

Europe's Pregnancy Rates Hold in Move to SET

BY KATE JOHNSON
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PRAGUE — Europe maintained its in vitro fertilization success rates in 2003 compared with the previous year despite a reduction in multiple pregnancies, according to data presented at the annual meeting of the European Society of Human Reproduction and Embryology.

The European in vitro fertilization (IVF) clinical pregnancy rate was 29.5% per em-

bryo transfer, reported Dr. Anders Nyboe Andersen, coordinator of the European IVF Monitoring (EIM) Consortium.

In comparison, the latest figures (2004) from the United States' Society for Assisted Reproductive Technology (SART) show a 40.6% pregnancy rate per embryo transfer, said California fertility expert Dr. David Adamson in an interview.

In the United States, that figure translates to a live birth rate of roughly 33% per embryo transfer across all age groups

(42.5% in women under age 35 years), said Dr. Adamson. The European live birth rate per embryo transfer is not known because the EIM Consortium includes 28 European countries and does not routinely follow IVF patients beyond the ultrasound confirmation of a gestational sac, said Dr. Andersen, also of the University of Copenhagen. However, assuming similar rates of miscarriage in Europe and the United States, the European live birth rate per embryo transfer would be roughly

24%. (In its 2002 World Report on IVF, the International Committee for Monitoring Assisted Reproduction reports an IVF delivery rate of 17% for Europe and 25% for the United States.)

Although this calculation suggests Europe has lower IVF success rates compared with the United States, Europe also reports lower multiple pregnancy rates—but an exact comparison is difficult to make. The latest figures from the EIM Consortium show that 22% of all IVF deliveries in Europe

OPANA® (Oxymorphone Hydrochloride) Tablets

Rx only 5 mg and 10 mg

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

INDICATIONS AND USAGE
OPANA is indicated for the relief of moderate to severe acute pain where the use of an opioid is appropriate.

CONTRAINDICATIONS
OPANA is contraindicated in patients with a known hypersensitivity to oxymorphone hydrochloride, morphine analogs such as codeine, or any of the other ingredients of OPANA; 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, hypercarbia, and in any patient who has or is suspected of having paralytic ileus.

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

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

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

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

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

OPANA tablets may be abused by crushing, chewing, snorting or injecting the product. These practices pose a significant risk to the abuser that could result in overdose and death (see **WARNINGS: 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 Licensure Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

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

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

Drug addiction is characterized by a preoccupation with the procurement, hoarding, and abuse of drugs for non-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. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. OPANA, 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 poses a risk of overdose and death. This risk is increased with concurrent abuse of OPANA with alcohol and other substances. In addition, parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV. Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

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

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

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 consciousness, which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

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

Hepatic Impairment
A study of OPANA ER (an extended-release formulation of oxymorphone) in patients with hepatic disease indicated greater plasma concentrations than those with normal hepatic function (see **CLINICAL PHARMACOLOGY**). OPANA 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 is contraindicated for patients with moderate and severe hepatic impairment (see **CONTRAINDICATIONS, WARNINGS, and DOSAGE AND ADMINISTRATION**).

PRECAUTIONS
General
Opioid analgesics should be used with caution, especially in conditions of acute alcoholism; and should be reserved for cases where the benefits of opioid analgesia outweigh the known potential risks of respiratory depression, altered mental state and postural hypotension. OPANA 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 should be used with caution in the following conditions: acute alcoholism; adrenocortical insufficiency (e.g., Addison's disease); CNS depression or coma; delirium tremens; kyphoscoliosis associated with respiratory depression; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of pulmonary or renal function; moderate impairment of hepatic function; and toxic psychosis.

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

Interactions with Mixed Agonist/Antagonist Opioid Analgesics
Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol, and buprenorphine) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as oxymorphone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxymorphone and/or may precipitate withdrawal symptoms in these patients.

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

Use in Pancreatic/Biliary Tract Disease
OPANA, like other opioids, may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis.

Physical Dependence and Tolerance
Physical dependence is the occurrence of withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an opioid antagonist or mixed opioid agonist/antagonist agent. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). The development of physical dependence and/or tolerance is not unusual

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

In general, OPANA should not be abruptly discontinued (see **DOSAGE AND ADMINISTRATION: Cessation of Therapy**). Information for Patients/Caregivers (See full prescribing information for details on information for patients).

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

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

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

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

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

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

Other
Anticholinergics or other medications with anticholinergic activity when used concurrently with opioid analgesics may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. In addition, CNS side effects have been reported (confusion, disorientation, respiratory depression, apnea, seizures) following coadministration of cimetidine with opioid analgesics; a causal relationship has not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: No evidence of carcinogenic potential was observed in rats. No evidence of carcinogenic potential was observed in mice.

Mutagenesis: Oxymorphone hydrochloride was not mutagenic when tested in the *in vitro* bacterial reverse mutation assay (Ames test) at concentrations of ≤ 5270 μ g/plate, or in an *in vitro* mammalian cell chromosome aberration assay performed with human peripheral blood lymphocytes at concentrations ≤ 5000 μ g/ml with or without metabolic activation. Oxymorphone hydrochloride tested positive in both the rat and mouse *in vivo* micronucleus assays.

Impairment of fertility: The dose of oxymorphone that produced no adverse effects on reproductive findings in female rats is 0.4-times a total human daily dose of 120 mg based on body surface area.

Pregnancy
The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on fetal development. The use of OPANA 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 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 increase in the incidence of stillborn pups. An increase in neonatal death occurred at doses ≥ 5 mg/kg/day. Post-natal survival of the pups was reduced throughout weaning following

treatment of the dams with 25 mg/kg/day. Low pup birth weight and decreased postnatal weight gain occurred in pups born to oxymorphone-treated female rats given a dose of 25 mg/kg/day. This dose is ≈ 2 times a total human daily dose of 120 mg, based on body surface area.

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

Labor and Delivery
Opioids cross the placenta and may produce respiratory depression and psycho-physiological effects in neonates. OPANA 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 nalmeferene, 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 is administered to a nursing woman. Ordinarily, nursing should not be undertaken while a patient is receiving oxymorphone because of the possibility of sedation and/or respiratory depression in the infant.

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

Geriatric Use
OPANA should be used with caution in elderly patients. The plasma levels of oxymorphone are about 40% higher in elderly (≥ 65 years of age) than in younger subjects (see **CLINICAL PHARMACOLOGY**).

Of the total number of subjects in clinical studies of OPANA, 31 percent were 65 and over, while 7 percent were 75 and over. No overall differences in effectiveness were observed between these subjects and younger subjects. There were several adverse events that were more frequently observed in subjects 65 and over compared to younger subjects. These adverse events included dizziness, somnolence, confusion, and nausea. In general, dose selection for elderly patients should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Hepatic Impairment
A study of OPANA ER in patients with hepatic disease indicated greater plasma concentrations than those with normal hepatic function (see **CLINICAL PHARMACOLOGY**). OPANA 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 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 cautiously with lower doses of OPANA and titrated slowly while carefully monitoring for side effects (see **DOSAGE AND ADMINISTRATION**).

Gender Differences
In clinical trials with OPANA, the overall incidence rates for one or more adverse events were similar among females and male subjects receiving OPANA and placebo.

ADVERSE REACTIONS

Adverse Reactions Reported in Placebo-Controlled Trials
The following table lists adverse reactions that were reported in at least 2% of patients in placebo-controlled trials.

MedDRA Preferred Term	OPANA (N=557)	Placebo (N=270)
Nausea	19.0%	11.5%
Pyrexia	14.2%	8.1%
Somnolence	9.3%	2.2%
Vomiting	9.0%	7.0%
Pruritus	7.9%	3.7%
Headache	6.8%	4.4%
Dizziness (Exc Vertigo)	6.5%	2.2%
Constipation	4.1%	1.1%
Confusion	2.7%	0.7%

Adverse Reactions Reported in All Clinical Trials

A total of 591 patients were treated with OPANA in the Phase 2/3 controlled clinical trials. The clinical trials consisted of patients with acute post-operative pain (n=557) and cancer pain (n=34) trials.

The adverse reactions are presented in the following manner: most common, common, and less common adverse reactions.

The most common adverse drug reactions ($\geq 10\%$) reported at least once by patients treated with OPANA in the clinical trials were nausea and pyrexia.

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

Cardiac disorders: tachycardia
Gastrointestinal disorders: vomiting, constipation, dry mouth, abdominal distention, and flatulence

General disorders and administration site conditions: sweating increased
Nervous system disorders: dizziness (exc vertigo), somnolence, headache, anxiety, and sedation

Psychiatric disorders: confusion
Respiratory, thoracic and mediastinal disorders: hypoxia
Skin & subcutaneous tissue disorders: pruritus
Vascular disorders: hypotension

Other less common adverse reactions known with opioid treatment that were seen $<1\%$ in the OPANA trials include the following: Abdominal pain, agitation, allergic reactions, vision blurred, bradycardia, central nervous system depression, clamminess, appetite decreased, dehydration, depressed level of consciousness, depression, dermatitis, diarrhoea, difficult micturition, disorientation, dyspepsia, dysphoria, dyspnea, edema, euphoric mood, fatigue, feeling jittery, flushing, hallucination, hot flashes, hypersensitivity, hypertension, ileus, insomnia, lethargy, mental impairment, mental status changes, miosis, nervousness, oxygen saturation decreased, palpitation, postural hypotension, respiratory depression, respiratory distress, respiratory rate decreased, restlessness, syncope, urinary retention, urticaria, visual disturbances, weakness, and weight decreased.

OVERDOSAGE

Signs and Symptoms
Acute overdose with OPANA 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 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 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 and 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. Therefore, an appropriate dose of naloxone hydrochloride should be administered (usual initial adult dose 0.4 mg-2 mg) preferably by the intravenous route and simultaneously with efforts at respiratory resuscitation. Nalmefene is an alternative pure opioid antagonist, which may be administered as a specific antidote to respiratory depression resulting from opioid overdose. Since the duration of action of OPANA 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, opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression. They should be administered cautiously to persons who are known, or suspected to be, physically dependent on any opioid agonist including OPANA. 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 intravenous route and simultaneously precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. If respiratory depression is associated with muscular rigidity, administration of a neuromuscular blocking agent may be necessary to facilitate assisted or controlled ventilation. Muscular rigidity may also respond to opioid antagonist therapy.

SAFETY AND HANDLING
OPANA contains oxymorphone, which is a controlled substance. Oxymorphone is controlled under Schedule II of the Controlled Substances Act. Oxymorphone, like all opioids, is liable to diversion and misuse and should be handled accordingly. Patients and their families should be instructed to flush any OPANA tablets that are no longer needed.

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

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature].
Dispense in tight container as defined in the USP, with a child-resistant closure (as required).

DEA Order Form Required.
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were twins and 1.1% were triplets (down from a twin rate of 23% and a triplet rate of 1.3% the previous year). However, given the fact that the consortium does not keep a final tally of all IVF deliveries, its figure on multiple birth rates can only be an estimate. In comparison, the United States records multiple pregnancies, not multiple births (which tend to be lower because of the high rate of miscarriage) and last year reported a twin pregnancy rate of 27% and a 4.5% rate of triplet and higher-order pregnancies, according to Dr. William Gibbons, president of SART.

Europe's reportedly lower multiple pregnancy rates are attributed to its transition

toward single embryo transfer (SET), and a continuing trend toward the transfer of fewer embryos. Overall, the 28 European countries in the EIM Consortium reported a 16% rate of SET in their IVF cycles, said Dr. Nyboe Andersen. This is in contrast to an elective SET rate of 1.2% in the United States, according to SART—although the overall SET rate is presumed to be higher, since other U.S. patients receive SET non-electively because they have only one good embryo to transfer. According to the 2002 World Report on IVF, the average number of embryos transferred in European patients was 2.2 vs. 2.9 in the United States.

Guidelines released at the end of 2004

from the American Society for Reproductive Medicine and SART recommended for the first time that SET should be considered "in patients with the most favorable prognosis" (Fertil. Steril. 2004;82:773-4), and consequences of those guidelines may be reflected in the 2005 data. However, SET is a hard sell in the United States compared with Europe, because while many European countries provide some coverage for IVF treatment, most U.S. patients pay for it themselves.

"There is a certain amount of fear among [U.S.] centers that if they do SET, they may see a dramatic fall in pregnancy rates, which in turn may cause patients to

go elsewhere for treatment," said Dr. Bradley Van Voorhis, of the University of Iowa Hospitals and Clinics in Iowa City.

Indeed, the world's first randomized trial comparing SET with double embryo transfer (DET) in an unselected group of women did much to fuel such fears (Hum. Reprod. 2006;21:338-43). Investigators in the Netherlands found that although SET reduced multiple pregnancies in unselected patients, it also significantly reduced the overall pregnancy rate compared with DET (21.4% vs. 40.3%), while in a more select group of patients (younger and with at least one good-quality embryo), the pregnancy rates in the two groups did not differ significantly (33% for SET vs. 30% for DET).

Building on this experience, Dr. Van Voorhis' clinic implemented a mandatory SET policy 2 years ago for select women with a good prognosis and high risk for multiple pregnancy, and noted no decline in success rates.

But achieving this kind of success for SET—maintaining pregnancy rates while reducing the number of embryos transferred—involves a complex art of balancing safety and success, choosing which patients can receive fewer embryos, and choosing which embryos are most likely to result in a pregnancy, said Dr. Adamson.

"SET is a very good and important strategy, and I think that we need to do more of it in the United States in order to reduce the rate of multiple pregnancies," he said. "But this is not something that works for all patients, and that really needs to be ... emphasized. It's not possible to make a single rule that applies to all patients, and that really needs to be strongly emphasized. It's not possible to make a single rule that applies to all patients; we certainly do not believe that in the United States. ... We don't believe that regulation by the government which tells patients how they should make reproductive choices is the appropriate thing to do."

That type of government regulation is largely resisted by Europe's high SET rate. The free IVF treatment provided by many European countries comes with legislative strings attached that mandate SET or severely restrict the number of embryos placed in certain women. European physicians have feared that this approach could limit pregnancy, and this is generally assumed to be one of the reasons for Europe's lower overall IVF pregnancy rate.

But certain European countries such as Sweden appear to have mastered the art of using SET effectively. "In Sweden we have shown no overall decline in pregnancy rates," said Dr. Karl Nygren, chair of the EIM Consortium. "It has been possible to maintain the pregnancy rate even with a dramatic shift to 70% SET in Sweden, and we have reduced our twin pregnancy rate to 5%," Dr. Nygren said. The consortium reported a Swedish pregnancy rate of roughly 34% per embryo transfer, which is significantly lower than the U.S. rate of 40.6%.

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 an 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 a 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.

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 over-sedation 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, hypercarbia, 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). Oxymorphone, this or 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 persistent throughout the period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines.)

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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 WARNINGS: 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 because 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% ethanol. 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 an abuse liability 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. Preoccupation with achieving adequate pain relief can be an 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. Tolerance, an 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 psychotropic 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 encouraged.
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 relapse 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 appropriate and measures that help to limit abuse of opioid drugs.
Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms (see PRECAUTIONS: Usage, Pregnancy and PRECAUTIONS: Labor and Delivery).

Respiratory Depression: Respiratory depression is the chief hazard of OPANA ER. Respiratory depression is a life-threatening 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 such as: asthma, chronic obstructive pulmonary disease, or pulmonary, severe obesity, sleep apnea syndrome, myxedema, hypokalemia, CNS depression or coma. In these patients, even usual therapeutic doses in the moderate and severe respiratory depression may be markedly exaggerated. Furthermore, opioid analgesics can produce effects on pupillary response and consciousness, which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.
Hypotensive Effect: OPANA ER, like all opioid analgesics, may cause severe hypotension in a patient with hypovolemia. The hypotensive effect has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. OPANA ER, like all opioid analgesics, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

Hepatic Impairment: A study of OPANA ER in patients with hepatic disease indicated greater plasma concentrations than those with normal hepatic function (see CLINICAL PHARMACOLOGY). OPANA ER should be used with caution in patients with mild to moderate hepatic impairment (see CONTRAINDICATIONS, WARNINGS, and DOSAGE AND ADMINISTRATION).
PRECAUTIONS
General: Opioid analgesics should be used with caution especially when combined with other drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known potential risks of respiratory depression, altered mental state and postural hypotension. OPANA 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/hypokalemia 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 convulsions in some clinical settings.
OPANA ER is intended for use in patients who require more than several days continuous treatment with an opioid analgesic.
Amputation Surgery and Post-Operative Use: OPANA ER is not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative pain).
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 over-sedation 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.
OPANA ER is only indicated for postoperative use in the patient if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persistent throughout an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate (See American Pain Society guidelines).
Patients who are already receiving OPANA ER as part of ongoing analgesic therapy may be safely continued on the drug if appropriate dosage adjustments are made considering the procedure, the drug used, and the patient's clinical and physiologic response to the surgical intervention (see DOSAGE AND ADMINISTRATION).
OPANA ER, like other opioids, decreases bowel motility. Ileus is a common post-operative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in post-operative patients receiving opioids. Standard supportive therapy should be implemented.
Use in Pancreatic/Biliary Tract Disease: OPANA ER, like other opioids, may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis.

Physical Dependence and Tolerance: Physical dependence is the occurrence of withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an opioid antagonist or mixed opioid agonist/antagonist agent. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). The development of physical dependence and tolerance is not unusual during chronic opioid therapy.
If OPANA ER is abruptly discontinued in a physically-dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including: irritability, anxiety, pain, aches, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.
In general, OPANA ER should not be abruptly discontinued. However, OPANA ER, like other opioids, can be safely discontinued without the development of withdrawal symptoms by slowly tapering the daily dose (see DOSAGE AND ADMINISTRATION: Cessation of Therapy).
Information for Patients/Caregivers: (See full prescribing information for details on information for patients).
Use in Drug and Alcohol Addiction: OPANA ER is not approved for use in detoxification or maintenance treatment of opioid addiction. However, the history of an addictive disorder does not necessarily preclude the use of this medication for the treatment of chronic pain. These patients will require intensive monitoring for signs of misuse, abuse, or addiction.

Drug-Drug Interactions: Oxymorphone is highly metabolized principally in the liver and undergoes reduction or conjugation with glucuronic acid to form inactive metabolites. (See PHARMACOKINETICS: Metabolism).
Use with CNS Depressants: The concomitant use of other CNS depressants including sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, and tranquilizers, may produce additive CNS depressant effects. OPANA ER, like all opioid analgesics, should be started at 1/3 to 1/2 of the usual dose in patients who are concurrently receiving other central nervous system depressants including sedatives and hypnotics, general anesthetics, phenothiazines, tranquilizers, and alcohol because respiratory depression, hypotension, and profound sedation or coma may result. Additive effects resulting in respiratory depression, hypotension, profound sedation or coma may result. Additive effects resulting in respiratory depression, hypotension, profound sedation or coma may result if these drugs are taken in combination with the usual doses of OPANA ER. No specific interaction between oxymorphone and monoamine oxidase inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.
When combined therapy with any of the above medications is contemplated, the dose of one or both agents should be reduced (see WARNINGS and DOSAGE AND ADMINISTRATION).
Interactions with Mixed Agonist/Antagonist Opioid Analgesics: Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol, or buprenorphine) should not be administered to patients who have received or are receiving a course of therapy with a pure opioid agonist analgesic, such as OPANA ER. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of OPANA ER and/or may precipitate withdrawal symptoms.
Other: Anticholinergics or other medications with anticholinergic activity when used concurrently with opioid analgesics may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
In addition, CNS side effects have been reported (confusion, disorientation, respiratory depression, apnea, seizures) following coadministration of cimetidine with opioid analgesics; no clear-cut cause and effect relationship was established.

Mutagenesis: Oxymorphone hydrochloride was not mutagenic when tested in the *in vitro* bacterial reverse mutation assay (Ames test) at concentrations of $\leq 5270 \mu\text{g}/\text{plate}$, or in an *in vitro* mammalian cell chromosome aberration assay performed with human peripheral blood lymphocytes at concentrations $\leq 5000 \mu\text{g}/\text{ml}$ 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 fetal development. The use of OPANA ER in pregnancy, in nursing mothers, or in women of child-bearing potential requires that the benefits of this 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 doses evaluated during developmental toxicity studies in rats ($\leq 25 \text{ mg}/\text{kg}/\text{day}$) or rabbits ($\leq 50 \text{ mg}/\text{kg}/\text{day}$). 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 pathway study resulted in a mean litter size (85%) at a dose of 25 mg/kg/day, attributed to an increased incidence of stillborn pups. An increase in neonatal death occurred at $\geq 5 \text{ mg}/\text{kg}/\text{day}$. Post-natal survival of the pups was reduced throughout weaning following treatment of the dams with 25 mg/kg/day. Low pup birth weight and decreased postnatal weight gain occurred in pups born to oxymorphone-treated female rats given a dose of 25 mg/kg/day. This dose is $\sim 3\text{-}4$ times the maximum recommended 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. Supportive therapy should be implemented.
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.

Adverse Reactions Reported in Placebo-Controlled Trials: The following table lists adverse reactions that were reported in at least 2% of patients in placebo-controlled trials (N=5).
Adverse Reactions Reported in Placebo-Controlled Clinical Trials with Incidence $\geq 2\%$ in Patients Receiving OPANA ER.

MedDRA Preferred Term	OPANA ER (N=1259)	Placebo (N=461)
Nausea	27.6%	13.2%
Constipation	27.6%	13.2%
Dizziness (Excit Vertigo)	17.8%	7.6%
Somnolence	17.2%	2.2%
Vomiting	15.6%	4.1%
Pruritus	15.2%	7.6%
Headache	12.2%	5.6%
Sweating increased	8.6%	8.7%
Dry mouth	6.4%	0.7%
Sedation	5.9%	7.6%
Diarrhea	4.3%	5.6%
Insomnia	4.0%	2.0%
Fatigue	3.9%	1.3%
Appetite decreased	2.9%	4.4%
Abdominal pain	2.5%	1.5%

Adverse Reactions Reported in All Clinical Trials: A total of 2011 patients were treated with OPANA ER in Phase 2/3 controlled and open-label clinical trials. The clinical trials consisted of patients with moderate to severe chronic pain and post surgical pain.
The adverse reactions are presented in the following manner: most common, common, and less common adverse reactions.

The most common adverse drug reactions ($\geq 10\%$) reported at least once by patients treated with OPANA ER in the clinical trials organized by MedDRA (Medical Dictionary for Regulatory Activities) System Organ Class were:

CNS disorders: somnolence, dizziness increased, and sedation.
The common ($\geq 1\%$ - $<10\%$) adverse drug reactions reported at least once by patients treated with OPANA ER in the clinical trials organized by MedDRA (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 include 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, hallucination, hot flashes, hypersensitivity, hypotension, hypoxia, ileus, mental impairment, mental status changes, miosis, oxygen saturation decreased, palpitation, postural hypotension, respiratory depression, respiratory distress, respiratory rate increased, syncope, tachycardia, urinary retention, urticaria, and visual disturbances.

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

OPANA ER is a specific antidote to respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.
Specific Antidote: A specific antidote to respiratory depression which may result from overdosage or unusual sensitivity to opioids including OPANA ER. Therefore, an appropriate dose of naloxone hydrochloride should be administered (usual initial adult dose 0.4 mg/2 mg) preferably by the intravenous route and simultaneously with efforts at respiratory resuscitation. Nalmefene is an alternative pure opioid antagonist, which may be used for the management of hypoxia in 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.

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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 cautiously with lower doses of OPANA ER and titrated slowly while carefully monitored for side effects (see DOSAGE AND ADMINISTRATION).
Gender Differences: When normalized for body weight, gender differences were not observed (see CLINICAL PHARMACOLOGY). In clinical studies, the overall incidence rates for one or more adverse events were slightly higher among females than males for both OPANA ER subjects and placebo subjects.

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Headache	12.2%	5.6%
Sweating increased	8.6%	8.7%
Dry mouth	6.4%	0.7%
Sedation	5.9%	7.6%
Diarrhea	4.3%	5.6%
Insomnia	4.0%	2.0%
Fatigue	3.9%	1.3%
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Abdominal pain	2.5%	1.5%

Adverse Reactions Reported in All Clinical Trials: A total of 2011 patients were treated with OPANA ER in Phase 2/3 controlled and open-label clinical trials. The clinical trials consisted of patients with moderate to severe chronic pain and post surgical pain.
The adverse reactions are presented in the following manner: most common, common, and less common adverse reactions.