not be adequate to protect health care workers. Implementation of more effective accounting procedures and measures to restrict access to drugs of this class (appropriate to the practice setting) may minimize the risk of self-administration by health care providers.

HOW SUPPLIED

Hydromorphone Hydrochloride Tablets 2 mg: (Description of Hydromorphone Hydrochloride Tablets 2 mg to be determined).

Package Size to be determined

Hydromorphone Hydrochloride Tablets 4 mg: (Description of Hydromorphone Hydrochloride Tablets 4 mg to be determined).

Package Size to be determined

STORAGE: Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature]. Protect from light.

A schedule CII Narcotic. DEA Order Form Is Required.

