003466/September 2006

OPANA®
(Oxymorphone Hydrochloride) INJECTION
1mg/mL

CII

Opioid
Analgesic

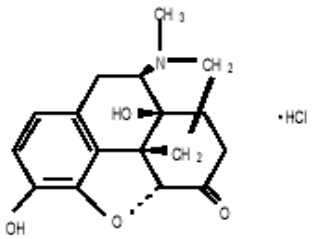
Rx only

DESCRIPTION

OPANA (oxymorphone hydrochloride) Injection, is a semi-synthetic opioid analgesic. OPANA Injection is available in 1 mg/mL, 1 mL ampules of oxymorphone hydrochloride. In addition, each 1 mg/mL ampule contains 8.0 mg/mL sodium chloride. pH is adjusted with hydrochloric acid.

Chemically, oxymorphone hydrochloride is 4, 5a-epoxy-3, 14-dihydroxy-17-methylmorphinan-6-one hydrochloride, a white or slightly off-white, odorless powder, which is sparingly soluble in alcohol and ether, but freely soluble in water. The molecular weight of oxymorphone hydrochloride is 337.80. The pK_a1 and pK_a2 of oxymorphone at 37°C are 8.17 and 9.54, respectively. The octanol/aqueous partition coefficient at 37°C and pH 7.4 is 0.98.

The structural formula for oxymorphone hydrochloride is as follows:



CLINICAL PHARMACOLOGY

Oxymorphone is an opioid agonist whose principal therapeutic action is analgesia. Administered parenterally, 1 mg of OPANA Injection is approximately equivalent in analgesic activity to 10 mg of morphine sulfate. Other members of the class known as opioid agonists include substances such as morphine, oxycodone, hydromorphone, fentanyl, codeine, hydrocodone and tramadol. In addition to analgesia, other pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of

relaxation, respiratory depression, constipation, miosis, and cough suppression. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic effect with increasing doses. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression.

Central Nervous System

The precise mechanism of the analgesic action is unknown. However, specific CNS (central nervous system) opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug. In addition, opioid receptors have been identified within the PNS (peripheral nervous system). The role that these receptors play in these drugs' analgesic effects is unknown.

Opioids produce respiratory depression, likely by a direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and electrical stimulation.

Opioids depress the cough reflex by direct effect on the cough center in the medulla oblongata. Antitussive effects may occur with doses lower than those usually required for analgesia. Opioids cause miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations (see **OVERDOSAGE: Signs and Symptoms**).

Gastrointestinal Tract and Other Smooth Muscle

Opioids cause a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasms of sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System

Opioids produce peripheral vasodilation which may result in orthostatic hypotension. Release of histamine can occur and may contribute to opioid-induced hypotension. Manifestations of histamine release may include orthostatic hypotension, pruritus, flushing, red eyes, and sweating. Animal studies have shown that oxymorphone has a lower propensity to cause histamine release than other opioids.

Endocrine System

Opioid agonists have been shown to have a variety of effects on the secretion of hormones. Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon in humans and other species, rats and dogs.

Thyroid stimulating hormone (TSH) has been shown to be both inhibited and stimulated by opioids.

Immune System

Opioids have been shown to have a variety of effects on components of the immune system in *in-vitro* and animal models. The clinical significance of these findings is unknown.

Pharmacodynamics

Concentration-Efficacy Relationships

The minimum effective plasma concentration of oxymorphone for analgesia varies widely among patients, especially among patients who have been previously treated with potent agonist opioids. As a result, patients need to be individually titrated to achieve a balance between therapeutic and adverse effects. The minimum effective analgesic concentration of oxymorphone for any individual patient may increase over time due to an increase in pain, progression of disease, development of a new pain syndrome and/or development of analgesic tolerance.

Concentration-Adverse Experience Relationships

OPANA Injection is associated with typical opioid-related adverse experiences. There is a general relationship between increasing opioid plasma concentration and increasing frequency of adverse experiences such as nausea, vomiting, CNS effects, and respiratory depression.

As with all opioids, the dose must be individualized (see **DOSAGE AND ADMINISTRATION**). The effective analgesic dose for some patients will be too high to be tolerated by other patients.

Pharmacokinetics

The onset of action of parenterally administered OPANA Injection is rapid; initial effects are usually perceived within 5 to 10 minutes. Its duration of action is approximately 3 to 6 hours.

Distribution

After an IV dose, the steady state volume of distribution was 3.08 ± 1.14 L/kg in healthy male and female subjects.

Metabolism

Oxymorphone is highly metabolized, principally in the liver, and undergoes reduction or conjugation with glucuronic acid to form both active and inactive products. The two major metabolites of oxymorphone are oxymorphone-3-glucuronide and 6-OH-oxymorphone. The mean plasma AUC for oxymorphone-3-glucuronide is approximately 90-fold higher than the parent compound. The pharmacologic activity of the glucuronide metabolite has not been evaluated. 6-OH-oxymorphone has been shown in animal studies to have analgesic bioactivity. The mean plasma 6-OH-oxymorphone AUC is approximately 70% of the oxymorphone AUC following single oral doses but is essentially equivalent to the parent compound at steady-state.

Excretion

Because oxymorphone is extensively metabolized, <1% of the administered dose is excreted unchanged in the urine. On average, 33% to 38% of the administered dose is excreted in the urine as oxymorphone-3-glucuronide and 0.25% to 0.62% is excreted as 6-OH-oxymorphone in subjects with normal hepatic and renal function. In animals given radiolabeled oxymorphone, approximately 90% of the administered radioactivity was recovered within 5 days of dosing. The majority of oxymorphone-derived radioactivity was found in the urine and feces.

Special Populations

Elderly

The effects of OPANA Injection on the elderly have not been studied. However, the plasma levels of oral oxymorphone administered as an extended-release tablet were about 40% higher in elderly than in younger subjects.

Gender

The effects of OPANA Injection on gender have not been studied. However, in a study with an extended-release formulation of oral oxymorphone, there was a consistent tendency for female subjects to have slightly higher AUC_{ss} and C_{max} values than male subjects. However, gender differences were not observed when AUC_{ss} and C_{max} were adjusted by body weight.

Hepatic Impairment

The effects of hepatic impairment on the pharmacokinetics of OPANA Injection have not been studied. The liver plays an important role in the pre-systemic clearance of orally administered oxymorphone. Accordingly the bioavailability of orally administered oxymorphone may be markedly increased in patients with moderate-severe liver disease. In a study with an extended-release formulation of oral oxymorphone (OPANA ER), the disposition of oxymorphone was compared in 6 patients with mild, 5 patients with moderate, and one patient with severe hepatic impairment, and 12 subjects with normal hepatic function. The bioavailability of oral oxymorphone was increased by 1.6-fold in patients with mild hepatic impairment and by 3.7-fold in patients with moderate hepatic impairment. In one patient with severe hepatic impairment, the bioavailability was

increased by 12.2-fold. The half-life of oral oxymorphone was not significantly affected by hepatic impairment.

Pre-systemic clearance of OPANA Injection is not expected, however, oxymorphone is extensively metabolized by the liver.

Renal Impairment

The effects of renal impairment on the pharmacokinetics of OPANA Injection have not been studied. However, in a study with an extended-release formulation of oral oxymorphone, an increase of 26%, 57%, and 65% in oxymorphone bioavailability was observed in mild (creatinine clearance 51-80 mL/min; n=8), moderate (creatinine clearance 30-50 mL/min; n=8), and severe (creatinine clearance <30 mL/min; n=8) patients, respectively, compared to healthy controls.

Drug-Drug Interactions

In vitro studies revealed little to no biotransformation of oxymorphone to 6-OH-oxymorphone by any of the major cytochrome P450 (CYP P450) isoforms at therapeutically relevant oxymorphone plasma concentrations.

No inhibition of any of the major CYP P450 isoforms was observed when oxymorphone was incubated with human liver microsomes at concentrations of =50 µM. An inhibition of CYP 3A4 activity occurred at oxymorphone concentrations =150 µM. Therefore, it is not expected that oxymorphone, or its metabolites will act as inhibitors of any of the major CYP P450 enzymes *in vivo.*

Increases in the activity of the CYP 2C9 and CYP 3A4 isoforms occurred when oxymorphone was incubated with human hepatocytes. However, clinical drug interaction studies with OPANA ER showed no induction of CYP450 3A4 or 2C9 enzyme activity, indicating that no dose adjustment for CYP 3A4- or 2C9-mediated drug-drug interactions is required. Studies with OPANA Injection have not been conducted.

INDICATIONS AND USAGE

OPANA Injection is indicated for the relief of moderate to severe pain. It is also indicated for preoperative medication, for support of anesthesia, for obstetrical analgesia, and for relief of anxiety in patients with dyspnea associated with pulmonary edema secondary to acute left ventricular dysfunction.

CONTRAINDICATIONS

OPANA Injection should not be administered to patients with a known hypersensitivity to oxymorphone hydrochloride or to any of the other ingredients in OPANA Injection, or with known hypersensitivity to morphine analogs such as codeine.

OPANA Injection is contraindicated in patients with respiratory depression except in monitored settings and in the presence of resuscitative equipment and in patients with

acute or severe bronchial asthma, upper airway obstruction, or hypercarbia. OPANA Injection is contraindicated in any patient who has or is suspected of having paralytic ileus.

OPANA Injection should not be used in the treatment of pulmonary edema secondary to a chemical respiratory irritant. Opioid analgesics cause pooling of blood in the extremities by decreasing peripheral vascular resistance. This effect results in decreases in venous return, cardiac work, and pulmonary venous pressure, and blood is shifted from the central to peripheral circulation which would not be beneficial in the treatment of pulmonary edema secondary to a chemical respiratory irritant.

OPANA Injection is contraindicated in patients with moderate and severe hepatic impairment (see **CLINICAL PHARMACOLOGY**, **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

WARNINGS

OPANA Injection is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.

Respiratory Depression

Respiratory depression is the chief hazard of OPANA Injection. Respiratory depression is a particular potential problem in elderly or debilitated patients as well as in those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate therapeutic doses may dangerously decrease pulmonary ventilation.

OPANA Injection should be administered with extreme caution to patients with conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve such as: asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, CNS depression or coma. In these patients, even usual therapeutic doses of oxymorphone may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea. Alternative non-opioid analgesics should be considered, and oxymorphone should be employed only under careful medical supervision at the lowest effective dose in such patients.

Misuse, Abuse and Diversion of Opioids

OPANA Injection contains oxymorphone, an opioid agonist with an abuse liability similar to morphine and a Schedule II controlled substance. Opioid agonists have the potential for being abused and are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

Oxymorphone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing oxymorphone in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

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

Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Interactions with Alcohol and Drugs of Abuse

Oxymorphone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression because respiratory depression, hypotension, and profound sedation or coma may result.

Drug Abuse and Addiction

Controlled Substance

OPANA Injection contains oxymorphone, an opioid with an abuse liability similar to morphine and other opioids and is a Schedule II controlled substance. Oxymorphone, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion (see **WARNINGS: Misuse, Abuse and Diversion of Opioids**).

Drug addiction is characterized by a preoccupation with the procurement, hoarding, and abuse of drugs for non-medicinal purposes. Drug addiction is treatable, utilizing a multi-disciplinary approach, but relapse is common.

"Drug seeking" behavior is very common to addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated claims of loss of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. OPANA Injection, like other opioids, may be diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Abuse of OPANA Injection poses a risk of overdose and death. This risk is increased with concurrent abuse of OPANA Injection with alcohol and other substances. In addition, parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms (see **PRECAUTIONS: Pregnancy** and **PRECAUTIONS: Labor and Delivery**).

Interactions with Other Central Nervous System Depressants

Patients receiving other opioid analgesics, general anesthetics, phenothiazines, other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with oxymorphone may exhibit an additive CNS depression (see **PRECAUTIONS: Drug-Drug Interactions**). Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with the usual dose of OPANA Injection.

Head Injury and Increased Intracranial Pressure

In the presence of head injury, intracranial lesions or a preexisting increase in intracranial pressure, the possible respiratory depressant effects of opioid analgesics and their potential to elevate cerebrospinal fluid pressure (resulting from vasodilation following CO_2 retention) may be markedly exaggerated. Furthermore, opioid analgesics can produce effects on pupillary response and consciousness, which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

Hypotensive Effect

OPANA Injection, like all opioid analgesics, may cause severe hypotension in an individual whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. OPANA Injection, like all opioid analgesics, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

Hepatic Impairment

The effects of OPANA Injection on hepatic impairment have not been studied. However, a study of OPANA ER in patients with hepatic disease indicated greater plasma concentrations than those with normal hepatic function (see **CLINICAL PHARMACOLOGY**). OPANA Injection should be used with caution in patients with mild impairment. These patients should be started with the lowest dose and titrated slowly while carefully monitoring for side effects. OPANA Injection is contraindicated for patients with moderate and severe hepatic impairment (see **CONTRAINDICATIONS**, **WARNINGS**, and **DOSAGE AND ADMINISTRATION**).

PRECAUTIONS

General

Opioid analgesics should be used with caution, especially when combined with other drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known potential risks of respiratory depression, altered mental state and postural hypotension. OPANA Injection should be used with caution in elderly and debilitated patients and in patients who are known to be sensitive to central nervous system depressants, such as those with cardiovascular, pulmonary, renal, or hepatic disease.

OPANA Injection should be used with caution in the following conditions: acute alcoholism; adrenocortical insufficiency (e.g., Addison's disease); CNS depression or coma; delirium tremens; kyphoscoliosis associated with respiratory depression; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of pulmonary or renal function; moderate impairment of hepatic function; and toxic psychosis.

The administration of all opioids may obscure the diagnosis or clinical course in patients with acute abdominal conditions. All opioids may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.

Interactions with Mixed Agonist/Antagonist Opioid Analgesics

Agonist/antagonist 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 oxymorphone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxymorphone and/or may precipitate withdrawal symptoms in these patients.

Ambulatory Surgery and Post-Operative Use

OPANA Injection, like other opioids, decreases bowel motility. Ileus is a common post-operative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in post-operative patients receiving opioids. Standard supportive therapy should be implemented.

Use in Pancreatic/Biliary Tract Disease

OPANA Injection, like other opioids, may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis.

Physical Dependence and Tolerance

Physical dependence is the occurrence of withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an opioid antagonist or mixed opioid agonist/antagonist agent. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external

factors). The development of physical dependence and/or tolerance is not unusual during chronic opioid therapy.

If OPANA Injection is abruptly discontinued in a physically-dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

In general, OPANA Injection should not be abruptly discontinued (see **DOSAGE AND ADMINISTRATION: Cessation of Therapy**).

Use in Drug and Alcohol Addiction

OPANA Injection is not approved for use in detoxification or maintenance treatment of opioid addiction. However, the history of an addictive disorder does not necessarily preclude the use of this medication for the treatment of chronic pain. These patients will require intensive monitoring for signs of misuse, abuse, or addiction.

Drug-Drug Interactions

Oxymorphone is highly metabolized principally in the liver and undergoes reduction or conjugation with glucuronic acid to form both active and inactive products (see **CLINICAL PHARMACOLOGY** and **PHARMACOKINETICS: Metabolism**).

Use with CNS Depressants

The concomitant use of other CNS depressants including sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and alcohol may produce additive CNS depressant effects. OPANA Injection, like all opioid analgesics, should be started at 1/3 to 1/2 of the usual dose in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, and alcohol because respiratory depression, hypotension, and profound sedation or coma may result, and titrated slowly as necessary for adequate pain relief.

Additive effects resulting in respiratory depression, hypotension, profound sedation or coma may result if these drugs are taken in combination with the usual doses of OPANA Injection. No specific interaction between oxymorphone and monoamine oxidase inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

When combined therapy with any of the above medications is contemplated, the dose of one or both agents should be reduced (see **WARNINGS** and **DOSAGE AND ADMINISTRATION**).

Use with Mixed Agonist/Antagonist Opioid Analgesics

Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol, or buprenorphine) should not be administered to patients who have received or are receiving a course of therapy with a pure opioid agonist analgesic, such as OPANA Injection. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of OPANA Injection and/or may precipitate withdrawal symptoms.

Other

Anticholinergics or other medications with anticholinergic activity when used concurrently with opioid analgesics may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

It has been reported that the incidence of bradycardia was increased when oxymorphone was combined with propofol for induction of anesthesia.

In addition, CNS side effects have been reported (confusion, disorientation, respiratory depression, apnea, seizures) following coadministration of cimetidine with opioid analgesics; a causal relationship has not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Long-term studies have been completed to evaluate the carcinogenic potential of oxymorphone in both Sprague-Dawley rats and CD-1 mice. Oxymorphone HCl was administered to Sprague-Dawley rats (2.5, 5, and 10 mg/kg/day in males and 5, 10, and 25 mg/kg/day in females) for 2 years by oral gavage. The systemic drug exposure (AUC ng•h/mL) at the 10 mg/kg/day dose in male rats was 0.34-fold and at the 25 mg/kg/day dose in female rats was 1.5-fold the human exposure at a dose of 260 mg/day. No evidence of carcinogenic potential was observed in rats. Oxymorphone HCl was administered to CD-1 mice (10, 25, 75 and 150 mg/kg/day) for 2 years by oral gavage. The systemic drug exposure (AUC ng•h/mL) at the 150 mg/kg/day dose in mice was 14.5-fold (in males) and 17.3-fold (in females) times the human exposure at a dose of 260 mg/day. No evidence of carcinogenic potential was observed in mice.

Mutagenesis: Oxymorphone hydrochloride was not mutagenic when tested in the *in vitro* bacterial reverse mutation assay (Ames test) at concentrations of =5270 µg/plate, or in an *in vitro* mammalian cell chromosome aberration assay performed with human peripheral blood lymphocytes at concentrations =5000 µg/ml with or without metabolic activation. Oxymorphone hydrochloride tested positive in both the rat and mouse *in vivo* micronucleus assays. An increase in micronucleated polychromatic erythrocytes occurred in mice given doses of =250 mg/kg and in rats given doses of 20 and 40 mg/kg. A subsequent study demonstrated that oxymorphone hydrochloride was not aneugenic in mice following administration of up to 500 mg/kg. Additional studies indicate that the increased incidence of micronucleated polychromatic erythrocytes in rats may be secondary to increased body temperature following oxymorphone administration. Doses associated with increased micronucleated polychromatic erythrocytes also produce a

marked, rapid increase in body temperature. Pretreatment of animals with sodium salicylate minimized the increase in body temperature and prevented the increase in micronucleated polychromatic erythrocytes after administration of 40 mg/kg oxymorphone.

Impairment of fertility: Oxymorphone hydrochloride did not affect reproductive function or sperm parameters in male rats at any dose tested (=50 mg/kg/day via oral gavage). In female rats, an increase in the length of the estrus cycle and decrease in the mean number of viable embryos, implantation sites and corpora lutea were observed at doses of oxymorphone =10 mg/kg/day via oral gavage. The dose of oxymorphone associated with reproductive findings in female rats is 0.8 times a total human daily dose of 120 mg OPANA based on a body surface area. The dose of oxymorphone that produced no adverse effects on reproductive findings in female rats (i.e., NOAEL) is 0.4-times a total human daily dose of 120 mg OPANA based on body surface area.

Pregnancy

The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on fetal development. The use of OPANA Injection in pregnancy, in nursing mothers, or in women of child-bearing potential requires that the possible benefits of the drug be weighted against the possible hazards to the mother and the child (see **PRECAUTIONS**).

Teratogenic Effects

Pregnancy Category C

Oxymorphone hydrochloride administration did not cause malformations at any doses evaluated during developmental toxicity studies in rats (=25 mg/kg/day via oral gavage) or rabbits (=50 mg/kg/day via oral gavage). These doses are ~2 times and 8 times a total human daily dose of 120 mg of OPANA (an immediate-release oral tablet formulation), based on body surface area. There were no developmental effects in rats treated with 5 mg/kg/day or rabbits treated with 25 mg/kg/day. Fetal weights were reduced in rats and rabbits given doses of =10 mg/kg/day and 50 mg/kg/day, respectively. These doses are ~0.8 and 4 times respectively a total human daily dose of 120 mg of OPANA, based on body surface area. There were no effects of oxymorphone hydrochloride on intrauterine survival at doses =25 mg/kg/day in rats, or =50 mg/kg/day in rabbits (see Non-teratogenic Effects, below). In a study that was conducted prior to the establishment of Good Laboratory Practices (GLP) and not according to current recommended methodology, a single subcutaneous injection of oxymorphone hydrochloride on gestation day 8 was reported to produce malformations in offspring of hamsters that received 10 times a total human daily dose of 120 mg of OPANA, based on body surface area. This dose also produced 83% maternal lethality.

There are no adequate and well-controlled studies in pregnant women. OPANA Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic Effects

Oxymorphone hydrochloride administration to female rats during gestation in a pre- and postnatal developmental toxicity study reduced mean litter size (18%) at a dose of 25 mg/kg/day via oral gavage, attributed to an increase in the incidence of stillborn pups. An increase in neonatal death occurred at doses =5 mg/kg/day. Post-natal survival of the pups was reduced throughout weaning following treatment of the dams with 25 mg/kg/day. Low pup birth weight and decreased postnatal weight gain occurred in pups born to oxymorphone-treated female rats given a dose of 25 mg/kg/day. This dose is ~2 times a total human daily dose of 120 mg of OPANA, based on body surface area.

Prolonged use of opioid analgesics during pregnancy may cause fetal-neonatal physical dependence. Neonatal withdrawal may occur. Symptoms usually appear during the first days of life and may include convulsions, irritability, excessive crying, tremors, hyperactive reflexes, fever, vomiting, diarrhea, sneezing, yawning, and increased respiratory rate.

Labor and Delivery

OPANA Injection should be used with caution during labor. Sinusoidal fetal heart rate patterns may occur with the use of opioid analgesics.

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. Occasionally, opioid analgesics may prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor. Neonates whose mothers received opioid analgesics during labor should be observed closely for signs of respiratory depression. A specific opioid antagonist, such as naloxone or nalmefene, should be available for reversal of opioid-induced respiratory depression in the neonate.
Opioid analgesics, including OPANA Injection, may cause respiratory depression in the newborn. The effect of OPANA Injection, if any, on the later growth, development, and functional maturation of the child is unknown.

Nursing Mothers

It is not known whether oxymorphone is excreted in human milk. Because many drugs, including some opioids, are excreted in human milk, caution should be exercised when OPANA Injection is administered to a nursing woman. Ordinarily, nursing should not be undertaken while a patient is receiving oxymorphone because of the possibility of sedation and/or respiratory depression in the infant.

Pediatric Use

Safety and effectiveness of OPANA Injection in pediatric patients below the age of 18 years have not been established.

Geriatric Use

OPANA Injection should be used with caution in elderly patients. Though not studied with the injection formulation, the plasma levels of OPANA ER tablets are about 40%

higher in elderly (=65 years of age) than in younger subjects (see **CLINICAL PHARMACOLOGY**).

However, of the total number of subjects in clinical studies of OPANA (immediate release formulation) tablet, 31 percent were 65 and over, while 7 percent were 75 and over. No overall differences in effectiveness were observed between these subjects and younger subjects. There were several adverse events that were more frequently observed in subjects 65 and over compared to younger subjects. These adverse events included dizziness, somnolence, confusion, and nausea. In general, dose selection for elderly patients 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.

Hepatic Impairment

The effects of OPANA Injection on hepatic impairment have not been studied. However, a study of OPANA ER in patients with hepatic disease indicated greater plasma concentrations than those with normal hepatic function (see **CLINICAL PHARMACOLOGY**). OPANA Injection should be used with caution in patients with mild impairment. These patients should be started with the lowest dose and titrated slowly while carefully monitoring for side effects. OPANA Injection is contraindicated for patients with moderate and severe hepatic impairment (see **CONTRAINDICATIONS**, **WARNINGS**, and **DOSAGE AND ADMINISTRATION**).

Renal Impairment

The effects of OPANA Injection on renal impairment have not been studied. However, in a study of OPANA ER, patients with moderate to severe renal impairment were shown to have an increase in bioavailability ranging from 57-65% (see **CLINICAL PHARMACOLOGY**). These patients should be started cautiously with lower doses of OPANA Injection and titrated slowly while carefully monitored for side effects (see **DOSAGE AND ADMINISTRATION**).

Gender Differences

The effects of OPANA Injection on gender have not been studied. However, in clinical trials with OPANA, the overall incidence rates for one or more adverse events were similar among females and male subjects receiving OPANA and placebo.

ADVERSE REACTIONS

Cardiac disorders: tachycardia, bradycardia, palpitations
Eye disorders: miosis, diplopia, vision blurred
Gastrointestinal disorders: nausea, vomiting, dry mouth, constipation, abdominal pain, ileus paralytic
General disorders and administration site conditions: fatigue, asthenia, injection site reaction
Hepatobilliary disorders: biliary colic

Immune system disorders: hypersensitivity (dermatitis allergic, urticaria NOS, pruritus, swelling face)
Metabolism and nutrition disorders: anorexia,
Nervous system disorders: somnolence, sedation, dizziness, headache, mental impairment NOS, central nervous system depression NOS
Psychiatric disorders: dysphoria, euphoric mood, nervousness, restlessness, confusional state, insomnia, agitation, hallucination, depression, drug dependence
Renal and urinary disorders: ureteral spasm, urinary hesitation, urinary retention, oliguria
Respiratory, thoracic, and mediastinal disorders: respiratory depression, atelectasis, bronchospasm, laryngospasm, laryngeal oedema, apnoea
Skin and subcutaneous tissue disorders: pruritus, sweating increased
Social circumstances: drug abuser
Vascular disorders: hypotension, orthostatic hypotension, flushing

OVERDOSAGE

Signs and Symptoms

Acute overdosage with OPANA Injection is 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, constricted pupils and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

OPANA Injection may cause miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations (see **CLINICAL PHARMACOLOGY: Central Nervous System**).

Treatment

In the treatment of OPANA Injection overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The opioid antagonist naloxone hydrochloride is a specific antidote against respiratory depression, which may result from overdosage or unusual sensitivity to opioids including OPANA Injection. Therefore, an appropriate dose of naloxone hydrochloride should be administered (usual initial adult dose 0.4 mg-2 mg) preferably by the intravenous route and simultaneously with efforts at respiratory resuscitation. Nalmefene is an alternative pure opioid antagonist, which may be administered as a specific antidote to respiratory depression resulting from opioid overdose. Since the duration of action of OPANA Injection may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered according to the antagonist labeling as needed to maintain adequate respiration.

In patients receiving OPANA Injection, opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression. They should be administered cautiously to persons who are known, or suspected to be, physically dependent on any opioid agonist including OPANA Injection. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. In an individual physically dependent on opioids, administration of the usual dose of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. If respiratory depression is associated with muscular rigidity, administration of a neuromuscular blocking agent may be necessary to facilitate assisted or controlled ventilation. Muscular rigidity may also respond to opioid antagonist therapy.

DOSAGE AND ADMINISTRATION

OPANA Injection is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine and other opioids.

OPANA Injection, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion.

Selection of patients for treatment with OPANA Injection should be governed by the same principles that apply to the use of similar opioid analgesics (see **INDICATIONS AND USAGE**). Physicians should individualize treatment in every case (see **DOSAGE AND ADMINISTRATION**), using non-opioid analgesics, prn opioids and/or combination products, and chronic opioid therapy in a progressive plan of pain management such as outlined by the World Health Organization, the Agency for Healthcare Research and Quality, and the American Pain Society.

As with any opioid drug product, it is necessary to adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. In the selection of the initial dose of OPANA Injection, attention should be given to the following:

1. The total daily dose, potency and specific characteristics of the opioid the patient has been taking previously;
2. The relative potency estimate used to calculate the equivalent oxymorphone dose needed;
3. The patient’s degree of opioid tolerance;
4. The age, general condition, and medical status of the patient;
5. Concurrent non-opioid analgesic and other medications;
6. The type and severity of the patient's pain;
7. The balance between pain control and adverse experiences.
8. Risk factors for abuse, addiction or diversion, including a prior history of abuse, addiction or diversion.

The following dosing recommendations, therefore, can only be considered as suggested approaches to what is actually a series of clinical decisions over time in the management of the pain of each individual patient.

Initiation of Therapy

Subcutaneous or intramuscular administration: initially 1 mg to 1.5 mg, repeated every 4 to 6 hours as needed. Intravenous: 0.5 mg initially. In non debilitated patients the dose can be cautiously increased until satisfactory pain relief is obtained. For analgesia during labor 0.5 mg to 1 mg intramuscularly is recommended.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Conversion from Oral OPANA to OPANA Injection

Given the absolute oral bioavailability of approximately 10%, patients receiving oral OPANA may be converted to OPANA Injection by administering one-tenth the patient's total daily oral oxymorphone dose as OPANA Injectable in four or six equally divided doses (e.g., total daily Oral dose/ [10 x 4]). For example, approximately 1 mg of OPANA Injectable IM every 6 hours (4 mg total IM dose) may be required to provide pain relief equivalent to a total daily dose of 40 mg oral OPANA. The dose can be titrated to optimal pain relief or combined with acetaminophen/NSAIDs for optimal pain relief. Due to patient variability with regard to opioid analgesic response, upon conversion patients should be closely monitored to ensure adequate analgesia and to minimize side effects.

Individualization of Dose

Once therapy is initiated, pain relief and other opioid effects should be frequently assessed. Patients should be titrated to adequate pain relief (generally mild or no pain). Patients who experience breakthrough pain may require dosage adjustment or non-opioid therapy such as acetaminophen or NSAIDs.

If signs of excessive opioid-related adverse experiences are observed, the next dose may be reduced. Dose adjustments should be made to obtain an appropriate balance between pain relief and opioid-related adverse experiences. 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 should continue to an acceptable level of pain control.

During periods of changing analgesic requirements, including initial titration, frequent contact is recommended between physician, other members of the health-care team, the patient and the caregiver/family. Patients and family members should be advised of the potential common side effects to decrease fear of the use of opioids and promote their optimal use.

Patients with Hepatic Impairment

The effects of OPANA Injection on hepatic impairment have not been studied. However, OPANA Injection is contraindicated in patients with moderate and severe hepatic dysfunction. OPANA Injection should be used with caution in patients with mild hepatic impairment. These patients with mild hepatic impairment should be started with the lowest dose and titrated slowly while carefully monitoring side effects (see **CLINICAL PHARMACOLOGY**, **CONTRAINDICATIONS**, and **PRECAUTIONS**).

Patients with Renal Impairment

The effects of OPANA Injection on renal impairment have not been studied. However, there are 57% and 65% increases in oxymorphone bioavailability in patients with moderate to severe renal impairment, respectively, treated with OPANA ER (see **CLINICAL PHARMACOLOGY** and **PRECAUTIONS**). Accordingly, OPANA Injection should be administered cautiously and in reduced dosages to patients with creatinine clearance rate less than 50 mL/min.

Use with CNS depressants

OPANA Injection, like all opioid analgesics, should be started at 1/3 to 1/2 of the usual dose in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, and alcohol because respiratory depression, hypotension and profound sedation or coma may result. No specific interaction between oxymorphone and monoamine oxidase inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate (see **PRECAUTIONS: General** and **PRECAUTIONS: Drug-Drug Interactions**)

Geriatrics

Caution should be exercised in the selection of the starting dose of OPANA Injection for an elderly patient starting at the low end of the dosing range.

Maintenance of Therapy

OPANA Injection is intended as an opioid analgesic for the management of moderate to severe pain where the use of an opioid analgesic is appropriate. During therapy, continual re-evaluation of the patient receiving OPANA Injection is important, with special attention to the maintenance of pain control and the relative incidence of side effects associated with therapy. If the level of pain increases, effort should be made to identify the source of increased pain, while adjusting the dose and/or using adjuvant analgesics such as acetaminophen or NSAIDs.

Cessation of Therapy

When the patient no longer requires therapy with OPANA Injection, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient.

SAFETY AND HANDLING

OPANA Injection contains oxymorphone, which is a controlled substance. Oxymorphone is controlled under Schedule II of the Controlled Substances Act. Oxymorphone, like all opioids, is liable to diversion and misuse and should be handled accordingly.

OPANA Injection may be targeted for theft and diversion. Healthcare professionals should contact their State Medical Board, State Board of Pharmacy or State Control Board for information on how to detect or prevent diversion of this product.

HOW SUPPLIED

OPANA (oxymorphone hydrochloride) Injection is supplied as follows:

1 mg/mL 1 mL ampules (paraben/sodium dithionite-free) (box of 10)
NDC 63481-624-10

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

DEA Order Form Required

Protect from light.

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, Pennsylvania 19317

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NDC 63481-624-10

1 mL X 10 ampules

OPANA®

(oxymorphone hydrochloride) Injection

1 mg per mL

R_x only

Each 1 mL contains:
Oxymorphone Hydrochloride, USP . . . 1 mg
Sodium chloride 8 mg/mL. pH is adjusted with hydrochloric acid.
Usual Dosage: See package insert for complete prescribing information.
Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).
PROTECT FROM LIGHT.

FOR INTRAMUSCULAR, SUBCUTANEOUS OR INTRAVENOUS USE

ENDO PHARMACEUTICALS

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1 mg per mL

OPANA®
(oxymorphone hydrochloride) Injection

NDC 63481-624-10

1 mL X 10 ampules

OPANA®
(oxymorphone hydrochloride) Injection

1 mg per mL

R_x only

Each 1 mL contains:
Oxymorphone Hydrochloride, USP . . . 1 mg
Sodium chloride 8 mg/mL. pH is adjusted with hydrochloric acid.
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PROTECT FROM LIGHT.

FOR INTRAMUSCULAR, SUBCUTANEOUS OR INTRAVENOUS USE

ENDO PHARMACEUTICALS

1 mL X 10 ampules

OPANA®
(oxymorphone hydrochloride) Injection

1 mg per mL

FPO - Code 128
542787

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, Pennsylvania 19317

Manufactured by:
DSM Pharmaceuticals, Inc.
Greenville, North Carolina 27834

NDC 63481-624-01

OPANA® *(oxymorphone hydrochloride) Injection*

1 mg/mL

1 mL ampule

C II

For Intramuscular, Subcutaneous, or Intravenous Use Only

Manufactured for
Endo Pharmaceuticals Inc.
Chadds Ford, PA 19317

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