

Classification Puts Childhood Vasculitis in Order

BY MARY ANN MOON
Contributing Writer

A new international classification for childhood vasculitis promises to improve existing criteria by bringing them into line with current clinical practice, reported Dr. Seza Ozen and fellow associates.

The new criteria, endorsed by the European League Against Rheumatism and the Paediatric Rheumatology European

Society, were needed to update existing criteria and make them more specific.

It is the first internationally agreed-upon classification of the vasculitides observed in children, and was devised by gathering opinions from a wide range of pediatric rheumatologists and nephrologists from around the world, reported Dr. Ozen of Hacettepe University, Ankara, Turkey, and associates (Ann. Rheum. Dis. 2006;65:936-41).

The working group of experts updated

the classification of Henoch-Schönlein purpura, Kawasaki disease, childhood polyarteritis nodosa, Wegener's granulomatosis, and Takayasu arteritis.

"It was agreed that vessel size would form the backbone of the criteria," as had been decided at the Chapel Hill Consensus Conference for adult vasculitides, the investigators noted.

In addition, small-vessel vasculitis was divided according to the presence or absence of granulomas, "as this feature has

important distinguishing implications." A category of "other vasculitides" was added for those disorders in which an etiologic process was defined or which did not fit into existing categories.

For Henoch-Schönlein purpura, the primary change was that palpable purpura is now a mandatory criterion. Biopsy findings also were clarified, and since arthritis is common in the childhood type of this disorder, it is now included in the criteria.

The existing criteria for Kawasaki disease were retained. But since coronary artery disease is so important in this disorder, children who have typical echocardiographic changes can now be classified as having Kawasaki disease even if they do

not fulfill four of the remaining criteria.

In addition, the perineal desquamation frequently noted in Kawasaki disease has been included under "changes in extremities."

"Pediatric data during the last 10 years have shown

that polyarteritis nodosa in children is hard to classify using the definitions applicable to adults," Dr. Ozen and associates said. "We decided that abnormal angiography or a characteristic biopsy are mandatory criteria for the diagnosis of the disease" in children.

In addition, the criterion of hepatitis B surface antigen was eliminated, since this is no longer a major feature in pediatrics, "thanks to improving vaccination" practices. And since cutaneous disease is common in childhood polyarteritis nodosa, it has been added to the new criteria.

For Wegener's granulomatosis, subglottic, tracheal, or endobronchial stenosis has been added as a new criterion, because these are frequent features of the childhood disease.

Changes in technology prompted a revision of the criterion concerning radiographic imaging so that CT results are now included. And antineutrophil cytoplasmic antibody testing has also been added.

For Takayasu arteritis, the angiographic criterion was updated to reflect changes in technology, and it is now a mandatory criterion.

Hypertension is common and often is the only presenting sign in pediatric patients, so it has been included as a criterion even though it is nonspecific.

Overall, the new classification should benefit pediatricians and rheumatologists in practice, noted Dr. Ozen and associates. "We believe this was an important task, as appropriate classification criteria for vasculitis in children have been missing for far too long.

"The next step will be to validate these criteria using patients and control groups," they said. ■

OPANA® ER (Oxymorphone Hydrochloride) Extended-Release Tablets 5 mg, 10 mg, 20 mg and 40 mg

Rx only.
Brief Summary (For full Prescribing Information including Dosage and Administration, and Patient Information, refer to package insert.)

WARNING:
OPANA ER contains oxymorphone, which is a morphine-like opioid agonist and is a Schedule II controlled substance, with abuse liability similar to other opioid analgesics.
Oxymorphone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OPANA ER in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.
OPANA ER is an extended-release oral formulation of oxymorphone indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.
OPANA ER is NOT intended for use as a prn analgesic.
OPANA ER TABLETS are to be swallowed whole and are not to be broken, chewed, dissolved, or crushed. Taking broken, chewed, dissolved, or crushed OPANA ER TABLETS leads to rapid release and absorption of a potentially fatal dose of oxymorphone.
Patients must not consume alcoholic beverages, or prescription medications containing alcohol, while on OPANA ER therapy. The co-ingestion of alcohol with OPANA ER may result in increased plasma levels and a potentially fatal overdose of oxymorphone.

INDICATIONS AND USAGE
OPANA ER is indicated for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.
OPANA ER is not intended for use as a prn analgesic.

OPANA ER is not indicated for pain in the immediate post-operative period (12-24 hours following surgery) for patients not previously taking opioids because of the risk of oversedation and respiratory depression requiring reversal with opioid antagonists.

OPANA ER is not indicated for pain in the post-operative period if the pain is mild or not expected to persist for an extended period of time.

CONTRAINDICATIONS
OPANA ER is contraindicated in patients with a known hypersensitivity to oxymorphone hydrochloride, morphine analogs such as codeine, or any of the other ingredients of OPANA ER; in patients with moderate or severe hepatic impairment or in any situation where opioids are contraindicated such as: patients with respiratory depression (in the absence of resuscitative equipment or in unmonitored settings), acute or severe bronchial asthma, hypercapnia, and in any patient who has or is suspected of having paralytic ileus.

OPANA ER is not indicated for pain in the immediate post-operative period (the first 12-24 hours following surgery), or for pain that is not expected to persist for an extended period of time. OPANA ER is only indicated for post-operative use if the patient is already receiving the drug prior to surgery or if the post-operative pain is expected to be moderate or severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines).

WARNINGS
OPANA ER TABLETS are to be swallowed whole, and are not to be broken, chewed, crushed or dissolved. Taking broken, chewed, dissolved, or crushed OPANA ER TABLETS could lead to the rapid release and absorption of a potentially fatal dose of oxymorphone.
Patients must not consume alcoholic beverages, or prescription or non-prescription medications containing alcohol, while on OPANA ER therapy. The co-ingestion of alcohol with OPANA ER may result in increased plasma levels and a potentially fatal overdose of oxymorphone.

Misuse, Abuse and Diversion of Opioids
OPANA ER contains oxymorphone, an opioid agonist similar to morphine, and is 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 OPANA ER in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

OPANA ER tablets may be abused by crushing, chewing, snorting or injecting the product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see WARNINGS and PRECAUTIONS: Drug Abuse and Addiction).

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. Oxymorphone may also cause respiratory depression, hypotension, and profound sedation or coma may result. An *in vivo* study examined the effect of alcohol (40%, 20%, 4%, and 0%) on the bioavailability of a single dose of 40 mg of OPANA ER in healthy, fasted volunteers. The results showed that the oxymorphone mean AUC was 13% higher (not statistically significant) after co-administration of 240 mL of 40% alcohol. The AUC was essentially unaffected in subjects following the co-administration of OPANA ER and ethanol (240 mL of 20% or 4% ethanol).

There was a highly variable effect on C_{max} with concomitant administration of alcohol and OPANA ER. The change in C_{max} ranged from a decrease of 50% to an increase of 270% across all conditions studied. Following concomitant administration of 240 mL of 40% ethanol the C_{max} increased on

average by 70%, and up to 270% in individual subjects. Following the concomitant administration of 240 mL of 20% ethanol the C_{max} increased on average by 31% and up to 260% in individual subjects. Following the concomitant administration of 240 mL of 4% ethanol, the C_{max} increased by 7% on average and as much as 110% for individual subjects.

Drug Abuse and Addiction: Controlled Substance: OPANA ER contains oxymorphone, an opioid with a potential similar to morphine and other opioid agonists and is a Schedule II controlled substance. OPANA ER and other opioids used in analgesia, can be abused and are 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-medical 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. Precaution 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 withdrawal symptoms. Signs 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 ER, 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 ER poses a risk of overdose and death. This risk is increased with concurrent abuse of OPANA ER with alcohol and other substances. In addition, parenteral drug abuse is commonly associated with transmission of infectious disease such as hepatitis and HIV.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are important 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, especially after intra-uterine exposure. **Pregnancy and PRECAUTIONS: Labor and Delivery.**

Respiratory Depression: Respiratory depression is the chief hazard of OPANA ER. 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 ER should be administered with extreme caution to patients with conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve, including 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 cause respiratory depression, hypotension, profound sedation, or coma (see PRECAUTIONS: Drug Abuse and Addiction). **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 CO₂ retention) may be markedly exaggerated. Furthermore, opioid analgesics can produce effects on pupillary response and, consequently, which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

Hypotensive Effect: OPANA ER, like all opioid analgesics, may cause severe hypotension in an individual 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 myocardial and postural hypotension. OPANA ER 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. **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 myocardial and postural hypotension. OPANA ER 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 ER 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 oxymorphone may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Oxymorphone may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate impairment of fertility. The dose of oxymorphone that produced no adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

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 ER in pregnancy, in nursing mothers, or in women of child-bearing potential requires that the possible benefits of the drug be weighed 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) or rabbits (≤50 mg/kg/day).

There are no adequate and well-controlled studies in pregnant women. OPANA ER 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, attributed to an increased incidence of stillborn pups. An increase in neonatal death occurred at ≥5 mg/kg/day. Post-natal survival of pups was reduced throughout the 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 3-3.4 times the human dose of 40 mg every 12 hours on a body surface area basis.

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: Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. OPANA ER is not recommended for use in women during and immediately prior to labor, when use of shorter acting analgesics or other analgesic techniques are more appropriate. A specific opioid antagonist, such as naloxone or nalmefene, should be available for reversal of opioid-induced respiratory depression in the neonate.

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 ER 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 neonate.

Pediatric Use: Safety and effectiveness of OPANA ER in pediatric patients below the age of 18 years have not been established. **Geriatric Use:** OPANA ER should be used with caution in elderly patients. Elderly patients on oxymorphone are about 40% higher in elderly (≥65 years of age) than in younger subjects (see CLINICAL PHARMACOLOGY). Elderly patients should initially receive smaller starting doses of oxymorphone and dose titration should proceed cautiously.

Of the total number of subjects in clinical studies of OPANA ER, 27 percent were 65 and over, while 9 percent were 75 and over. No overall differences in safety or 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.

Hepatic Impairment: A study of OPANA ER in patients with hepatic disease indicated greater plasma concentrations than those with normal hepatic function. In patients with moderate to severe hepatic impairment, OPANA ER should be used with caution in patients with mild impairment. These patients should be started with the lowest dose and titrated slowly with careful monitoring for side effects. OPANA ER is contraindicated for patients with moderate and severe hepatic impairment (see CONTRAINDICATIONS, WARNINGS, and DOSAGE AND ADMINISTRATION).

Renal Impairment: 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 with the lowest dose and titrated slowly with careful monitoring for side effects. OPANA ER is contraindicated for patients with moderate and severe hepatic impairment (see CONTRAINDICATIONS, WARNINGS, and DOSAGE AND ADMINISTRATION).

Use with CNS Depressants: The concomitant use of other CNS depressants including sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with oxymorphone may experience respiratory depression, hypotension, profound sedation, or coma (see PRECAUTIONS: Drug Abuse and Addiction). **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 CO₂ retention) may be markedly exaggerated. Furthermore, opioid analgesics can produce effects on pupillary response and, consequently, which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

Hypotensive Effect: OPANA ER, like all opioid analgesics, may cause severe hypotension in an individual 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 myocardial and postural hypotension. OPANA ER 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. **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 myocardial and postural hypotension. OPANA ER 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. **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 myocardial and postural hypotension. OPANA ER 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. **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 myocardial and postural hypotension. OPANA ER 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. **CONTRAINDICATIONS, WARNINGS, and DOSAGE AND ADMINISTRATION.**

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.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

Pregnancy: The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

The most common adverse drug reactions (≥10%) reported at least once by patients treated with OPANA ER in the clinical trials were nausea, constipation, dizziness (exc. vertigo), vomiting, pruritus, somnolence, headache, sweating increased and sedation.

The common (≥1% - <10%) adverse drug reactions reported at least once by patients treated with OPANA ER in the clinical trials organized by MedDRA's (Medical Dictionary for Regulatory Activities) System Organ Class were:

Eye disorders: vision blurred
Gastrointestinal disorders: diarrhea, abdominal pain, dyspepsia

General disorders and administration site conditions: dry mouth, appetite decreased, fatigue, lethargy, weakness, pyrexia, dehydration, weight decreased, edema

Nervous system disorders: insomnia
Psychiatric disorders: anxiety, confusion, disorientation, restlessness, nervousness, depression

Respiratory, thoracic and mediastinal disorders: dyspnea

Vascular disorders: flushing and hypertension
Other less common adverse reactions known with opioid treatment that were seen <1% in the OPANA ER trials included the following in alphabetical order:

abdominal distention, agitation, allergic reactions, bradycardia, central nervous system depression, clamminess, depressed level of consciousness, dermatitis, difficult micturition, dysphoria, euphoric mood, feeling jittery, hallucinations, hot flashes, hypersensitivity, hypotension, hypoxia, ileus, mental impairment, mental status changes, miosis, oxygen saturation decreased, palpitation, postural hypotension, respiratory depression, respiratory distress, respiratory rate decreased, syncope, tachycardia, urinary retention, urticaria, and visual disturbances.

OVERDOSAGE
Signs and Symptoms: Acute overdose with OPANA ER 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 overdose, apnea, circulatory collapse, cardiac arrest and death may occur.

OPANA ER 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 ER overdose, 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 as pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation. Elimination or evacuation of gastric contents may be necessary in order to eliminate unabsorbed drug. Before attempting treatment by gastric emptying or activated charcoal, care should be taken to secure the airway.

The opioid antagonist naloxone hydrochloride is a specific antidote against respiratory depression which may result from overdose or unusual sensitivity to opioids including OPANA ER. Therefore, an appropriate dose of naloxone hydrochloride should be administered (usual initial 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 used as an adjunct to naloxone in the management of respiratory depression resulting from opioid overdose. Since the duration of action of OPANA ER 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 ER, opioid antagonists should not be administered in the absence of a clinically significant respiratory or circulatory depression secondary to OPANA ER overdose. They should be administered cautiously to persons who are known, or suspected to be, physically dependent on an opioid agonist including OPANA ER. 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 may 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