PRODUCT MONOGRAPH

^{N}OPANA®ER

Oxymorphone Hydrochloride Extended Release Tablets
5 mg, 10 mg, 20 mg, and 40 mg

Opioid Analgesic

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
Oral	Extended release tablets: 5 mg, 10 mg, 20 mg, and 40 mg	calcium sulfate dihydrate, D&C Yellow No. 10 (20 mg, 40 mg), dextrose monohydrate, ethylcellulose, FD&C Blue No. 1 (20 mg), FD&C Yellow No. 6 (10 mg, 20 mg, 40 mg), hypromellose, iron oxide red (5 mg), lactose (40 mg), locust (carob) bean gum, microcrystalline cellulose, polyethylene glycol, polysorbate 80 (5 mg, 10 mg, 20 mg), silicon dioxide, sodium stearyl fumarate, titanium dioxide, triacetate (40 mg), triacetin, xanthan gum.

INDICATIONS AND CLINICAL USE

Adults

OPANA ER (oxymorphone hydrochloride extended release tablets) is indicated for the management of pain severe enough to require daily, continuous, long-term opioid treatment, and:

- that is opioid-responsive; and,
- for which alternative treatment options are inadequate.

OPANA ER is not indicated as an as-needed (prn) analgesic.

Geriatrics (≥ 65 years of age)
In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or other drug therapy.

Pediatrics (< 18 years of age)
The safety and efficacy of OPANA ER has not been studied in the pediatric population. Therefore, the use of OPANA ER is not recommended in patients under 18 years of age.

CONTRAINDICATIONS

OPANA ER (oxymorphone hydrochloride extended release tablets) is contraindicated in:

- Patients who are hypersensitive to this drug, to any ingredient in the formulation or component of the container, or with known hypersensitivity to morphine analogs such as codeine. For a complete listing of excipients, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.
- Patients who have had surgical procedures and/or underlying disease that may result in narrowing of the gastrointestinal tract, or have "blind loops" of the gastrointestinal tract or gastrointestinal obstruction.
- Patients who have ileus of any type.
- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis).
- Patients with mild, intermittent or short duration pain that can otherwise be managed.
- The management of acute pain.
- The management of perioperative pain.
- Patients with acute asthma or other obstructive airway, and status asthmaticus.
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood, and cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).
- Patients who consume alcohol, or any medications containing alcohol
- Patients with moderate or severe hepatic impairment (see **ACTION AND CLINICAL PHARMACOLOGY, WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).
- Women who are breast-feeding, pregnant, or during labour and delivery

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

Limitations of Use
Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, OPANA ER should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics), or would be otherwise inadequate to provide sufficient management of pain (e.g., immediate-release opioids) (see DOSAGE AND ADMINISTRATION).

Addiction, Abuse, and Misuse
OPANA ER poses risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Each patient's risk should be assessed prior to prescribing OPANA ER, and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS). OPANA ER should be stored securely to avoid theft or misuse.

Life-threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of OPANA ER. Patients should be monitored for respiratory depression, especially during initiation of OPANA ER or following a dose increase. OPANA ER should be swallowed whole; crushing, chewing, or dissolving OPANA ER Extended Release Tablets can cause rapid release and absorption of a potentially fatal dose of Oxymorphone Hydrochloride (see WARNINGS AND PRECAUTIONS).

Accidental Exposure
Accidental consumption of even one dose of OPANA ER, especially by children, can result in a fatal overdose of (Oxymorphone Hydrochloride) (see DOSAGE AND ADMINISTRATION subsection Disposal, for instructions on proper disposal).

Neonatal Opioid Withdrawal Syndrome
Prolonged maternal use of OPANA ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see WARNINGS AND PRECAUTIONS).

Interaction with Alcohol
The co-ingestion of alcohol with OPANA ER may result in increased plasma levels and a potentially fatal overdose of Oxymorphone Hydrochloride (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

OPANA ER MUST be administered on an empty stomach, at least one hour prior to or two hours after eating. The co-ingestion of food with OPANA ER may result in increased plasma levels and a potential overdose of oxymorphone (see **ACTION AND CLINICAL PHARMACOLOGY**: **Pharmacokinetics: Food Effect**).

General

Patients who have received **OPANA ER** should be closely monitored, especially for signs of respiratory depression, until a stable maintenance dose is reached.

Tablet strengths of 20 mg or higher are only for opioid tolerant patients requiring oxymorphone equivalent dosages of 20 mg or higher per day. A single dose of 20 mg or higher may lead to severe medical consequences, including fatal respiratory depression, in patients not previously exposed to similar daily doses of opioids at the time of starting or switching to OPANA ER (see **DOSAGE AND ADMINISTRATION)**.

Addiction, Abuse and Misuse

OPANA ER tablets are a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, OPANA ER should be prescribed and handled with caution. This risk is increased when the tablet is crushed, broken, or chewed, and with concurrent consumption of alcohol or other CNS depressants. With abuse by parenteral route, the tablet contents may cause lethal complications. OPANA ER tablets are intended for oral use only.

Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse and abuse.

Opioids, such as OPANA ER, should be used with particular care in patients with a history of alcohol and illicit/prescription drug abuse. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

Patients must be instructed NOT to give OPANA ER to anyone else. Diversion will have serious medical consequences, including death.

Dependence/Tolerance – Withdrawal Syndrome

OPANA ER contains oxymorphone, a strong opioid. As with other opioids, tolerance and physical dependence may develop upon repeated administration of OPANA ER and there is a potential for development of psychological dependence.

Physical dependence and tolerance reflect the neuro-adaptation of the opiate receptors to chronic exposure to an opiate, and are separate and distinct from abuse and addiction. Tolerance, as well as physical dependence, may develop upon repeated administration of opioids, and are not by themselves evidence of an addictive disorder or abuse.

Patients on prolonged therapy should be tapered gradually from the drug if it is no longer required for pain control. Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist.

Physical dependence is a state of adaptation that is manifested by an opioid-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist. The opioid abstinence or withdrawal syndrome is characterized by some

or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, piloerection, myalgia, mydriasis, irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate. In general, opioids should not be abruptly discontinued (see **DOSAGE AND ADMINISTRATION, Cessation of Therapy**).

Cardiovascular

Hypotensive Effect: OPANA ER, 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. Like all opioid analgesics, OPANA ER should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

Gastrointestinal

Constipation: Constipation is a frequent side effect reported with opioid treatment. Patients should be advised on measures to prevent constipation and prophylactic laxative use should be considered. Extra caution should be used in patients with chronic constipation.

Acute Abdominal Conditions: The administration of opioids may obscure the diagnosis or clinical course of acute abdominal conditions. Therefore, it is important to make sure that the patient is not suffering from intestinal occlusion, including ileus, before initiation of treatment.

Endocrine and Metabolism

OPANA ER should be administered with caution and in reduced dosages in patients with adrenocortical insufficiency, myxedema, and hypothyroidism.

Genitourinary

OPANA ER, like all opioid analgesics, should be administered with caution and in reduced dosages in patients with prostatic hypertrophy or urethral stricture.

Hepatic/Biliary/Pancreatic

OPANA ER should be used with caution in patients with mild hepatic 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 or severe hepatic impairment (see **CONTRAINDICATIONS**, and **DOSAGE AND ADMINISTRATION**).

OPANA ER, like other opioids, may cause spasm of the sphincter of Oddi and should be used with caution in patients with inflammatory or obstructive bowel disorders, or acute pancreatitis secondary to biliary tract disease, and in patients about to undergo biliary surgery.

Neurologic

Interactions with Central Nervous System Depressants (Including Alcohol):
OPANA ER should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics, general anesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, benzodiazepines, centrally-active anti-emetics and other CNS depressants including alcohol. Respiratory depression, hypotension and profound sedation, coma or death may result. When such combination therapy is contemplated, a substantial reduction in the dose of one or both agents should be considered and patients should be carefully monitored (see DRUG INTERACTIONS).

Head Injury and Increased Intracranial Pressure: In the presence of head injury, intracranial lesions or a pre-existing increase in intracranial pressure, the possible respiratory depressant effects of opioid analgesics and their potential to elevate cerebrospinal fluid pressure (resulting from vasodilation following CO_2 retention) may be markedly exaggerated. Furthermore, opioid analgesics can produce effects on pupillary response and consciousness, which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries. OPANA ER is contraindicated in patients with increased cerebrospinal or intracranial pressure, and head injury (see **CONTRAINDICATIONS**).

Psychomotor Impairment: Oxymorphone may impair mental and/or physical ability required for the performance of potentially hazardous tasks such as driving a car or operating machinery. This is particularly likely at the start of therapy or following an increase in dose. Patients should be advised not to drive a car or operate machinery unless they are tolerant to the effects of OPANA ER.

Perioperative Considerations
OPANA ER is contraindicated for perioperative pain relief. In the case of planned chordotomy or other pain-relieving operations, patients should not be treated with OPANA ER within 24 hours before or after the operation. Thereafter, if OPANA ER is to be continued after the patient recovers from the postoperative period, a new dosage should be administered in accordance with the changed need for pain relief. The risk of withdrawal in opioid-tolerant patients should be addressed as clinically indicated (see **DOSAGE AND ADMINISTRATION**, **Cessation of Therapy**).

The administration of analgesics in the perioperative period should be managed by health care providers with adequate training and experience (e.g., by an anesthesiologist).

Neonatal Opioid Withdrawal Syndrome (NOWS)
Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

Use of OPANA ER is contraindicated in pregnant women (see **CONTRAINDICATIONS**).

Renal

There are 57% and 65% increases in oxymorphone bioavailability in patients with moderate and severe renal impairment, respectively. Patients with moderate renal insufficiency (creatinine clearance rate less than 50 mL/min.) should be started on a reduced OPANA ER dose and closely monitored during dose titration. In patients with severe renal insufficiency, an increased dosing interval should also be considered and these patients should, in addition, be monitored during maintenance therapy for development of opioid-related adverse reactions (see **DOSAGE AND ADMINISTRATION).**

Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of OPANA ER, the risk is greatest during the initiation of therapy or following a dose increase. Patients should be closely monitored for respiratory depression when initiating therapy with OPANA ER and following dose increases.

To reduce the risk of respiratory depression, proper dosing and titration of OPANA ER are essential (see DOSAGE AND ADMINISTRATION). Overestimating the OPANA ER dose when converting patients from another opioid product can result in fatal overdose with the first dose.

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 (COPD) or corpulmonale, 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.

Severe pain antagonizes the respiratory-depressant effects of opioids. However, should pain suddenly subside, these effects may rapidly become manifest. Patients who are scheduled for regional anesthetic procedures or other interruptions of pain transmission pathways should not receive OPANA ER within 24 hours of the procedure. Concomitant administration of oxymorphone with other opioid analgesics is associated with an increased risk of respiratory failure. Therefore, it is important to reduce the dose of oxymorphone when other opioid analgesics are given concomitantly.

Use in Drug and Alcohol Addiction

OPANA ER has no approved use in the management of addictive disorders.

Patient Counseling Information

A patient information sheet is included in the package of OPANA ER tablets dispensed to the patient.

Patients receiving OPANA ER should be given the following instructions by the physician:

1. **OPANA ER should be administered on an empty stomach, at least one hour prior to or two hours after eating. The co-ingestion of food with OPANA ER may result in increased plasma levels and a potential overdose of oxymorphone.**

2. **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.**

3 Patients should be informed that accidental ingestion or use by individuals (including children) other than the patient for whom it was originally prescribed, may lead to severe, even fatal, consequences.

4 Patients should be advised that OPANA ER contains oxymorphone, an opioid pain medicine.

5 Patients should be advised that OPANA ER should only be taken as directed. The dose of OPANA ER should not be adjusted without consulting with a physician.

6 OPANA ER should be swallowed whole (not crushed and swallowed or snorted, dissolved, broken, divided, sucked or chewed) due to a risk of fatal oxymorphone overdose.

7 Patients should not combine OPANA ER with central nervous system depressants (sleep aids, tranquilizers) because dangerous additive effects may occur resulting in serious injury or death.

8 Patients should be advised to consult their physician or pharmacist if other medications are being used or will be used with OPANA ER.

9 Patients should be advised that if they have been receiving treatment with OPANA ER and cessation of therapy is indicated, it may be appropriate to taper the OPANA ER dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms.

10 Patients should be advised of the most common adverse reactions that may occur while taking OPANA ER: nausea, constipation, dizziness, vomiting, somnolence, and pruritus.

11 Patients should be advised that OPANA ER may cause drowsiness, dizziness, or lightheadedness and may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery). Patients started on OPANA ER or patients whose dose has been adjusted should be advised not to drive a car or operate machinery unless they are tolerant to the effects of OPANA ER.

12 As with other opioids, patients taking OPANA ER should be advised of the potential for constipation; patients should be advised on measures to prevent constipation and prophylactic

laxative use should be considered.

13 Patients should be advised that OPANA ER is a potential drug of abuse. They should protect it from theft or misuse.

14 Patients should be advised that OPANA ER should never be given to anyone other than the individual for whom it was prescribed.

15. Patients should be advised that OPANA ER 20 mg or higher is for use only in opioid tolerant patients.

Special Populations

Pregnant Women: OPANA ER is contraindicated during pregnancy, labour and delivery due to impaired uterine contractility and the risk of neonatal respiratory depression. No clinical data on pregnant women exposed to OPANA ER are available. The potential teratogenic risk for humans from the use of oxymorphone and other opiates during pregnancy is unknown.

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening (see WARNINGS AND PRECAUTIONS – NEONATAL OPIOID WITHDRAWAL SYNDROME).

Use of OPANA ER is contraindicated in pregnant women (see CONTRAINDICATIONS).

Nursing Women: It is not known whether oxymorphone is excreted in human milk. Since many drugs, including some opioids, are excreted in human milk, OPANA ER is contraindicated during breastfeeding.

Pediatrics (under 18 years of age): The safety and efficacy of OPANA ER has not been studied in the pediatric population. Therefore, the use of OPANA ER is not recommended in patients under 18 years of age.

Geriatrics (≥ 65 years of age): In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or other drug therapy. The elderly are more prone to central nervous system (CNS) adverse effects, gastrointestinal disturbances. Concomitant use of other medications, especially tricyclic antidepressants, increases the risk of confusion and constipation. Diseases of the prostate gland and the urinary tract are often seen in the elderly. This contributes to the increased risk of urinary retention. (see **CLINICAL PHARMACOLOGY- DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most serious adverse reaction associated with opioid therapy is respiratory depression. Use of an opioid dose that is higher than the opioid tolerance level of the patient may lead to fatal respiratory depression. Respiratory depression due to overexposure may be more likely in certain subgroups of

patients, such as in the elderly, in the debilitated, and in those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate doses may lead to fatal respiratory depression (see **WARNINGS AND PRECAUTIONS).**

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

As expected, the most frequently occurring AEs in clinical trials were those typically associated with opioids: nausea, constipation, dizziness (excluding vertigo), vomiting, somnolence, and pruritus NOS (not otherwise specified).

A total of 2,011 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.

Three pivotal double-blind, placebo-controlled studies were conducted to support the efficacy and dosing recommendations for OPANA ER in patients who had moderate to severe osteoarthritis or chronic lower back pain. Table 1 captures all treatment-emergent adverse events (incidence > 2%) in patients who were exposed to OPANA ER or placebo (regardless of causality) in the pivotal clinical studies.

Table 1: Adverse Reactions Reported in the Placebo-Controlled Pivotal Clinical Trials with Incidence ≥2%, Regardless of Causality in Patients Receiving OPANA ER.

MedDRA Preferred Term	OPANA ER (N=1259)	Placebo (n=461)
Nausea	33%	13%
Constipation	28%	13%
Dizziness (excl Vertigo)	18%	8%
Somnolence	17%	2%
Vomiting	16%	4%
Pruritus	15%	8%
Headache	12%	6%
Sweating increased	9%	9%
Dry mouth	6%	< 1%
Sedation	6%	8%
Diarrhea	4%	6%
Insomnia	4%	2%
Fatigue	4%	1%
Appetite decreased	3%	< 1%
Abdominal pain	3%	2%

The **common** (≥1% to <10%) adverse drug reactions reported at least once by patients treated with oxymorphone hydrochloride extended-release tablets in the clinical trials organized by MedDRA's (Medical Dictionary for Regulatory Activities) System Organ Class and not represented in Table 1:

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 oxymorphone hydrochloride extended-release tablets trials include the following:

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

Post-Market Adverse Drug Reactions
The post-marketing experience in the United States with OPANA (immediate release oxymorphone hydrochloride tablets not marketed in Canada) and OPANA ER has included events that coincide with the adverse event profiles identified in the clinical studies. A comprehensive and proactive surveillance program has not detected any areas of sustained signal activity when the drug is used as prescribed.

Recently, cases of death due to product abuse have been reported in the United States.

DRUG INTERACTIONS

Overview
Oxymorphone is highly metabolized, principally in the liver, and undergoes reduction or conjugation with glucuronic acid to form both active and inactive metabolites. Clinical drug interaction studies with OPANA ER showed no induction of CYP450 3A4 or 2C9 enzyme activity, indicating that no dose adjustment for CYP 3A4- or 2C9-mediated drug-drug interactions, is required. (see **ACTION AND CLINICAL PHARMACOLOGY** and **PHARMACOKINETICS: Metabolism**).

Drug-Drug Interactions

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 ER (oxymorphone hydrochloride extended release tablets), 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, and titrated slowly as necessary for adequate pain relief, because additive effects resulting in respiratory depression, hypotension, and profound sedation or coma may result (see **WARNINGS** and **DOSAGE AND ADMINISTRATION**.

OPANA ER, like other opioids, may enhance the neuromuscular blocking action of muscle relaxants and may cause an increased degree of respiratory depression.

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.

Monoamine oxidase inhibitors
Monoamine oxidase inhibitors (MAOIs) may cause CNS excitation or depression, hypotension or hypertension if co-administered with opioids. OPANA ER is contraindicated in patients taking MAOIs or within 14 days of stopping such treatment. MAO inhibitors (including procarbazine) should not be taken within two weeks of using OPANA ER.

Alcohol Interaction Studies
The results obtained from *in vitro* and *in vivo* studies, conclude that there is an interaction between ethanol and oxymorphone hydrochloride extended release tablets, when the two are coadministered. This interaction is manifested as an ethanol dose-related increase in peak plasma concentration (Cmax). Co-administration of OPANA ER 40 mg tablet with 240 mL of 40% ethanol resulted in a 1.7-fold increase in C_{max} on average and up to a 2.7-fold increase in individual subjects. In this study, the extent of absorption (AUC) was essentially unaffected in subjects following the co-administration of OPANA ER and ethanol (240 mL of 40%, 20% or 4% ethanol). (see **ACTION AND CLINICAL PHARMACOLOGY**; **Pharmacokinetics – Ethanol Effect**).

In addition to the pharmacokinetic interaction described above, oxymorphone may also be expected to have additive effects when used in conjunction with alcohol, due to central nervous system depression and the potential for developing respiratory depression, hypotension, profound sedation or coma.

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 (see CONTRAINDICATIONS)

<u>Drug-Food Interactions</u>

Two studies examined the effect of food on the bioavailability of single doses of 20 and 40 mg of OPANA ER in healthy volunteers. The administration of OPANA ER 20 and 40 mg tablets with food resulted in a 1.6-fold and 1.5-fold increase in peak oxymorphone plasma concentration (Cmax) respectively. As a result, OPANA ER should be dosed at least one hour prior to or two hours after eating (see **DOSAGE AND ADMINISTRATION**).

Cimetidine
CNS side effects have been reported (e.g., confusion, disorientation, respiratory depression, apnea, seizures) following co-administration of cimetidine with opioid analgesics; a causal relationship has not been established.

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.

No inhibition of any of the major CYP-P450 isoforms was observed when oxymorphone was incubated with human liver microsomes at concentrations of ≤ 50 µM. An inhibition of CYP3A4 activity occurred at oxymorphone concentrations ≥150 µM. Therefore, it is not expected that oxymorphone or its metabolites will act as inhibitors of any of the major CYP-P450 enzymes *in vivo*.

Drug-Lifestyle Interaction

The concomitant use of alcohol should be avoided (see **WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions Box**).

DOSAGE AND ADMINISTRATION

Dosage Considerations

OPANA ER (oxymorphone hydrochloride extended release tablets) is an opioid agonist and a Schedule I controlled substance with an abuse liability similar to morphine and other opioids.

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

OPANA ER should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics), or would be otherwise inadequate to provide sufficient management of pain (e.g., immediate-release opioids).

OPANA ER should be swallowed whole; crushing, chewing, or dissolving OPANA ER Extended Release Tablets can cause rapid release and absorption of a potentially fatal dose of Oxymorphone Hydrochloride (see WARNINGS AND PRECAUTIONS).

OPANA ER should be administered on an empty stomach, at least one hour prior to or two hours after eating. The co-ingestion of food with OPANA ER may result in increased plasma levels and a potential overdose of oxymorphone (see **ACTION AND CLINICAL PHARMACOLOGY**: **Pharmacokinetics: Food Effect**).

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 (see CONTRAINDICATIONS; ACTION AND CLINICAL PHARMACOLOGY: **Pharmacokinetics: Ethanol Effect)**

Selection of patients for treatment with OPANA ER should be governed by the same principles that apply to the use of other extended-release opioid analgesics (see **INDICATIONS AND CLINICAL USE**).

Physicians should individualize treatment in every case using non-opioid analgesics, as needed opioids and/or combination products, and chronic opioid therapy in a progressive plan of pain management such as outlined by the World Health Organization, the Canadian Pain Society and the American Pain Society.

Healthcare professionals should follow appropriate pain management principles of careful assessment and ongoing monitoring (see **WARNINGS AND PRECAUTIONS**).

As with any opioid drug product, it is necessary to adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience.

In the selection of the initial dose of OPANA ER, attention should be given to the following:

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

Recommended Dose and Dosage Adjustment

While symmetric (same dose AM and PM) around-the-clock every 12 hour dosing is appropriate for the majority of patients, some patients may benefit from asymmetric dosing (different dose given in AM than in PM) tailored to their pain pattern. It is usually appropriate to treat a patient with only one extended-release opioid for around the- clock therapy.

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

Initiation of Therapy

Opioid Naive Patients (patients currently not routinely receiving opioids)
It is recommended that the dose be individually titrated, preferably at increments of 5 mg every 12 hours every 3-7 days, to a level that provides adequate analgesia and minimizes side effects under the close

supervision of the prescribing physician (see **CLINICAL TRIALS: 12-Week Study in Opioid-Naïve Patients with Chronic Low Back Pain**).

Tablet strengths of 20 mg or higher are only for opioid tolerant patients requiring oxymorphone equivalent dosages of 20 mg or higher per day. A single dose of 20 mg or higher may lead to severe medical consequences, including fatal respiratory depression, in patients not previously exposed to similar daily doses of opioids at the time of starting or switching to OPANA ER.

Opioid Tolerant Patients (patients currently receiving opioids regularly)

Conversion from Other Oral Opioids to OPANA ER

Discontinue all other around-the-clock- opioid analgesic medications when OPANA ER therapy is initiated.

For conversion from other opioids to OPANA ER, physicians and other healthcare professionals are advised to refer to published relative potency information, keeping in mind that conversion ratios are only approximate. In general, it is safest to start the OPANA ER therapy by administering half of the calculated total daily dose of OPANA ER (see conversion ratio table below) in 2 divided doses, every 12 hours. The initial dose of OPANA ER can be gradually adjusted until adequate pain relief and acceptable side effects have been achieved.

The following table provides approximate equivalent doses, which may be used as a guideline for conversion. **The conversion ratios and approximate equivalent doses in this conversion table are only to be used for the conversion from current opioid therapy to OPANA ER.**

In a Phase 3 clinical trial with an open-label titration period, patients were converted from their current opioid to OPANA ER using the following table as a guide. In general, patients were able to successfully titrate to a stabilized dose of OPANA ER within 4 weeks (see CLINICAL TRIALS: 12 Week Study in Opioid Experienced Patients with Chronic Low Back Pain). There is substantial patient variation in the relative potency of different opioid drugs and formulations.

Table # 2: Conversion Ratios to OPANA ER

Opioid	**Approximate Equivalent Dose Oral**	**Oral Conversion Ratio[a]**
Oxymorphone	10 mg	1
Hydrocodone	20 mg	0.5
Oxycodone	20 mg	0.5
Methadone[b]	20 mg	0.5
Morphine	30 mg	0.333

a Ratio for conversion of oral opioid dose to approximate oxymorphone equivalent dose. Select opioid and multiply the dose by the conversion ratio to calculate the approximate oral oxymorphone equivalent.

- **The conversion ratios and approximate equivalent doses in this conversion table are only to be used for the conversion from current opioid therapy to OPANA ER.**
- Sum the total daily dose for the opioid and multiply by the conversion ratio to calculate the oxymorphone total daily dose.
- For patients on a regimen of mixed opioids, calculate the approximate oral oxymorphone dose for each opioid and sum the totals to estimate the total daily oxymorphone dose.
- The dose of OPANA ER can be gradually adjusted, at increments of 5-10 mg every 12 hours every 3-7 days, until

adequate pain relief and acceptable side effects have been achieved (see Individualization of Dose).

b **It is extremely important to monitor all patients closely when converting from methadone to other opioid agonists.** The ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure. Methadone has a long half-life and tends to accumulate in the plasma.

Individualization of Dose

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

If signs of excessive opioid-related adverse experiences are observed, the next dose may be reduced. Dose adjustments should be made to obtain an appropriate balance between pain relief and opioid-related adverse experiences. If significant adverse events occur before the therapeutic goal of mild or no pain is achieved, the events should be treated aggressively. Once adverse events are under control, upward titration should continue to an acceptable level of pain control.

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

Patients with Hepatic Impairment

OPANA ER is contraindicated in patients with moderate and severe hepatic dysfunction. OPANA ER should be used with caution in patients with mild hepatic impairment. These patients with mild hepatic impairment should be started with the lowest dose and titrated slowly while carefully monitoring side effects (see **ACTION AND CLINICAL PHARMACOLOGY, CONTRAINDICATIONS,** and **WARNINGS AND PRECAUTIONS**).

Patients with Renal Impairment

A study of OPANA ER in subjects with renal impairment demonstrated that moderate-to-severe renal insufficiency was associated with a reduction in the renal excretion of oxymorphone and its principal urinary metabolite resulting in an increased bioavailability. (see **ACTION AND CLINICAL PHARMACOLOGY** and **WARNINGS AND PRECAUTIONS**). Accordingly, OPANA should be administered cautiously and in reduced dosages to patients with creatinine clearance rate less than 50 mL/min.

Use with CNS Depressants

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 or hypnotics, general anesthetics, phenothiazines, and tranquilizers, because respiratory depression, hypotension and profound sedation or coma may result (see **WARNINGS AND PRECAUTIONS**: **General** and **DRUG INTERACTIONS : Drug-Drug Interactions**).

Geriatrics
Caution should be exercised in the selection of the starting dose of OPANA ER for an elderly patient starting at the low end of the dosing range. This will address the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy in this patient population.

Use in Children and Adolescents
OPANA ER is not recommended for use in children and adolescents below age 18 as dosage requirements for the safe and efficacious use of OPANA ER have not been established for this patient population.

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

Cessation of Therapy
When the patient no longer requires therapy with OPANA ER, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient. A gradual downward titration in small increments, such as in step of 50%, every 2 days is recommended until the lowest possible dose is reached, at which time therapy may be safely discontinued.

Missed Dose
Patients should be advised not to take extra tablets or a double dose to make up for a missed dose. OPANA ER should be taken once approximately every 12 hours.

Disposal
OPANA ER should be kept in a safe place, out of the sight and reach of children before, during and after use. OPANA ER should not be used in front of children, since they may copy these actions.

Unused or expired OPANA ER should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets. If temporary storage is required before disposal, a sealed child-proof container, such as a biohazard waste container or a lockable medication box could be obtained from a pharmacy.

OPANA ER should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended.

OVERDOSAGE
For management of suspected drug overdose, contact your regional Poison Control Centre.

Signs and Symptoms
Opioid overdose is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma,

skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and sometimes bradycardia and hypotension. In severe overdose, apnea, circulatory collapse, cardiac arrest, and death may occur.

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

Treatment

In the treatment of OPANA ER overdose, primary attention should be given to the reestablishment 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 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 administered as a specific antidote to respiratory depression resulting from opioid overdose. Since the duration of action of OPANA ER may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered according to the antagonist labeling as needed to maintain adequate respiration. See prescribing information for the specific opioid antagonist for details of proper use.

In patients receiving OPANA ER, opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression, secondary to OPANA ER overdose. They should be administered cautiously to persons who are known, or suspected to be, physically dependent on any opioid agonist including OPANA ER. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. In an individual physically dependent on opioids, administration of the usual dose of the antagonist 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.

ACTION AND CLINICAL PHARMACOLOGY

CLINICAL PHARMACOLOGY

Oxymorphone is an opioid agonist whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, oxycodone, hydromorphone, fentanyl, codeine, hydrocodone, and tramadol. In addition to analgesia, other pharmacological effects of

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

Central Nervous System

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

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

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

Gastrointestinal Tract and Other Smooth Muscle

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

Cardiovascular System

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

Endocrine System

Opioids have been shown to have a variety of effects on the secretion of hormones. Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon in humans and other species, rats and dogs. Thyroid stimulating hormone (TSH) has been shown to be both inhibited and stimulated by opioids.

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

Pharmacodynamics
Concentration-Efficacy Relationships
Studies in healthy volunteers reveal predictable relationships between OPANA ER dosage and plasma oxymorphone concentrations.

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

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

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

Pharmacokinetics

Absorption
The absolute oral bioavailability of oxymorphone is approximately 10%. Steady-state concentrations were achieved after 3 days of multiple dose administration.

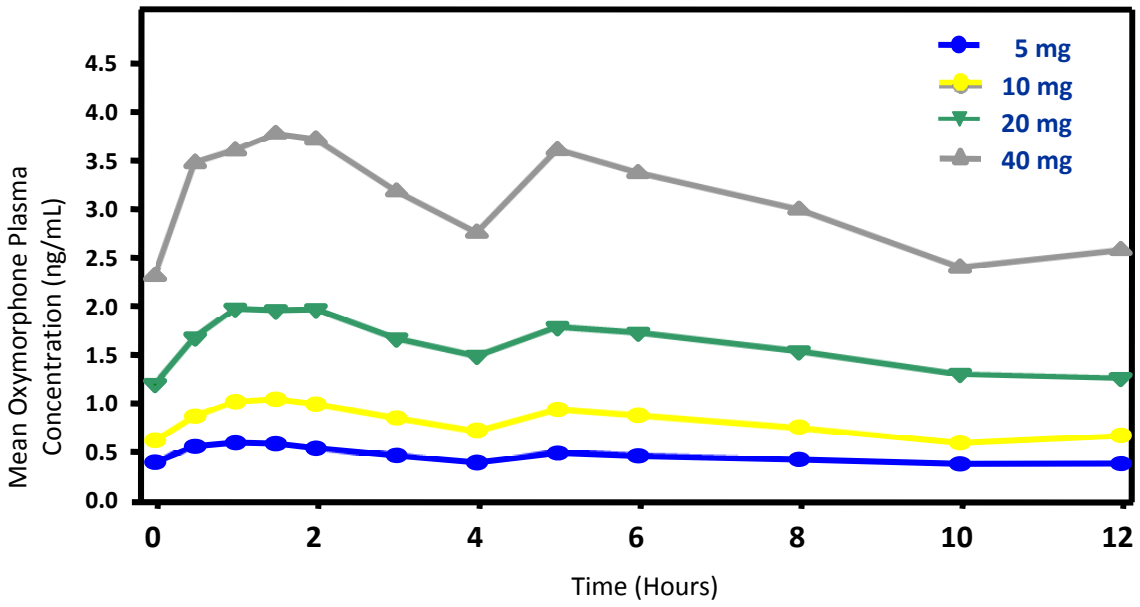
Pharmacokinetic parameter values obtained following the administration of single and multiple doses of OPANA ER tablets are presented in Table # 3. Under steady-state conditions, dose proportionality has been established for the 5 mg, 10 mg, 20 mg, and 40 mg tablet strengths OPANA ER for both peak plasma levels (C_{max}) and extent of absorption (AUC).

Table # 3: Mean (±SD) OPANA ER Pharmacokinetic Parameters

Regimen	Dosage	Cmax (ng/mL)	AUC[a] (ng•hr/mL)	$T_{1/2}$ (hr)
Single Dose	5 mg	0.27 ± 0.13	2.13 ± 1.28	11.30 ± 10.81
	10 mg	0.65 ± 0.29	6.66 ± 3.55	9.83 ± 5.68
	20 mg	1.21 ± 0.77	15.08 ± 6.95	9.89 ± 3.21
	40 mg	2.59 ± 1.65	35.37 ± 16.19	9.35 ± 2.94
Multiple Doses[b]	5 mg	0.70 ± 0.55	5.60 ± 3.87	NA
	10 mg	1.24 ± 0.56	9.77 ± 3.52	NA
	20 mg	2.54 ± 1.35	19.28 ± 8.32	NA
	40 mg	4.47 ± 1.91	36.98 ± 13.53	NA

NA = not applicable
a Values presented are AUC_T and AUC_{tau} for single and multiple doses, respectively
[b] Results after 5 days of every 12 hours dosing.

Figure # 1: Mean Steady-State Plasma Concentration of OPANA ER



Food Effect

Two studies examined the effect of food on the bioavailability of single doses of 20 and 40 mg of OPANA ER in healthy volunteers. The administration of OPANA ER 20 and 40 mg tablets with food resulted in a 1.6-fold and 1.5-fold increase in peak oxymorphone plasma concentration (Cmax) respectively, but did not significantly affect the extent of absorption of oxymorphone (increases in mean AUC of up to 12% were observed).

After a single oral dose of 40 mg, a mean peak oxymorphone plasma concentration of 2.8 ng/mL is achieved at a median Tmax of 1 hour in fasted subjects, while a peak of 4.25 ng/mL is achieved at a median Tmax of 2 hours in subjects who received the dose following a high-fat breakfast. Similarly, following the administration of a single oral dose of 20 mg, mean peak oxymorphone plasma concentrations of 1.1 and 1.8 ng/mL were observed under fasting and fed conditions, respectively. As a result, OPANA ER should be dosed at least one hour prior to or two hours after eating (see **DOSAGE AND ADMINISTRATION**).

Ethanol Effect

***In Vivo* OPANA ER Formulation-Alcohol Interaction**

An *in vivo* study examined the effect of alcohol (40%, 20% and 4%) on the bioavailability of a single dose of 40 mg of OPANA ER in healthy, fasted volunteers. Following a single oral 40 mg dose, a mean peak plasma oxymorphone concentration 2.4 ng/mL was observed at a median Tmax of 2 hours in fasted subjects. Following co-administration of OPANA ER and alcohol (240 mL of 40% ethanol) to fasted

subjects, the mean peak oxymorphone concentration was 3.9 ng/mL at a median Tmax of 1.5 hours (range 0.75 – 6 hours).

Co-administration of 240 mL of 40% ethanol and a 40 mg dose of OPANA ER resulted in a 1.7-fold increase in C_{max} on average, and up to a 2.7-fold increase in individual subjects. Co-administration of 240 mL of 20% ethanol, caused a 1.3-fold increase in C_{max} on average and up to a 2.6-fold increase in individual subjects, while co-administration of 240 mL of 4% ethanol, increased C_{max} by 1.1-fold. Co-administration of ethanol and OPANA ER did not significantly affect the extent of absorption of oxymorphone (increases in mean AUC of up to 11% were observed following co-administration of 40% ethanol).

Oxymorphone may be expected to have additive effects when used in conjunction with alcohol, due to central nervous system depression and the potential for respiratory depression, hypotension, profound sedation, coma, or death.

Alcoholic beverages or medications containing alcohol must not be consumed/co-administered while on OPANA ER therapy.

Distribution
Formal studies on the distribution of oxymorphone in various tissues have not been conducted. Oxymorphone is not extensively bound to human plasma proteins; binding is in the range of 10% to 12%.

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

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

Special Populations and Conditions

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

Geriatrics: The plasma levels of oxymorphone administered as an extended-release tablet were about 40% higher in elderly than in younger subjects.

The steady-state plasma concentrations of oxymorphone, 6-OH-oxymorphone, and oxymorphone-3-glucuronide are approximately 40% higher in elderly subjects (≥ 65 years of age) than in young subjects (18 to 40 years of age). On average, age greater than 65 years was associated with a 1.4-fold increase in oxymorphone AUC and a 1.5-fold increase in C_{max}. This observation does not appear related to a difference in body weight, metabolism, or excretion of oxymorphone (see **WARNINGS AND PRECAUTIONS**: **Geriatric Use**).

Gender:
The effect of gender was evaluated following single- and multiple-doses of OPANA ER in male and female adult volunteers. There was a consistent tendency for female subjects to have slightly higher AUC_{ss} and C_{max} values than male subjects; however, gender differences were not observed when AUC_{ss} and C_{max} were adjusted by body weight.

Hepatic Insufficiency: The liver plays an important role in the pre-systemic clearance of orally administered oxymorphone. Accordingly, the bioavailability of orally administered oxymorphone may be markedly increased in patients with moderate-severe liver disease. In a study with an extended-release formulation of oxymorphone, the disposition of oxymorphone was compared in 6 patients with mild, 5 patients with moderate, and one patient with severe hepatic impairment, and 12 subjects with normal hepatic function. The bioavailability of oxymorphone was increased by 1.6-fold in patients with mild hepatic impairment and by 3.7-fold in patients with moderate hepatic impairment. In one patient with severe hepatic impairment, the bioavailability was increased by 12.2-fold. The half-life of oxymorphone was not significantly affected by hepatic impairment. OPANA ER is contraindicated in patients with moderate or severe hepatic impairment (see **CONTRAINDICATIONS; DOSAGE AND ADMINISTRATION: Patients with Hepatic Impairment**).

Renal Insufficiency: In a study with a extended-release formulation of oxymorphone involving 24 patients with renal dysfunction, an increase of 26%, 57%, and 65% in oxymorphone bioavailability was observed in mild (creatinine clearance 51-80 mL/min; n=8), moderate (creatinine clearance 30-50 mL/min; n=8), and severe (creatinine clearance <30 mL/min; n=8) patients, respectively, compared to healthy controls.

STORAGE AND STABILITY

Store at 15°-30°C.

Dispensed in tight container, with a child-resistant closure.

Patients and their families should be instructed to return the unused tablets that are no longer needed, to the pharmacist to be destroyed.

DOSAGE FORMS, COMPOSITION AND PACKAGING

OPANA ®ER (oxymorphone hydrochloride tablets) are supplied in bottles of 100 with child-resistant closure, as follows:

5 mg: Pink, octagon shape, film coated, convex tablets debossed with "5" on one side and plain on the other.

10 mg: Light orange, octagon shape, film coated, convex tablets debossed with "10" on one side and plain on the other.

20 mg: Light green, octagon shape, film coated, convex tablets debossed with "20" on one side and plain on the other.

40 mg: Yellow, octagon shape, film coated, convex tablets debossed with "40" on one side and plain on the other.

Non-medicinal ingredients: calcium sulfate dihydrate, D&C Yellow No. 10 (20 mg, 40 mg), dextrose monohydrate, ethylcellulose, FD&C Blue No. 1 (20 mg), FD&C Yellow No. 6 (10 mg, 20 mg, 40 mg), iron oxide red (5 mg,),, lactose (40 mg), locust (carob) bean gum, microcrystalline cellulose, polyethylene glycol, polysorbate 80 (5 mg, 10 mg, 20 mg), silicon dioxide, sodium stearyl fumarate, titanium dioxide, triacetate (40 mg), triacetin, xanthan gum.

TIMERx® a proprietary controlled-release delivery system regulates the drug release from OPANA ER tablets by controlling the rate of penetration of water into the strong polysaccharide gel matrix and the subsequent expansion of gel which releases the active drug.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common name: oxymorphone hydrochloride

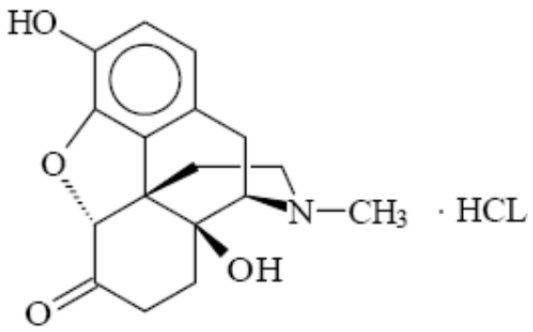
Chemical name: 4,5α□-Epoxy-3,14-dihydroxy-17-methylmorphinan-6-one hydrochloride
Morphinan-6-one,4,5-epoxy-3,14-dihydroxy-17-methyl-,hydrochloride,(5α)-.

Molecular formula and molecular mass:

Molecular formula: $C_{17}H_{19}NO_4 \cdot HCl$

Molecular weight: 337.86 (oxymorphone hydrochloride salt)
301.41 (oxymorphone base)

Structural formula: Oxymorphone hydrochloride



Physicochemical properties: White or slightly off-white, odorless powder, which is sparingly soluble in alcohol and ether, but freely soluble in water. The pKa_1 and pKa_2 of oxymorphone at 37°C are 8.17 and 9.54, respectively. The octanol/aqueous partition coefficient at 37°C and pH 7.4 is 0.98.

CLINICAL TRIALS

OPANA ER (oxymorphone hydrochloride extended release)

The safety and efficacy of OPANA ER have been evaluated in three pivotal clinical studies including subjects with osteoarthritis and chronic back pain.

Osteoarthritis (OA)

Two double-blind, controlled studies were conducted to compare the analgesic effects of OPANA ER to placebo and another controlled-release formulation in patients with osteoarthritis.

In the first study (treatment duration = 4 weeks; N = 491) which examined both the 20mg and the 40mg doses, the OPANA ER 40 mg treatment was statistically significantly better than placebo as assessed by actual change from baseline to Week 3 in Arthritis Pain Intensity (-29.8 vs. -18.4 respectively, p= 0.008), and was also statistically significantly better than placebo at Week 4 (-33.7 vs. -19.7 respectively, p=0.0017).Secondary efficacy measures were supportive of the primary efficacy outcome.

The second OA study (treatment duration = 2 weeks; N = 370) included doses of 10mg, 40mg and 50 mg. OPANA ER 40 mg and 50 mg were statistically significantly better than placebo (p=0.012 and 0.006 respectively) in relieving pain due to OA as measured by the change from baseline in the arthritis pain intensity VAS score.

Chronic Low Back Pain

This double blind flexible dose study examined the efficacy and safety of OPANA ER in subjects with chronic low back pain (treatment duration = 18 days; N = 330), and compared OPANA ER to placebo and another controlled-release opioid formulation. The results support the efficacy of treatment with OPANA ER for the relief of chronic low back pain. The VAS pain intensity score showed a statistically superior effect of OPANA ER over placebo (p=0.0001). During the double-blind treatment phase, satisfactory pain relief was achieved on an average daily dose of approximately 79 mg oxymorphone ER.

The efficacy and safety of OPANA ER have also been evaluated in double-blind, controlled clinical trials in opioid-naïve and opioid-experienced patients with moderate to severe pain including chronic low back pain. In the following studies, OPANA ER provided statistically and clinically superior analgesia compared to placebo on primary and secondary outcome measures.

12-Week Study in Opioid-Naïve Patients with Chronic Low Back Pain

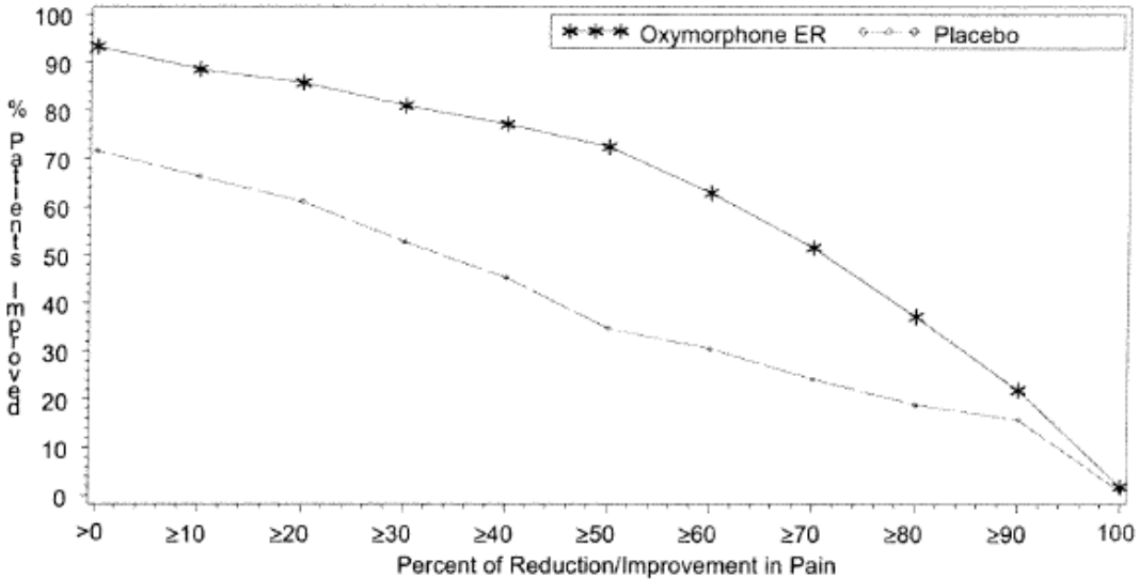
Patients with chronic low back pain who were suboptimally responsive to their current non-opioid therapy entered a 4-week, open-label dose titration phase. Patients initiated therapy with two days of treatment with OPANA ER 5 mg, every 12 hours. Thereafter, patients were titrated to a stabilized dose, at increments of 5-10 mg every 12 hours every 3-7 days. Of the patients who were able to stabilize within the Open-Label Titration Period, the mean±SD VAS score at Screening was 69.4±11.8 mm and at Baseline (beginning of Double-Blind Period) were 18.5±11.2 mm and 19.3±11.3 mm for the OPANA ER and placebo groups, respectively. Sixty three percent of the patients enrolled were able to titrate to a tolerable dose and were randomized into a 12-week double-blind treatment phase with placebo or their stabilized dose of OPANA ER. The mean ±SD stabilized doses were 39.2±26.4 mg and 40.9±25.3 mg for the OPANA ER and placebo groups, respectively; total daily doses ranged from 10-140 mg. During the first 4 days of double-blind treatment patients were allowed an unlimited number of oxymorphone

immediate release, 5 mg tablets, every 4-6 hours as supplemental analgesia; thereafter the use of oxymorphone immediate release was limited to two tablets per day. This served as a tapering method to minimize opioid withdrawal symptoms in placebo patients.

Sixty-eight percent of patients treated with OPANA ER completed the 12-week treatment compared to forty seven percent of patients treated with placebo. OPANA ER provided superior analgesia compared to placebo. The analgesic effect of OPANA ER was maintained throughout the double-blind treatment period in 89% of patients who completed the study. These patients reported a decrease, no change, or a 10 mm increase in VAS score from Day 7 until the end of the study.

A significantly higher proportion of OPANA ER patients (81.4%) had at least a 30% reduction in pain score from screening to study endpoint compared to placebo patients (51.7%). The proportion of patients with various degrees of improvement from screening to study endpoint is shown in Figure 1.

Figure #1: Percent Reduction in Average Pain Intensity from Screening to Final Visit

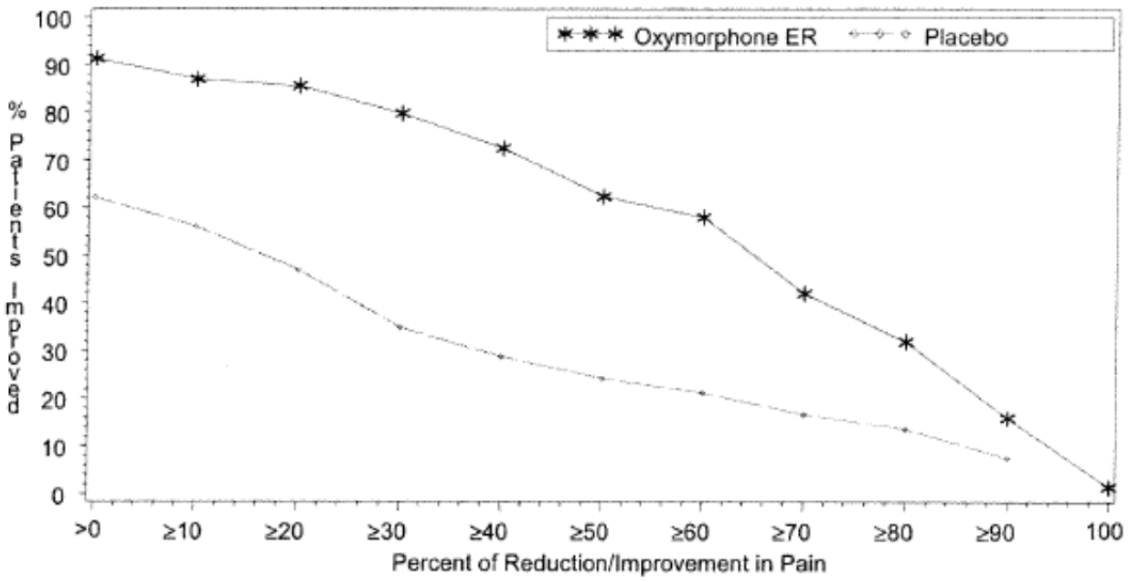


12-Week Study in Opioid-Experienced Patients with Chronic Low Back Pain
Patients currently on chronic opioid therapy entered a 4-week, open-label titration phase with OPANA ER dosed every 12 hours at an approximated equianalgesic dose of their pre-study-opioid medication.

Seventy percent of patients treated with OPANA ER and 26% of patients treated with placebo completed the 12-week treatment. OPANA ER provided superior analgesia compared to placebo. The analgesic effect of OPANA ER was maintained throughout the double-blind treatment period in 80 % of patients who completed the study. These patients reported a decrease, no change, or a 10 mm increase in VAS score from Day 7 until the end of the study.

A significantly higher proportion of OPANA ER patients (79.7%) had at least a 30% reduction in pain score from screening to study endpoint compared to placebo patients (34.8%). Proportion of patients with various degrees of improvement from screening to study endpoint is shown in Figure 2.

Figure #2: Percent Reduction in Average Pain Intensity from Screening to Final Visit



DETAILED PHARMACOLOGY

Oxymorphone is an opioid agonist whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, oxycodone, hydromorphone, fentanyl, codeine, hydrocodone and tramadol. In addition to analgesia, other pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, and cough suppression. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic effect with increasing doses. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression.

Nonclinical Testing:

Primary Pharmacodynamics

Results from binding studies showed that both oxymorphone and its primary metabolite, 6-hydroxymoxymorphone, exhibited binding activity at each of the opioid receptor subtypes: mu, delta 1, delta 2, and kappa. In comparison to other opioids, oxymorphone was consistently more active than morphine. Oxymorphone was generally, 2-, 5-, and >10 times more active than hydromorphone, oxycodone and morphine, respectively. Secondary pharmacodynamic findings, suggested that

oxymorphone administration at high doses produced behavioral, respiratory, cardiovascular, gastrointestinal, thermoregulatory and antitussive effects consistent with other opioids.

Pharmacokinetics

In vivo metabolic studies were conducted in mice and rats to determine the primary metabolites of oxymorphone. Following single-dose oral administration, peak plasma radioactivity was found between 30 min and 3 hours. At 24 hours, the amount of radioactivity recovered was approximately doubled from the amount recovered at the 3-hour time point, and may be indicative of enterohepatic recirculation. Plasma protein binding in both species was uniformly low, approximately 19% bound when tested across a range of concentrations 0.05, 0.5 and 5.0 μM (5μM = 0.017 ng/ml).

TOXICOLOGY

Oxymorphone has been thoroughly evaluated for single and repeat-dose oral toxicity in mice, rats and dogs, mutagenicity/genotoxicity, carcinogenicity in mice and rats, developmental toxicity in rats and rabbits, and reproductive toxicity in rats.

These studies included:

- Three-month toxicity studies in mice, rats and dogs;
- A complete genetic toxicology battery
- Two year carcinogenicity studies in mice and rats
- Studies evaluating the effects of oxymorphone on fertility, embryo/fetal and postnatal development.

Table # 4: Overview of Toxicology Program with Oxymorphone

Study Type	Method of Administration and Duration	Species/Strain	Oxymorphone mg/kg
Single Dose Toxicity	Intravenous N/A	CD-1 Mice	0.0/0.0, 10.0/0.0, 30.0/0.0, 100.0/0.0, 200.0/0.0, 0.3/0.0, 10.0/0.2, 30.0/0.6, 100.0/2.0, 200.0/4.0, 0.3/0.006, 3.0/0.0, 3.0/0.06
	Intravenous N/A	Sprague-Dawley Crl:CD®BR (VAF) Rats	0.0/0.0, 10.0/0.0, 30.0/0.0, 100.0/0.0, 0.3/0.0, 1.0/0.0, 10.0/0.2, 30.0/0.6, 100.0/2.0, 3.0/0.0, 0.3/0.006, 1.0/0.02, 3.0/0.06
Repeat dose toxicity	Oral (Gavage) 13 weeks	CD-1 Mice	For the 5 Groups (1-5) Days 0-6: 0, 10, 25, 25, 25 Days 7-13: 0, 10, 25, 50, 50 Days 14-41: 0, 10, 25, 50, 75 Days 42-49: 0, 150, 25, 50, 75 Days 50-62: 0, 300, 25, 50, 75

Study Type	Method of Administration and Duration	Species/Strain	Oxymorphone mg/kg
			Days 63-91: 0, 300, 600, 50, 75
	Intravenous 2 weeks	CD-1 Mice	0, 0.3, 3.0, 30.0, 0.3/0.006, 3.0/0.06, 30.0/0.6
	Oral (Gavage) 13 weeks	Crl:CD® (SD)IGS BR Rats	For the 5 Groups (1-5) Days 0-6: 0, 10, 25, 25, 25 Days 7-13: 0, 10, 25, 50, 50 Days 14-91: 0, 10, 25, 50, 75
	Intravenous 2 weeks	Sprague-Dawley Crl:CD®(SD) Rats	0, 0.3, 0.9, 3.0, 30.0, 0.3/0.006, 0.9/0.018, 3.0/0.06, 30.0/0.6
	Oral (capsule) 36 days	Beagle Dogs	Phase 1: Days 0-2: 10 Days 7-9: 40 Days 14-16: 20 Phase 2: Days 21-24: 5 Days 25-28: 10 Days 29-32: 20 Days 33-36: 40
	Oral (capsule) 13 weeks	Beagle Dogs	For the 4 Groups (1-4) Days 0-2: 0, 0.1, 0.1, 0.1 Days 3-6: 0, 1, 2, 2 Days 7-29: 0, 2, 10, 20 Days 30-40: 0, 2, 10, 30 Days 41-91: 0, 2, 10, 40
Genotoxicity	*In vitro* N/A	*S. typhimurium and E. coli*	2.64, 7.91, 26.4, 79.1, 211, 632, 1897, 5270 µg/plate
	In vitro N/A	*S. typhimurium and E. coli*	62.5, 125, 250, 500, 1000 µg/plate
	In vitro N/A	Chinese Hamster Ovary Cells	Non-Activated: 0.1, 0.5, 1.0, 5.0, 7.5 µg/mL Activated: 0.1, 0.5, 1.0, 5.0, 10 µg/mL
	In vitro N/A	Human peripheral blood lymphocytes	4 Hours: 1318, 2635, 5270 µg/mL 20 Hours: 250, 700, 1100 µg/mL
	Oral (Gavage) Single dose	ICR Mice	Pilot Study: 250, 500, 750, 1054 mg/kg Micronucleus Assay: 125, 250, 500
	Oral (Gavage) Single dose	ICR Mice	250, 500
	Oral (Gavage) Single dose	ICR Mice	250, 500
	Oral (Gavage) Single dose	Crl:CD®(SD)IGS BR Rats	Pilot Study: 50, 75, 100, 150 Micronucleus Assay: 10, 20, 40

Study Type	Method of Administration and Duration	Species/Strain	Oxymorphone mg/kg
	Oral (Gavage) Single dose	Crl:CD®(SD)IGS BR Rats	40
	Oral (Gavage) Single dose	Crl:CD®(SD)IGS BR Rats	40
	Oral (Gavage) Single dose	Crl:CD®(SD)IGS BR Rats	40
	Oral (Gavage) Single dose	Crl:CD®(SD)IGS BR Rats	40
	Oral (Gavage) Single dose	Crl:CD®(SD)IGS BR Rats	40
	Oral (Gavage) Single dose	Crl:CD®(SD)IGS BR Rats	First Phase: 20, 40 Second Phase: 40
	Oral (Gavage) Single dose	Crl:CD®(SD)IGS BR Rats	40
Carcinogenicity	Oral (Gavage) Single dose	Swiss Crl:CD®-1(ICR)BR mice	0, 10, 25, 75, 150
	Oral (Gavage) Single dose	Sprague-Dawley Crl:CD®(SD)IGS BR Rats	Male: 0, 2.5, 5, and 10 Female: 0, 5, 10, and 25
Reproductive and Developmental Toxicity	Oral (Gavage) M: 29 days prior to pairing – one day prior to euthanasia F: 14 days prior to pairing – Gestation day 7	Crl:CD®(SD)IGS BR Rats	0, 0.1, 1.0, 10, 25, 50
	Oral (Gavage) M: 28 days prior to pairing – one day prior to euthanasia F: 14 days prior to pairing – Gestation day 7	Crl:CD®(SD)IGS BR Rats	0, 5, 10, 25
	Oral (Gavage) F:G6-G17	Crl:CD®(SD)IGS BR Rats	0, 1, 10, 25, 35, 50
	Oral (Gavage) F:G6-G17	Crl:CD®(SD)IGS BR Rats	0, 5, 10, 25
	Oral (Gavage) F;G6-L20	Crl:CD®(SD)IGS BR Rats	0, 1, 5, 10, 25
	Oral (Gavage) G7-G20	New Zealand White Rabbits	0, 1, 10, 25, 50, 75
	Oral (Gavage) G7-G20	New Zealand White Rabbits	0, 10, 25, 50
Other Toxicity Studies	Intradermal Topical Dermal Induction: 1 Dose Topical Induction: Day 8 for 48 hours Topical Challenge : Day 22 for 24 hours	Hartley Guinea Pigs	Dermal Induction: 0.2 mL Topical Induction: 200 mg Topical Challenge: 100 mg (30% w/w)
	Intravenous Single dose	New Zealand White Rabbits	1.0 mL (10 mg/mL)
	Intramuscular Single dose	New Zealand White Rabbits	1.0 mL (10 mg/mL)
	Subcutaneous Single dose	New Zealand White Rabbits	1.0 mL (10 mg/mL)
	In vitro N/A	Human blood, plasma or serum	0.1 mL (10 mg/mL)

In summary, the results of these studies support the safe clinical use of oxymorphone. In addition, results of these studies revealed that many of the effects associated with oxymorphone treatment are very similar to those attributed to other opioids. The oxymorphone-mediated effects described in these studies were in large part anticipated based upon the known effects and pharmacology of other opioids. Importantly, none of the toxicology findings attributed to high doses of oxymorphone represent a risk to humans given therapeutic doses of this medicine for the treatment of pain.

Single-Dose Toxicity

Single dose toxicity studies were performed in mice and rats at doses up to 300mg/kg. No signs were observed in either species at 0.3 mg/kg, Mortality was observed at the 100 mg/kg dose level in both species.

Repeat-Dose Toxicity

Repeat dose studies were performed up to 13 weeks in rodents and beagle dogs. Clinical signs (changes in activity, excessive licking/chewing, hyper-reactivity, straub tail [rodents]), and reductions in body weight and food consumption occurred in all studies, generally at all doses. These findings are consistent with effects of opioids. There were no histological findings in mice, rats or dogs that were indicative of target organ toxicity of oxymorphone. Moderate biliary hyperplasia occurred in dogs given high doses of oxymorphone for 13 weeks.

Genotoxicity Studies

Oxymorphone was not mutagenic in an Ames Bacterial Reverse Mutation Test, and did not produce structural or numerical chromosomal aberrations in human peripheral blood lymphocytes *in vitro.* Oxymorphone was found to be clastogenic in the *in vivo* micronucleus tests, similar findings have been reported for morphine.

Carcinogenicity Studies

Two 2-yr carcinogenicity studies of oxymorphone were conducted in both mice and rats. Results demonstrated that there was no evidence of carcinogenicity in either species.

Reproductive and Developmental Toxicity Studies

In studies of effects on fertility and early embryonic development, oxymorphone produced effects on ovulation in female rats, as evidenced by prolonged estrus cycles and decreases in corpora lutea, implantation sites and viable embryos. The no observed adverse effect level (NOAEL) for these findings was 5 mg/kg/day, which had an associated AUC of 1.8-times that in humans at therapeutic doses.

Oxymorphone did not cause any malformations or structural variations in the offspring of rats or rabbits given doses of oxymorphone yielding AUC values which were 9- and 6-fold greater, respectively than those in humans given 40 mg q12h.

Neonatal mortality occurred in rats following administration of oxymorphone to pregnant dams in a pre- and postnatal toxicity study. Similar findings have been described for other opioids.

Other Toxicity Studies

Additional genotoxicity studies were conducted to investigate the possible relationship of increased micronucleated polychromatic erythrocytes (MPCEs) to oxymorphone-induced changes in body temperature. This research was undertaken based on known effects of opioids on thermoregulatory mechanisms. These results indicated that the increased incidence of MPCEs following oxymorphone

administration was directly related to increased body temperature and not indicative of a carcinogenic risk by oxymorphone.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

[N]OPANA® ER
Oxymorphone Hydrochloride Extended Release Tablets

Read this carefully before you start taking OPANA ER and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about OPANA ER.

Serious Warnings and Precautions

- **Even if you take OPANA ER as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to overdose and death.**
- **Life-threatening breathing problems can happen while taking OPANA ER, especially if not taken as directed.**
- **Never give anyone your OPANA ER. They could die from taking it. If a person has not been prescribed OPANA ER, taking even one dose can cause a fatal overdose. This is especially true for children.**
- **Babies born to mothers who have taken OPANA ER (for short or long periods, in small or large doses) during their pregnancy can suffer life-threatening withdrawal symptoms. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has breathing changes (weak, difficult or fast), is unusually difficult to comfort, has tremors (shakiness), or has increased stools, sneezing, yawning, vomiting, or fever, seek immediate medical help for your baby.**

What is OPANA ER used for?

OPANA ER is used for the long-term management of pain, when:
- the pain is severe enough to require daily, around-the-clock painkillers
- the doctor determines that other treatment options are not able to effectively treat your pain

OPANA ER is NOT used ("as needed") to treat pain that you only have once in a while.

How does OPANA ER work?

OPANA ER is a painkiller belonging to the class of medicines known as opioids. OPANA ER is gradually released into your blood stream and interacts with proteins in the body called "opioid receptors" that are responsible for different opioid effects (desirable and undesirable). These receptors are found in the brain, the spinal cord and the gastrointestinal tract. It relieves pain by

acting on opioid receptors found on specific nerve cells of the spinal cord and brain.

What are the ingredients in OPANA ER?
Medicinal ingredients: Oxymorphone hydrochloride.
Non-medicinal ingredients: Calcium sulfate dehydrate, Dextrose monohydrate, Ethylcellulose, Locust bean gum, Silicified Microcrystalline Cellulose, Sodium Stearyl Fumarate, Purified Water, USP, Methylparaben, Opadry Clear, Opadry Pink, Opadry Gray, Opadry Lt Orange, Opadry White, Opadry Lt Green, Opadry Red, Opadry II Yellow, Xanthum gum.

OPANA ER comes in the following dosage forms:
OPANA ER is available in Extended Release Tablets of 5 mg, 10 mg, 20 mg & 40 mg.

Do not use OPANA ER if:
- you are allergic to Oxymorphone Hydrochloride or any of the other ingredients of OAPANA ER or to other opioids (drugs similar to morphine) such as codeine.
- your pain can be controlled by the occasional use of painkillers including those available without a prescription
- you have severe asthma, trouble breathing, or any heart problems
- you have bowel blockage or narrowing of the stomach or intestines
- you have a head injury or other risks for seizures
- you suffer from alcoholism or have convulsions
- you are going to have, or recently had, a planned surgery
- you have moderate and severe problems in the liver.
- you are pregnant or plan to become pregnant, breastfeeding, or in labour
- you are under 18 years of age

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take OPANA ER. Talk about any health conditions or problems you may have, including if you:
- have a history of illicit or prescription drug or alcohol abuse
- have severe kidney, liver disease
- have low blood pressure
- have past or current depression
- suffer from chronic or severe constipation
- have trouble breathing or lung problems
- have a head injury or brain problems
- have adrenal gland problems, such as Addison's disease
- have convulsions or seizures
- have thyroid problems
- have problems urinating or prostate problems
- have pancreas problems
- have severe mental problems or hallucinations (see or hear things that are not really there)

Other warnings you should know about:

Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to OPANA ER. Drowsiness, dizziness, or lightheadedness, can especially occur after the first dose and when the dose is increased.

To avoid changes in the amount of the medication in your blood stream, OPANA ER MUST be taken at least **one hour before, or two hours after eating.**

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with OPANA ER:

- alcohol, including prescription and non-prescription medications containing alcohol. Do not drink alcohol while taking OPANA ER. This can lead to drowsiness, depressed breathing, serious side effects or a fatal overdose
- other sedative drugs which may enhance the drowsiness caused by OPANA ER
- other opioid analgesics (for pain)
- general anesthetics (used during surgery)
- drugs used to help you sleep or to reduce anxiety
- antidepressants (for depression and mood disorders). Do not take OPANA ER with MAO inhibitors or if you have taken MAO in the last 14 days before treatment with OPANA ER.
- drugs used to treat serious mental or emotional disorders such as schizophrenia
- antihistamines (for allergies)
- anti-emetics (for prevention of vomiting)
- drugs used to treat muscle spasms and back pain
- warfarin and other coumarin anticoagulants (for prevention/treatment of blood clots)
- anti-retroviral, anti-fungal and antibiotic drugs

Do not take any new medicines while using OPANA ER until you have talked to your doctor and pharmacist and they have told you it is safe.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist.

How to take OPANA ER:

Swallow whole. Do not break, chew, dissolve or crush.

If OPANA ER tablets are crushed, chewed, dissolved or broken, oxymorphone will be released too fast. This can lead to serious and life-threatening breathing problems. Life-threatening breathing problems can also happen because of an overdose or if the dose you are using is too high for you. Get emergency medical help immediately if you:

- have trouble breathing, or have slow or shallow breathing
- have a slow heartbeat
- have severe sleepiness

- have cold, clammy skin
- feel faint, dizzy, confused, or cannot think, walk, or talk normally
- have a seizure
- have hallucinations

You MUST take OPANA ER on an empty stomach (at least one hour before or two hours after eating. Taking OPANA ER with food may result in more drug in your bloodstream and may lead to serious medical consequences.

Do not drink alcohol while using OPANA ER. It may increase the chance of having dangerous side effects including overdose and death.

You should only take OPANA ER twice a day (every 12 hours, or as directed by your doctor) to manage your pain.

Do not change your dose unless your doctor tells you to change it.

Do not take OPANA ER more often than prescribed.

While most patients obtain adequate pain relief with OPANA ER, your pain may vary and occasionally break through. This is not unusual. If this occurs, your doctor may prescribe additional pain medication.

It is important to let your doctor know whether or not your pain is under control. If you frequently need additional short-acting pain medication, or if pain is waking you at night, you may need a change in your OPANA ER dose.

If you continue to have pain, call your doctor.

Always follow your doctor's instructions carefully and do not change or stop your OPANA ER medication without first consulting with your doctor.

Usual Adult Starting Dose:

Dosage is individualized. Be sure to follow your doctor’s dosing instructions exactly.

You should not stop taking OPANA ER all at once if you have been taking it for more than a few days without talking to your doctor. OPANA ER can cause physical dependence. You can get sick with withdrawal symptoms if you stop OPANA ER all at once, because your body has become used to it.

Overdose:

Signs of overdose may include abnormally slow or weak breathing, dizziness, confusion or extreme drowsiness.

If you think you have taken too much OPANA ER, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss one dose, take it as soon as possible. However, if it is almost time for your next dose, then skip the missed dose. Do not take two doses at once. If you miss several doses in succession, talk to your doctor before restarting your medication.

Refilling Prescriptions for OPANA ER:

A new written prescription is required from your doctor each time you need more OPANA ER. Therefore, it is important that you contact your doctor before your current supply runs out.

What are possible side effects from using OPANA ER?

These are not all the possible side effects you may feel when taking OPANA ER. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:
- Drowsiness, insomnia
- Dizziness, fainting
- Nausea, vomiting, poor appetite, dry mouth
- Headache
- Problems with vision
- Weakness, uncoordinated muscle movement
- Itching
- Sweating
- Constipation
- Sedation

Talk with your doctor or pharmacist about ways to prevent constipation when you start using OPANA ER.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE **Overdose:** hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness,			✓

floppy muscles/low muscle tone cold and clammy skin.			
Respiratory Depression: Slow, shallow or weak breathing.			✓
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
Bowel Blockage (impaction): abdominal pain, severe constipation, nausea			✓
Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating.		✓	
Fast, Slow or Irregular Heartbeat: heart palpitations.		✓	
Low Blood Pressure: dizziness, fainting, light-headedness.	✓		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
We encourage you to report serious or unexpected side effects to Health Canada. The information is used to check for new safety concerns about health products. As a consumer, your report contributes to the safe use of health products for everyone.
3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:

-Fax to 1-866-678-6789 (toll-free), or
-Mail to: Canada Vigilance Program
Health Canada, Postal Locator 0701E
Ottawa, ON
K1A 0K9
Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

Storage:

Store OPANA ER at room temperature between 15º to 30 ºC.

Keep unused or expired OPANA ER in a secure place to prevent theft, misuse or accidental exposure.

Keep out of sight and reach of children and pets.

Disposal:

OPANA ER should never be thrown into household trash, where children and pets may find it. It should be returned to a pharmacy for proper disposal.

Do not give to other people, even if they have the same symptoms you have. It may harm them, even causing death, and it is against the law.

After you stop taking OPANA ER, return any unused medication to the pharmacy for safe disposal.

If you want more information about OPANA ER:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this patient medication information by visiting the Health Canada website or the sponsor website at http://www.paladinlabs.com or by calling at 1-888-867-7426.

This leaflet was prepared by: Paladin Labs Inc.

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