

Hyperandrogenism Seen as Central Part of PCOS

BY KATE JOHNSON
Montreal Bureau

Polycystic ovary syndrome is primarily a disorder of hyperandrogenism—either biochemical or clinical, or both, according to a newly released position statement from the Androgen Excess Society.

“Overall, ... women with oligomenorrhea and polycystic-appearing ovaries on ultrasonography but no evidence of hy-

perandrogenism do not have PCOS,” wrote the society’s seven-person task force of international experts (J. Clin. Endocrinol. Metab. [Epub doi:10.1210/jc.2006-0178]).

The task force also acknowledged a minority opinion that there may possibly be forms of polycystic ovary syndrome (PCOS) “without overt evidence of hyperandrogenism,” although “more data are required before validating this supposition.”

A diagnosis of hyperandrogenism can be made biochemically by the confirma-

tion of elevated circulating androgens or clinically with the observation of hirsutism, according to Dr. Ricardo Azziz, who chaired the Androgen Excess Society (AES) task force.

“People ... often rely heavily on biochemical androgen levels, which is a mistake because it can leave out those patients with hirsutism but normal androgen levels. You have to look at the clinical picture as well,” he said in an interview.

The AES position statement, produced

after a systematic review of 527 published, peer-reviewed medical articles, is aimed at establishing an evidence-based definition of PCOS, said Dr. Azziz, director of the Center for Androgen-Related Disorders and professor and chair of obstetrics and gynecology at Cedars-Sinai Medical Center at the University of California, Los Angeles.

The position statement stipulates that all three of the following criteria must be present for a diagnosis of PCOS:

Continued on following page

OPANA® (Oxymorphone Hydrochloride)

Tablets

5 mg and 10 mg

Rx only
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 or 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 increase 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 Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

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

Drug Abuse and Addiction
Controlled Substance

OPANA 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. 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 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, proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

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

Interactions with Other Central Nervous System Depressants

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

Head Injury and Increased Intracranial Pressure

In the presence of head injury, intracranial lesion, 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 when combined with other drugs, because of their potential to cause respiratory depression, altered mental state and postural hypotension. OPANA should be used with caution in elderly and debilitated patients and in patients who are 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 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 physiologically 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 highly metabolized principally in the liver and undergoes reduction or conjugation with glucuronic acid to form both active and inactive products (see **CLINICAL PHARMACOLOGY and PHARMACOKINETICS: Metabolism**).

Use with CNS Depressants

The concomitant use of other CNS depressants including sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and alcohol may produce additive CNS depressant effects. OPANA, 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 may be enhanced 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 $\mu\text{g}/\text{plate}$, or in an *in vitro* mammalian cell chromosome aberration assay performed with human peripheral blood lymphocytes at concentrations ≤ 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.

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 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 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, diarrhea, 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 overdosage 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 overdosage, 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 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 overdosage 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 overdosage or unusual sensitivity to opioids including OPANA. Therefore, an appropriate dose of naloxone hydrochloride should be administered (usual initial adult dose 0.4-2 mg) preferably by the intravenous route and simultaneously with efforts to improve respiratory status. Nalmefene is an alternative pure opioid antagonist, which may be administered as a specific antidote to respiratory depression resulting from opioid overdosage. 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, abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. In an individual physically dependent on opioids, administration of the usual dose of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. If respiratory depression is associated with muscular rigidity, administration of a neuromuscular blocking agent may be necessary to facilitate assisted or controlled ventilation. Muscular rigidity may also respond to opioid antagonist therapy.

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 light container as defined in the USP, with a child-resistant closure (as required).

Rx Only
DEA Order Form Required.
Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, Pennsylvania 19317

Manufactured by:
Novartis Consumer Health Inc.
Lincoln, NE 68517
Copyright © Endo Pharmaceuticals Inc. 2006
413242 E1/Rev. July, 2006

Current Definitions of PCOS Differ

NIH Criteria (1990)

Should include:

Hyperandrogenism, biochemical or clinical

Oligo-ovulation

Exclusion of other known disorders

Rotterdam Criteria (2003)

Should include at least two:

Clinical and/or biochemical signs of hyperandrogenism

Oligo-ovulation and/or anovulation

Polycystic ovaries

AES Statement (2006)

Should include:

Hyperandrogenism, either biochemical or clinical or both

Oligo-ovulation or polycystic ovaries or both

Exclusion of other androgen excess disorders

Source: Journal of Clinical Endocrinology and Metabolism

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 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 pain 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 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 pain analgesic.

OPANA ER is not indicated for pain in the immediate post-operative period (the first 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 to 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 if the pain is mild, 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 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, crushed or dissolved 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 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 200% 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 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 to appropriate medical care, or persistent requests for a prescription, 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 pain.

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 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 appropriate measures that help to limit abuse of opioid drugs.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms (see PRECAUTIONS: Usage in 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 such as: asthma, chronic obstructive pulmonary disease, or pulmonary edema; 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 maintaining a sufficient level of analgesia 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 doses.

Interactions with Other Central Nervous System Depressants: Patients receiving other opioid analgesics, general anesthetics, phenothiazines or other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with oxymorphone may experience respiratory depression, hypotension, profound sedation, or coma (see PRECAUTIONS: Drug-Drug Interactions).

Head Injury and Increased Intracranial Pressure: 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 ER, like all opioid analgesics, may cause severe hypotension in an individual whose ability to maintain blood pressure 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; 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, clinical course in patients with acute abdominal conditions. Oxymorphone may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.

OPANA ER is intended for use in patients who require more than several days continuous treatment with an opioid analgesic.

Ambulatory Surgery and Post-Operative Use: OPANA ER is not indicated for pre-emptive analgesia (administration of the 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 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.

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 persist for 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, other drugs given, and the temporary changes in physiology caused by 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 analgesics. Care 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 the syndrome: runny nose, 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, tremor, and 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 diversion.

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

Use with CNS Depressants: The concomitant use of other CNS depressants including sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and alcohol may produce additive 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 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 (e.g., buprenorphine, butorphanol, buprenorphine/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) and opioid analgesics may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

Carcinogenesis, Mutagenesis, Impairment of Fertility: (See Preclinical Studies.) 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 $\mu\text{g}/\text{plate}$, or in an *in vitro* mammalian cell chromosome aberration assay

performed with human peripheral blood lymphocytes at concentrations ≤ 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 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 ≥ 25 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 ~ 3 -fold higher than 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 nalmeftone, 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 infant.

Geriatric 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. The plasma levels of 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 effectiveness were observed between these subjects and younger subjects. There were, however, adverse events that were more frequently observed in subjects 65 and over compared to younger subjects. These adverse events included dizziness, nausea, and vomiting.

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 impairment. These patients should be started with the lowest dose and titrated slowly while carefully 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 (creatinine clearance ≤ 30 mL/min) showed no 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 monitoring 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.

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 (N=5)

Adverse Reactions Reported in Placebo-Controlled Clinical Trials (Intention-to-Treat): Patients Receiving OPANA ER.

Term	OPANA ER (N=1259)	Placebo (N=461)
Nausea	27.8%	13.2%
Dizziness (Exc Vertigo)	17.8%	7.6%
Somnolence	17.2%	2.2%
Vomiting	15.6%	4.1%
Pruritus	14.2%	7.6%
Headache	12.2%	5.6%
Sweating increased	8.6%	8.7%
Dry mouth	6.4%	0.7%
Diarrhea	6.4%	2.9%
Insomnia	4.3%	2.0%
Fatigue	3.9%	1.3%
Appetite decreased	2.9%	0.4%
Abdominal pain	2.8%	1.5%

Adverse Reactions Reported in All Clinical Trials: A total of 2011 patients were treated with OPANA ER in the 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.

Continued from previous page

► Hyperandrogenism—either biochemical or clinical, or both.

► Oligo-ovulation or polycystic ovaries, or both.

► Exclusion of other androgen excess disorders.

The two definitions that are currently used were established by expert panels—the first at the National Institutes of Health in 1990 and the second, in Rotterdam in 2003. They differ markedly on the necessity of hyperandrogenism for diagnosing PCOS and the relevance of an ultrasound finding of polycystic ovaries. (See box.)

The AES statement is a combination and clarification of the NIH and Rotterdam definitions and the first definition to come out of a review of evidence-based data, Dr. Aziz said. "With this definition, we capture what we think is the majority of patients with PCOS. It is broader than the NIH criteria but doesn't capture as much as the Rotterdam criteria, which were overly broad and resulted in the diagnosis of PCOS in women who simply had irregular ovulation and polycystic-looking ovaries. There may still be a few patients who may not be captured by this definition who in the future may be identified by new tests."

Another important aspect of the statement is its de-emphasis of ultrasound findings in the diagnosis, said Dr. Neil Goodman, a reproductive endocrinologist in private practice in Miami and professor of medicine at the University of Miami. "Up to 20% of women with regular cycles, no hirsutism, and no evidence of androgen excess can have a polycystic ovary appearance on ultrasound," said Dr. Goodman, who is chair of the American Association of Clinical Endocrinologists' task force on hyperandrogenic disorders and was not involved with the AES task force. "We need to document hyperandrogenism before we diagnose PCOS."

Race, Ethnicity Influence Heart Risks in PCOS

RANCHO MIRAGE, CALIF. — Cardiovascular risk factors varied considerably by race and ethnicity in women with polycystic ovary syndrome in a large study presented by Dr. Seth L. Feigenbaum at the annual meeting of the Pacific Coast Reproductive Society.

Dr. Feigenbaum, a reproductive endocrinologist in the San Francisco office of the Permanente Medical Group, and associates at the Kaiser Permanente Health Plan of Northern California compared 6,671 women aged 16-44 years who were diagnosed with polycystic ovary syndrome (PCOS) with 26,662 age-matched women in terms of three cardiovascular risk factors: obesity, diabetes, and hypertension.

Two-thirds of women with a diagnosis of PCOS were obese (a body mass index of 30 kg/m² or greater), compared with one-third of the age-matched controls. Compared with white women, black and Hispanic women with PCOS were significantly more likely, and Asian women were significantly less likely, to be obese.

Blacks were far more likely than Asians or Hispanics, and somewhat more likely than whites, to be hypertensive. Diabetes was most prevalent in Asians and Hispanics, followed by whites, then blacks. A multivariate regression analysis adjusting for variables showed distinct patterns:

- Asians had a twofold increased risk of diabetes, compared with whites.
- Blacks, by an odds ratio of 1.32, were considerably more likely than whites to have hypertension.
- Hispanics had higher rates of diabetes, but lower rates of hypertension than whites (OR 1.33 and 0.68, respectively).

—Betsy Bates

ELSEVIER GLOBAL MEDICAL NEWS