

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OPANA Injection safely and effectively. See full prescribing information for OPANA Injection.

OPANA® (Oxymorphone Hydrochloride) for Injection CII
Initial U.S. Approval: 1959

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

See full prescribing information for complete boxed warning.

- OPANA Injection exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions. (5.1)
- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. (5.2)
- Prolonged use of OPANA Injection during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.3)
- Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.4, 7)

Boxed Warning	12/2016
Indications and Usage (1)	12/2016
Dosage and Administration (2)	12/2016
Contraindications (4)	12/2016
Warnings and Precautions (5)	12/2016

INDICATIONS AND USAGE

OPANA Injection is an opioid agonist indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. (1)

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.

Limitations of Use (1)

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve OPANA injection for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products]:

- Have not been tolerated, or are not expected to be tolerated,
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia

DOSAGE AND ADMINISTRATION

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. (2.1)

- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- Subcutaneous or Intramuscular Administration: Initiate treatment with 1 mg to 1.5 mg, every 4 to 6 hours as needed for pain.
- Intravenous Administration: 0.5 mg initially (2.2)
- Do not stop OPANA Injection abruptly in a physically dependent patient. (2.8)

DOSAGE FORMS AND STRENGTHS

Injection 1 mg/mL 1 mL ampules

CONTRAINDICATIONS

- Significant respiratory depression. (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment. (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus. (4)
- Known hypersensitivity to oxymorphone, any other ingredients in OPANA injection (4)
- Moderate or severe hepatic impairment (4)

WARNINGS AND PRECAUTIONS

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.5)
- Anaphylaxis, Angioedema, and Other Hypersensitivity Reactions: If symptoms occur, stop administration immediately, discontinue permanently, and do not rechallenge with any oxymorphone formulation. (5.6)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.7)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of OPANA in patients with circulatory shock. (5.8)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of OPANA in patients with impaired consciousness or coma. (5.9)

ADVERSE REACTIONS

Adverse reactions ($\geq 2\%$ of patients): seen with the immediate release tablet formulation Nausea, pyrexia, somnolence, vomiting, pruritus, headache, dizziness, constipation, and confusion. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Endo Pharmaceuticals Inc. at 1-800-462-3636 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue OPANA if serotonin syndrome is suspected. (7)
- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with OPANA because they may reduce analgesic effect of OPANA or precipitate withdrawal symptoms. (7)
- Anticholinergics: May result in urinary retention and/or severe constipation, which may lead to paralytic ileus. (7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2016

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FULL PRESCRIBING INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse

OPANA injection exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing OPANA injection, and monitor all patients regularly for the development of these behaviors and conditions [see *Warnings and Precautions (5.1)*].

Life-threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of OPANA. Monitor for respiratory depression, especially during initiation of OPANA injection or following a dose increase [see *Warnings and Precautions (5.2)*].

Neonatal Opioid Withdrawal Syndrome

Prolonged use of OPANA injection during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see *Warnings and Precautions (5.3)*].

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see *Warnings and Precautions 5.4, Drug Interactions (7)*].

- Reserve concomitant prescribing of OPANA injection and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

1 INDICATIONS AND USAGE

OPANA injection is indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

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.

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve OPANA injection for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products

- Have not been tolerated, or are not expected to be tolerated,
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see *Warnings and Precautions (5)*].

Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse [see *Warnings and Precautions (5.1)*].

Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with OPANA injection and adjust the dosage accordingly [see *Warnings and Precautions (5.2)*].

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

2.2 Initial Dosage

Subcutaneous or intramuscular administration: initially 1 mg to 1.5 mg, repeated every 4 to 6 hours as needed.

Intravenous administration: 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.

Conversion from oral OPANA to OPANA injection

There is inter-patient variability in the potency of opioid drugs and opioid formulations. Therefore, a conservative approach is advised when determining the total daily dosage of OPANA. It is safer to underestimate a patient's 24-hour OPANA dosage than to overestimate the 24-hour OPANA dosage and manage an adverse reaction due to overdose.

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.

2.3 Dosage Modifications in Patients with Hepatic Impairment

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 *Warnings and Precautions (5.14)* and *Clinical Pharmacology 12.3*].

2.4 Dosage Modifications in Patients with Renal Impairment

The effects of OPANA injection on renal impairment have not been studied. However, in patients treated with OPANA, there is an increase in oxymorphone bioavailability in patients with moderate to severe renal impairment, compared to the subjects with normal renal function [see *Clinical Pharmacology (12.3)* and *Use in Specific Populations (8.7)*]. Accordingly, OPANA injection should be administered cautiously and in reduced dosages to patients with creatinine clearance rate less than 50 mL/min.

2.5 Dosage Modifications in Geriatric Patients

Exercise 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 [see *Warnings and Precautions (5.5) and Use in Specific Populations 8.5*].

2.6 Dosage Modifications with Concomitant Use with Central Nervous System 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 (CNS) depressants including sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, and alcohol, because respiratory depression, hypotension and profound sedation, coma or death may result [see *Warnings and Precautions (5.4) and Drug Interactions (7)*]. When combined therapy with any of the above medications is considered, the dose of one or both agents should be reduced.

Although no specific interaction between oxymorphone and monoamine oxidase inhibitors has been observed, OPANA injection is not recommended for use in patients who have received MAO inhibitors within 14 days [see *Drug Interactions (7)*].

2.7 Titration and Maintenance of Therapy

Individually titrate OPANA injection to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving OPANA injection to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse [see *Warnings and Precautions (5.1)*]. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration.

If the level of pain increases after dosage stabilization, attempt to identify the source of increased pain before increasing the OPANA injection dosage. If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

2.8 Discontinuation of OPANA Injection

When a patient who has been taking OPANA injection regularly and may be physically dependent no longer requires therapy with OPANA injection, taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue OPANA injection in a physically-dependent patient [see *Warnings and Precautions (5.12), Drug Abuse and Dependence (9.2, 9.3)*].

3 DOSAGE FORMS AND STRENGTHS

Injection 1 mg/mL 1 mL ampules (paraben/sodium dithionite-free)

4 CONTRAINDICATIONS

OPANA injection is contraindicated in patients with:

- Significant respiratory depression [see *Warnings and Precautions (5.2)*]
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [see *Warnings and Precautions (5.5)*]
- Known or suspected gastrointestinal obstruction, including paralytic ileus [see *Warnings and Precautions (5.10)*]

- Hypersensitivity to oxymorphone (e.g., anaphylaxis, angioedema) [*see Warnings and Precautions (5.6), Adverse Reactions (6)*]
- Moderate or severe hepatic impairment [*see Warnings and Precautions (5.14)*].

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

OPANA injection contains oxymorphone, a Schedule II controlled substance. As an opioid, OPANA exposes users to the risks of addiction, abuse, and misuse [*see Drug Abuse and Dependence (9)*].

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed OPANA injection. Addiction can occur at recommended dosages and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing OPANA injection, and monitor all patients receiving OPANA injection for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as OPANA injection, but use in such patients necessitates intensive counseling about the risks and proper use of OPANA injection along with intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing OPANA injection. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug [*see Patient Counseling Information (17)*]. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status [*see Overdosage (10)*]. Carbon dioxide (CO₂) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of OPANA injection, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of OPANA injection.

To reduce the risk of respiratory depression, proper dosing and titration of OPANA injection are essential [*see Dosage and Administration (2)*]. Overestimating the OPANA injection dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

5.3 Neonatal Opioid Withdrawal Syndrome

Prolonged use of OPANA injection during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal

syndrome and ensure that appropriate treatment will be available [see *Use in Specific Populations (8.1)*, *Patient Counseling Information (17)*].

5.4 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of OPANA injection with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics [see *Drug Interactions (7)*].

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when OPANA injection is used with benzodiazepine or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs [see *Drug Interactions (7)* and *Patient Counseling Information (17)*].

5.5 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of OPANA injection in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: OPANA injection-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of OPANA [see *Warnings and Precautions (5.2)*].

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients [see *Use in Specific Populations (8.5)*].

Monitor such patients closely, particularly when initiating and titrating OPANA injection and when OPANA injection is given concomitantly with other drugs that depress respiration [see *Warnings and Precautions (5.2)*]. Alternatively, consider the use of non-opioid analgesics in these patients.

5.6 Anaphylaxis, Angioedema, and Other Hypersensitivity Reactions

Potentially life-threatening hypersensitivity reactions, including anaphylaxis and angioedema, have occurred in patients treated with OPANA injection in the postmarket setting. The most commonly described clinical features in these reports were swelling of the face, eyes, mouth, lips, tongue, hands, and/or throat; dyspnea; hives, pruritus, and/or rash; and nausea/vomiting. If anaphylaxis or other

hypersensitivity occurs, stop administration of OPANA injection immediately, discontinue OPANA injection permanently, and do not rechallenge with any formulation of oxymorphone. Advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction [*see Patient Counseling Information (17)*].

5.7 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

5.8 Severe Hypotension

OPANA injection may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) [*see Warnings and Precautions (5.8) and Drug Interactions (7)*]. Monitor these patients for signs of hypotension after initiating or titrating the dosage of OPANA injection. In patients with circulatory shock, OPANA injection may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of OPANA injection in patients with circulatory shock.

5.9 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In patients who may be susceptible to the intracranial effects of CO₂ retention (e.g., those with evidence of increased intracranial pressure or brain tumors), OPANA injection may reduce respiratory drive, and the resultant CO₂ retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with OPANA injection.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of OPANA in patients with impaired consciousness or coma.

5.10 Risks of Use in Patients with Gastrointestinal Conditions

OPANA injection is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The oxymorphone in OPANA injection may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

5.11 Increased Risk of Seizures in Patients with Seizure Disorders

The oxymorphone in OPANA injection may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during OPANA injection therapy.

5.12 Withdrawal

Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic,

including OPANA injection. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms [see *Drug Interactions (7)*].

When discontinuing OPANA injection, in a physically-dependent patient, gradually taper the dosage [see *Dosage and Administration (2.8)*]. Do not abruptly discontinue OPANA injection in these patients [see *Drug Abuse and Dependence (9.3)*].

5.13 Risks of Driving and Operating Machinery

OPANA injection may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of OPANA injection and know how they will react to the medication [see *Patient Counseling Information (17)*].

5.14 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 (12.3)*]. 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 (4)*, and *Dosage and Administration (2.3)*].

6 ADVERSE REACTIONS

The following serious adverse reactions are described, or described in greater detail, in other sections:

- Addiction, Abuse, and Misuse [see *Warnings and Precautions (5.1)*]
- Life-Threatening Respiratory Depression [see *Warnings and Precautions (5.2)*]
- Neonatal Opioid Withdrawal Syndrome [see *Warnings and Precautions (5.3)*]
- Interactions with Benzodiazepines or Other CNS Depressants [see *Warnings and Precautions (5.4)*]
- Anaphylaxis, Angioedema, and Other Hypersensitivity Reactions [see *Warnings and Precautions (5.6)*]
- Adrenal Insufficiency [see *Warnings and Precautions (5.7)*]
- Severe Hypotension [see *Warnings and Precautions (5.8)*]
- Gastrointestinal Adverse Reactions [see *Warnings and Precautions (5.10)*]
- Seizures [see *Warnings and Precautions (5.11)*]
- Withdrawal [see *Warnings and Precautions (5.12)*]

The following adverse reactions associated with the use of oxymorphone were identified in clinical studies or postmarketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac disorders: tachycardia, bradycardia, palpitations

Endocrine disorders: adrenal insufficiency

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), anaphylaxis

Metabolism and nutrition disorders: anorexia,

Nervous system disorders: somnolence, sedation, dizziness, headache, mental impairment NOS, central nervous system depression NOS, serotonin syndrome

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 angioedema

Social circumstances: drug abuser

Vascular disorders: hypotension, orthostatic hypotension, flushing

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in OPANA injection.

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids [see *Clinical Pharmacology (12.2)*].

7 DRUG INTERACTIONS

Table 2 includes clinically significant drug interactions with OPANA Injection.

Table 2: Clinically Significant Drug Interactions with OPANA Injection	
Benzodiazepines and other Central Nervous System (CNS) Depressants	
<i>Clinical Impact:</i>	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.
<i>Intervention:</i>	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation [see <i>Warnings and Precautions (5.4)</i>].
<i>Examples:</i>	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	

<i>Clinical Impact:</i>	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
<i>Intervention:</i>	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue OPANA injection if serotonin syndrome is suspected.
<i>Examples:</i>	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT ₃ receptor antagonists, drugs that effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
<i>Clinical Impact:</i>	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) [see <i>Warnings and Precautions</i> (5.2)]. If urgent use of an opioid is necessary, use test doses and frequent titration of small doses to treat pain while closely monitoring blood pressure and signs and symptoms of CNS and respiratory depression.
<i>Intervention:</i>	The use of OPANA injection is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
<i>Examples:</i>	phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
<i>Clinical Impact:</i>	May reduce the analgesic effect of OPANA injection and/or precipitate withdrawal symptoms.
<i>Intervention:</i>	Avoid concomitant use.
<i>Examples:</i>	butorphanol, nalbuphine, pentazocine, buprenorphine,
Muscle Relaxants	
<i>Clinical Impact:</i>	Oxymorphone may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
<i>Intervention:</i>	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of OPANA ER and/or the muscle relaxant as necessary.
Diuretics	

<i>Clinical Impact:</i>	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
<i>Intervention:</i>	Monitor patients for signs of urinary retention or reduced gastric motility when OPANA is used concomitantly with anticholinergic drugs.
Anticholinergic Drugs	
<i>Clinical Impact:</i>	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
<i>Intervention:</i>	Monitor patients for signs of urinary retention or reduced gastric motility when OPANA injection is used concomitantly with anticholinergic drugs.
Cimetidine	
<i>Clinical Impact:</i>	Cimetidine can potentiate opioid-induced respiratory depression.
<i>Intervention:</i>	Monitor patients for respiratory depression when OPANA ER and cimetidine are used concurrently.
Propofol	
<i>Clinical Impact:</i>	Incidence of bradycardia was increased when oxymorphone was combined with propofol for induction of anesthesia
<i>Intervention:</i>	Do not use concurrently with Propofol.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome [see *Warnings and Precautions* (5.3)]. Available data with OPANA in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, reduced postnatal survival of pups and an increased incidence of stillborn pups were observed following oral treatment of pregnant rats with oxymorphone during gestation and through lactation at doses 2.4 and 12 times the human daily dose of 20 mg/day (HDD), respectively. Reduced fetal weights were observed with oral administration of oxymorphone to pregnant rats and rabbits during organogenesis at exposures up to 4.9 and 48.8 times the HDD, respectively [see *Data*]. Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly [see *Warnings and Precautions (5.3)*].

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. OPANA injection is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including OPANA injection, can 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 dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data

Animal Data

Pregnant rats were treated with oxymorphone hydrochloride from Gestation Day 6 to 17 via oral gavage doses of 5, 10, or 25 mg/kg/day (2.4, 4.9, or 12.2 times the HDD based on body surface area, respectively). Reduced mean fetal weights were observed at 4.9 times the HDD. Maternal toxicity was noted in all treatment groups (reduced food consumption and body weights in all groups and mortality in the high dose group).

Pregnant rabbits were treated with oxymorphone hydrochloride from Gestation Day 7 to 20 via oral gavage doses of 10, 25, or 50 mg/kg/day (9.8, 24.4, or 48.8 times the HDD based on body surface area, respectively). Decreased mean fetal weights were noted at 48.8 times the HDD. Maternal toxicity was noted in all treatment groups (reduced food consumption and body weights).

Pregnant rats were treated with oxymorphone hydrochloride from Gestation Day 6 to Lactation Day 20 via oral gavage doses of 1, 5, 10, or 25 mg/kg/day (0.5, 2.4, 4.9, or 12.2 times the HDD based on body surface area, respectively). Increased neonatal death (postnatal day 0-1) was noted at 2.4 times the HDD. Decreased pup survival over the first week of life, reduced pup birth weight, and reduced postnatal weight gain were noted at 4.9 times the HDD. Maternal toxicity was noted in all treatment groups (reduced food consumption and body weights in all groups and mortality in the 10 and 25 mg/kg/day groups).

In a published study, neural tube defects (exencephaly and cranioschisis) were noted following subcutaneous administration of 153 mg/kg oxymorphone hydrochloride (62.2 times the HDD) on Gestation Day 8 to pregnant hamsters. This dose also produced significant maternal toxicity (20% maternal deaths).

8.2 Lactation

Risk Summary

There is no information regarding the presence of oxymorphone in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OPANA injection and any potential adverse effects on the breastfed child from OPANA injection or from the underlying maternal condition.

Clinical Considerations

Monitor infants exposed to OPANA injection through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breast-fed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OPANA and any potential adverse effects on the breastfed infant from OPANA or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [*Clinical Pharmacology (12.2), Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

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

8.5 Geriatric Use

Elderly patients (aged 65 years or older) may have increased sensitivity to oxymorphone. In general, use caution when selecting a dosage for an elderly patient, 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.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of OPANA injection slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression [*see Warnings and Precautions (5.5)*].

Oxymorphone is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 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 (12.3)*]. 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 Dosage and Administration (2.3), Contraindications (4), and Warnings and Precautions (5.14)*].

8.7 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 (12.3)*]. 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 (2.4)*].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

OPANA injection contains oxymorphone, a Schedule II controlled substance

9.2 Abuse

OPANA injection contains oxymorphone, a substance with a high potential for abuse similar to other opioids including fentanyl, hydromorphone, methadone, morphine, oxycodone and tapentadol. OPANA injection can be abused and is subject to misuse, addiction, and criminal diversion [*see Warnings and Precautions (5.1)*].

All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

“Drug-seeking” behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated “loss” of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating health care provider(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. Health care providers 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.

OPANA injection, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

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.

Risks Specific to Abuse of OPANA Injection

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 central nervous system depressants. Parenteral drug

abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. 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). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

OPANA injection should not be abruptly discontinued in a physically-dependent patient [*see Dosage and Administration (2.8)*]. If OPANA injection is abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and 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.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs [*see Warnings and Precautions (5.3), Use in Specific Populations (8.1)*].

10 OVERDOSAGE

Clinical Presentation

Acute overdose with OPANA injection can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations [*see Clinical Pharmacology (12.2)*].

Treatment of Overdose

In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support techniques.

The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to oxymorphone overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxymorphone overdose.

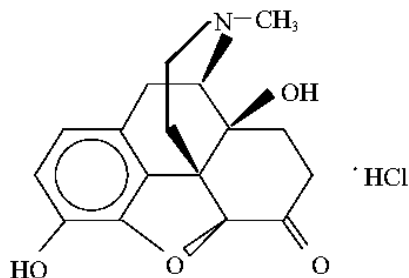
Because the duration of opioid reversal is expected to be less than the duration of action of oxymorphone in OPANA injection, carefully monitor the patient until spontaneous respiration is reliably re-established. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist

administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be initiated with care and by titration with smaller than usual doses of the antagonist.

11 DESCRIPTION

OPANA (oxymorphone hydrochloride) Injection, is an opioid agonist, available in 1 mg/mL, 1 mL ampules of oxymorphone hydrochloride for injection. The chemical name for oxymorphone hydrochloride is 4, 5 α -epoxy-3, 14-dihydroxy-17-methylmorphinan-6-one hydrochloride. The molecular weight is 337.80. The molecular formula is C₁₇H₁₉NO₄ · HCl and it has the following chemical structure.



Oxymorphone hydrochloride is white to off white odorless powder, which is sparingly soluble in alcohol and ether, but freely soluble in water

In addition, each 1 mg/mL ampule contains 8.0 mg/mL sodium chloride. pH is adjusted with hydrochloric acid.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Oxymorphone is a full opioid agonist and is relatively selective for the mu-opioid receptor, although it can bind to other opioid receptors at higher doses. The principal therapeutic action of oxymorphone is analgesia. Like all full opioid agonists, there is no ceiling effect for analgesia with oxymorphone. Clinically, dosage is titrated to provide adequate analgesia and may be limited by adverse reactions, including respiratory and CNS depression. The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.

12.2 Pharmacodynamics

Effects on the Central Nervous System

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

Oxymorphone causes 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 origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Oxymorphone causes 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 biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System

Oxymorphone produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes and sweating and/or orthostatic hypotension.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotrophic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon [*see Adverse Reactions (6)*].

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date [*see Adverse Reactions (6)*].

Effects on the 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. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration–Efficacy Relationships

The minimum effective analgesic concentration varies widely among patients, especially among patients who have been previously treated with potent agonist opioids. The minimum effective analgesic concentration of oxymorphone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance [*see Dosage and Administration (2.1)*].

Concentration–Adverse Reaction Relationships

There is a relationship between increasing oxymorphone plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions [*see Dosage and Administration (2.1, 2.2, 2.7)*].

12.3 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

Elimination

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.

Specific Populations

Geriatric

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.

Sex

The effects of OPANA injection on sex 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, sex 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 Interactions Studies

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 $\leq 50 \mu\text{M}$. An inhibition of CYP 3A4 activity occurred at oxymorphone concentrations $\geq 150 \mu\text{M}$. 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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No evidence of carcinogenic potential was observed in long-term animal studies in mice and rats. Oxymorphone hydrochloride 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. Systemic drug exposure (AUC) at the highest doses tested in male and female rats was 4.8 times and 21.2 times the human exposure at a dose of 20 mg/day, respectively. Oxymorphone hydrochloride was administered to male and female CD-1 mice (10, 25, 75 and 150 mg/kg/day) for 2 years by oral gavage. Systemic drug exposure (AUC) at 150 mg/kg/day in male and female mice was 205 times and 243 times the human exposure at a dose of 20 mg/day, respectively.

Mutagenesis

Oxymorphone hydrochloride was not mutagenic when tested in the *in vitro* bacterial reverse mutation assay (Ames test), or in an *in vitro* mammalian cell chromosome aberration assay performed with human peripheral blood lymphocytes. 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 $\geq 250 \text{ mg/kg}$ 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

Female rats were treated with oxymorphone hydrochloride beginning 14 days prior to mating through Gestation Day 7 via oral gavage doses of 5, 10, or 25 mg/kg/day (2.4, 4.9, or 12.2 times the human daily dose of 20 mg/day based on body surface area, respectively). Male rats were treated via oral gavage with the same oxymorphone hydrochloride doses beginning 28 days prior to and throughout mating. 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 4.9 times the human dose of 20 mg/day. No adverse effects of oxymorphone on male reproductive function or sperm parameters were observed.

16 HOW SUPPLIED/STORAGE AND HANDLING

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.]

Protect from light.

17 PATIENT COUNSELING INFORMATION

Serotonin Syndrome

Inform patients that OPANA injection could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their physicians if they are taking, or plan to take serotonergic medications [*see Drug Interactions (7)*].

Constipation

Advise patients of the potential for severe constipation [*see Adverse Reactions (6)*].

Distributed by:
Endo Pharmaceuticals Inc.
Malvern, PA 19355

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