PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

^{N}Oxy•IR®

Oxycodone Hydrochloride Immediate Release Tablets

Tablets, 5 mg, 10 mg and 20 mg, Oral

Purdue Pharma Standard

Opioid Analgesic

N02AA05

Purdue Pharma
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M2H3S7

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RECENT MAJOR LABEL CHANGES

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Oxy•IR® (oxycodone hydrochloride) is indicated for:

- relief of moderate to severe pain.

Oxy•IR is not indicated as an as-needed (prn) analgesic.

1.1 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of Oxy•IR has not been studied in the pediatric population. Therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (>65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range and titrated slowly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or other drug therapy (see 4 DOSAGE AND ADMINISTRATION and 10.3 Pharmacokinetics, Special Populations and Conditions, Geriatrics).

2 CONTRAINDICATIONS

Oxy•IR is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging.
- Patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction or strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).
- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis).
- Patients with mild pain that can be managed with other pain medications.
- Patients with acute or severe bronchial asthma, chronic obstructive airway, or 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).
- Women who are breast-feeding, pregnant or during labour and delivery (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX; 7.1.1 Pregnant Women, and 7.1.2 Breast-feeding).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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 risks of overdose and death with immediate release opioid formulations, Oxy•IR tablets should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide appropriate management of pain (see 4.1 Dosing Considerations).

- Addiction, Abuse, and Misuse

  Oxy•IR 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 Oxy•IR, and all patients should be monitored regularly for the development of these behaviours or conditions (7 WARNINGS AND PRECAUTIONS, General Addiction, Abuse and Misuse). Oxy•IR should be stored securely to avoid theft or misuse.

- Life-threatening Respiratory Depression: OVERDOSE

  Serious, life-threatening, or fatal respiratory depression may occur with use of Oxy•IR. Infants exposed in-utero or through breast milk are at risk of life-threatening respiratory depression upon delivery or when nursed. Patients should be monitored for respiratory depression, especially during initiation of Oxy•IR or following a dose increase.

  Oxy•IR must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving Oxy•IR can lead to dangerous adverse events including death (see 7 WARNINGS AND PRECAUTIONS, General Addiction, Abuse and Misuse). Further, instruct patients of the hazards related to taking opioids including fatal overdose.

- Accidental Exposure

  Accidental ingestion of even one dose of Oxy•IR, especially by children, can result in a fatal overdose of oxycodone (see 11 STORAGE, STABILITY AND DISPOSAL, Disposal, for instructions on proper disposal).

- Neonatal Opioid Withdrawal Syndrome

  Prolonged maternal use of Oxy•IR during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance, Neonatal Opioid Withdrawal Syndrome (NOWS)).

- Interaction with Alcohol

  The co-ingestion of alcohol with Oxy•IR should be avoided as it may result in dangerous additive effects, causing serious injury or death (see 7 WARNINGS AND PRECAUTIONS, General and 9.3 Drug-Behavioural Interactions).

- Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

  Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see 7 WARNINGS AND PRECAUTIONS, Neurologic, Interactions with CNS Depressants (including benzodiazepines and alcohol), and 9.2 Drug Interactions Overview, Interactions with CNS Depressants (including

benzodiazepines and alcohol)).

- Reserve concomitant prescribing of Oxy•IR and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are not possible.
- Limit dosages and durations to the minimum required.
- Follow patients closely for signs and symptoms of respiratory depression and sedation.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- For acute pain, it is recommended that Oxy•IR be used for a maximum of 7 days at the lowest dose that provides adequate pain relief.
- All doses of opioids carry an inherent risk of fatal or non-fatal adverse events. This risk is increased with higher doses. For the management of chronic non-cancer, non-palliative pain, it is recommended that 60 mg (90 morphine milligram equivalent) daily of Oxy•IR not be exceeded. Each patient should be assessed for their risk prior to prescribing Oxy•IR, as the likelihood of experiencing serious adverse events can depend upon the type of opioid, duration of treatment, level of pain as well as the patient's own level of tolerance. In addition, the level of pain should be assessed routinely to confirm the most appropriate dose and the need for further use of Oxy•IR (see 4.2 Recommended Dose and Dosage Adjustment, Adjustment or Reduction of Dosage).
- Oxy•IR should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics).
- Oxy•IR must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving Oxy•IR can lead to dangerous adverse events including death (see 7 WARNINGS AND PRECAUTIONS, General Addiction, Abuse and Misuse).
- Oxy•IR should be used with caution within 12 hours pre-operatively and within the first 12-24 hours post-operatively (see 7 WARNINGS AND PRECAUTIONS, Peri-operative Considerations).
- Oxy•IR is not indicated for rectal administration.
- Treatment goals and discontinuation: Before initiating treatment with Oxy•IR, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the health professional and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed.
- Oxy•IR should not be used longer than necessary.

4.2 Recommended Dose and Dosage Adjustment

- **Pediatrics (<18 years of age):** Health Canada has not authorized an indication for pediatric use (see INDICATIONS).
- **Adults (≥18 years of age):** Individual dosing requirements vary considerably based on each patient's age, weight, severity and cause of pain, and medical and analgesic history.
- **Patients Not Receiving Opioids at the Time of Initiation of Oxy•IR Treatment:** The usual initial

adult dose of Oxy•IR for patients who have not previously received opioid analgesics is 5 or 10 mg, orally, every 6 hours.

- **Patients Currently Receiving Opioids:** For patients who are receiving an alternate opioid, the "oral oxycodone equivalent" of the analgesic presently being used, should be determined. Having determined the total daily dosage of the present analgesic, Table 1 can be used to calculate the approximate daily oral oxycodone dosage that should provide equivalent analgesia. It is usually appropriate to treat a patient with only one opioid at a time. Further dose reductions should be considered due to incomplete cross-tolerance between opioids.
- **Opioid Rotation:** Conversion ratios for opioids are subject to variations in kinetics governed by genetics and other factors. When switching from one opioid to another, consider **reducing the calculated dose by 25-50%** to minimize the risk of overdose. Subsequently, up-titrate the dose, as required, to reach the appropriate maintenance dose.

Table 1 – Opioid Conversion Table[a]

Opioids	To convert to oral morphine equivalent	To convert from oral morphine multiply by	Daily 90 mg MED[b]
Morphine	1	1	90 mg
Codeine	0.15	6.67	600 mg
Hydromorphone	5	0.2	18 mg
Oxycodone	1.5	0.667	60 mg
Tapentadol	0.3-0.4	2.5-3.33	300 mg
Tramadol	0.1-0.2	6	***
Methadone	Morphine dose equivalence is not reliably established		

*** The maximum recommended daily dose of tramadol is 300 mg – 400 mg depending on the formulation.

a. Adapted from the 2017 Canadian guideline for opioids for chronic non-cancer pain. McMaster University; 2017
b. MED. Morphine Equivalent Dose

- **Patients with Hepatic and Renal Impairment:** In patients with any degree of hepatic or renal impairment, the dose initiation should follow a conservative approach. The recommended adult starting dose in these patients should be at 1/3 to 1/2 the usual starting dose followed by careful dose titration to adequate pain control according to their clinical situation (see 7.1.4 Geriatrics, 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency, and 10.3 Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency).
- **Geriatrics:** Respiratory depression has occurred in the elderly following administration of large initial doses of opioids to patients who were not opioid-tolerant or when opioids were co-administered with other agents that can depress respiration. Oxy•IR should be initiated at a low end of the dosing range and slowly titrated (see 7.1.4 Geriatrics and 10.3 Pharmacokinetics, Special Populations and Conditions, Geriatrics).

- **Use with Non-Opioid Medications:** If a non-opioid analgesic is being provided, it may be continued. If the non-opioid is discontinued, consideration should be given to increasing the opioid dose to compensate for the non-opioid analgesic. Oxy•IR can be safely used concomitantly with usual doses of other non-opioid analgesics.
- **Dose Titration:** Dose titration is the key to success with opioid analgesic therapy. **Proper optimization of doses scaled to the relief of the individual's pain should aim at administration of the lowest dose which will achieve the overall treatment goal of satisfactory pain relief with acceptable side effects.**

  Dosage adjustments should be based on the patient's clinical response.

  In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered.
- **Adjustment or Reduction of Dosage:** Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including Oxy•IR. Withdrawal (abstinence) symptoms may occur following abrupt discontinuation of therapy. These symptoms may include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning.

  Following successful relief of moderate to severe pain, periodic attempts to reduce the opioid dose should be made. Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal for the drug, these symptoms are usually mild (see 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance). Tapering should be individualized and carried out under medical supervision.

  Patient should be informed that reducing and/or discontinuing opioids decreases their tolerance to these drugs. If treatment needs to be re-initiated, the patient must start at the lowest dose and titrate up to avoid overdose.

  Opioid analgesics may only be partially effective in relieving dysesthetic pain, postherpetic neuralgia, stabbing pains, activity-related pain and some forms of headache. That is not to say that patients with these types of pain should not be given an adequate trial of opioid analgesics, but it may be necessary to refer such patients at an early time to other forms of pain therapy.

4.4 Administration

Oxy•IR may be taken with or without food, with a glass of water.

4.5 Missed Dose

If the patient forgets to take one or more doses, they should take their next dose at the next scheduled time and in the normal amount.

5 OVERDOSAGE

Symptoms

Serious overdosage with oxycodone may be characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence

progressing to stupor or coma, miosis, hypotonia, cold and clammy skin, toxic leukoencephalopathy, delayed post-hypoxic leukoencephalopathy and sometimes bradycardia, hypoglycemia and hypotension. Severe overdose may result in apnea, circulatory collapse, cardiac arrest pulmonary edema and death.

Treatment

Primary attention should be given to the establishment of adequate respiratory exchange through the provision of a patent airway and controlled or assisted ventilation. The opioid antagonist naloxone hydrochloride is a specific antidote against respiratory depression due to overdosage or as a result of unusual sensitivity to oxycodone. An appropriate dose of an opioid antagonist should therefore be administered, preferably by the intravenous route. The usual initial intravenous adult dose of naloxone is 0.4 mg or higher. Concomitant efforts at respiratory resuscitation should be carried out. Since the duration of action of oxycodone, particularly sustained release formulations, may exceed that of the antagonist, the patient should be under continued surveillance and doses of the antagonist should be repeated as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated.

In individuals physically dependent on opioids, the administration of the usual dose of narcotic antagonist will precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of antagonist administered. The use of narcotic antagonists in such individuals should be avoided if possible. If a narcotic antagonist must be used to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care by using dosage titration, commencing with 10% to 20% of the usual recommended initial dose.

Evacuation of gastric contents may be useful in removing unabsorbed drug, particularly when a sustained release formulation has been taken.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Immediate Release Tablets / 5 mg, 10 mg and 20 mg	Tablets: crospovidone, lactose, microcrystalline cellulose, stearic acid. Tablet coating: hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyethylene glycol, titanium dioxide.

Dosage Forms

- Oxy•IR 5 mg are round, scored, white, biconvex tablets imprinted with Oxy•IR on one side and 5 on the other.
- Oxy•IR 10 mg are white, scored, capsule-shaped tablets imprinted with Oxy•IR on one side and 10

on the other.

- Oxy•IR 20 mg are white, scored, oval shaped tablets imprinted with Oxy•IR on one side and 20 on the other.

Composition

Oxy•IR 5 mg, 10 mg and 20 mg tablets contain the following nonmedicinal ingredients:

- Tablet Core: crospovidone, lactose, microcrystalline cellulose and stearic acid
- Tablet Coating: hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol and titanium dioxide

Packaging

All strengths are available in opaque plastic bottles of 60 tablets.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Patients should be instructed not to give Oxy•IR tablets to anyone other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death. Oxy•IR should be stored securely to avoid theft or misuse.

Oxy•IR should only be prescribed by health professionals who are knowledgeable in the continuous administration of potent opioids, in the management of patients receiving potent opioids for the treatment of pain, and in the detection and management of respiratory depression, including the use of opioid antagonists.

Patients should be cautioned not to consume alcohol while taking Oxy•IR, as it may increase the chance of experiencing dangerous side effects, including death.

Hyperalgesia that will not respond to a further dose increase of oxycodone can occur at particularly high doses. An oxycodone dose reduction or change in opioid may be required. Please see 7 WARNINGS AND PRECAUTIONS, Neurologic, Opioid-induced Hyperalgesia.

- **Addiction, Abuse and Misuse:** Like all opioids, Oxy•IR is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, Oxy•IR should be prescribed and handled with caution. This risk is increased if Oxy•IR is taken with alcohol or other CNS depressants.

  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 Oxy•IR, should be used with particular care in patients with a history of alcohol and illicit/prescription drug abuse and other mental health disorders including, but not limited to, major depression and anxiety. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

  Oxy•IR tablets are intended for oral use only. The tablets should be swallowed whole, and not chewed or crushed. With parenteral abuse, the tablet excipients can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular

heart injury. Abuse of oral dosage forms can be expected to result in serious adverse events, including death.

- **Patient Counselling Information:** A patient information sheet should be provided to patients when Oxy•IR tablets are dispensed to them.

  Patients receiving Oxy•IR should be given the following instructions by the health professional:

1. 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.
2. Patients should be advised that Oxy•IR contains oxycodone, an opioid pain medicine.
3. Patients should be advised that Oxy•IR should only be taken as directed. The dose of Oxy•IR should not be adjusted without consulting with a health professional.
4. Oxy•IR must be swallowed whole (not cut, broken, chewed, dissolved or crushed) due to the risk of fatal oxycodone overdose.
5. Patients should be advised to report episodes of pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
6. Patients should not combine Oxy•IR with alcohol or other central nervous system depressants (sleep aids, tranquilizers) because dangerous additive effects may occur, resulting in serious injury or death.
7. Patients should be advised to consult their health professional or pharmacist if other medications are being used or will be used with Oxy•IR.
8. Patients should be advised that if they have been receiving treatment with Oxy•IR and cessation of therapy is indicated, it may be appropriate to taper the Oxy•IR dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms.
9. Patients should be advised that the most common adverse reactions that may occur while taking Oxy•IR are asthenia, constipation, dizziness, dry mouth, fatigue, headache, lethargy, nausea, pruritus, somnolence, sweating and vomiting.
10. Patients should be advised that Oxy•IR may cause drowsiness, dizziness, or light-headedness and may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery). Patients started on Oxy•IR 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 Oxy•IR.
11. Patients should be advised that Oxy•IR is a potential drug of abuse. They should protect it from theft or misuse.
12. Patients should be advised that Oxy•IR should never be given to anyone other than the individual for whom it was prescribed.
13. Women of childbearing potential who become or are planning to become pregnant should be advised to consult a health professional prior to initiating or continuing therapy with Oxy•IR. Women who are breast-feeding or pregnant should not use Oxy•IR.

Carcinogenesis and Mutagenesis

See 16 NON-CLINICAL TOXICOLOGY.

Cardiovascular

- **Hypotension:** Oxycodone administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of such drugs as phenothiazines and other tranquilizers, sedatives, hypnotics, tricyclic antidepressants or general anesthetics. These patients should be monitored for signs of hypotension after initiating or titrating the dose of Oxy•IR.

  The use of Oxy•IR in patients with circulatory shock should be avoided as it may cause vasodilation that can further reduce cardiac output and blood pressure.

Dependence/Tolerance

As with other opioids, tolerance, physical and psychological dependence, as well as opioid use disorder (OUD) may develop upon repeated administration of Oxy•IR.

Physical dependence and tolerance reflect the neuroadaptation of the opioid receptors to chronic exposure to an opioid 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 opioid use disorder.

Tolerance may occur to both the desired and undesired effects of drugs and may develop at different rates for different effects.

The patient may develop analgesic tolerance to the drug with chronic use.

Prolonged use of this product may lead to physical dependence and a withdrawal syndrome may occur upon abrupt cessation of therapy. When a patient no longer requires therapy with oxycodone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal (See 4.2 Recommended Dose and Dosage Adjustment, Adjustment or Reduction of Dosage). Given the increased risk for serious harms associated with increasing doses, opioid use should be limited to the minimum dose and duration needed to manage pain.

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

Repeated use of Oxy•IR may lead to Opioid Use Disorder (OUD). A higher dose and longer duration of opioid treatment may increase the risk of developing OUD. Abuse or intentional misuse of Oxy•IR may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with Oxy•IR and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see 4.1 Dosing Considerations). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their health professional.

Patients will require monitoring for signs of drug-seeking behavior (e.g., too early requests for refills). The health professional should conduct a review of concomitant opioids and psycho-active drugs (like

benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist. Some of the symptoms that may be associated with abrupt withdrawal of an opioid analgesic include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, anxiety, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning (see 8 ADVERSE REACTIONS and 4.2 Recommended Dose and Dosage Adjustment, Adjustment or Reduction of Dosage).

- **Use in Drug and Alcohol Addiction:** Oxy•IR is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia. Patients with a history of addiction to drugs or alcohol may be at higher risk of becoming addicted to Oxy•IR; extreme caution and awareness is warranted to mitigate the risk.
- **Neonatal Opioid Withdrawal Syndrome (NOWS):** Prolonged maternal use of opioid 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 Oxy•IR is contraindicated in pregnant women (see 2 CONTRAINDICATIONS).

Driving and Operating Machinery

Oxy•IR may impair the mental and/or physical abilities needed for certain potentially hazardous activities such as driving a car or operating machinery. Patients should be cautioned accordingly. Patients should also be cautioned about the combined effects of oxycodone with other CNS depressants, including other opioids, phenothiazine, sedatives, hypnotics and alcohol.

Endocrine and Metabolism

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

Gastrointestinal

Oxycodone and other morphine-like opioids have been shown to decrease bowel motility. Oxycodone may obscure the diagnosis or clinical course of patients with acute abdominal conditions and is also

contraindicated in patients with paralytic ileus, acute appendicitis and acute pancreatitis. (see 2 CONTRAINDICATIONS; 8.1 Adverse Reaction Overview, Nausea and Vomiting, and 8.1 Adverse Reaction Overview, Constipation).

Hepatic/Biliary/Pancreatic

Oxycodone may cause dysfunction and spasm of the Sphincter of Oddi, and an increase in intrabiliary pressure. Other opioid related effects may include a reduction in biliary and pancreatic secretions or elevations in serum amylase. Therefore, oxycodone has to be administered with caution in patients with pancreatitis and diseases of the biliary tract. Monitor patients with biliary tract disease for worsening symptoms.

Neurologic

- **Interactions with CNS Depressants (including benzodiazepines and alcohol):** Oxycodone should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics, general anesthetics, phenothiazines and other tranquilizers, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, benzodiazepines, gabapentinoids, baclofen, centrally-active anti-emetics and other CNS depressants. Respiratory depression, hypotension and profound sedation, coma or death may result.

  Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (see 9.2 Drug Interactions Overview, Interactions with CNS Depressants (including benzodiazepines and alcohol)). If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

  Advise both patients and caregivers about the risks of respiratory depression and sedation when Oxy•IR is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see 9.2 Drug Interactions Overview, Interactions with CNS Depressants (including benzodiazepines and alcohol)).

  Oxy•IR should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see 2 CONTRAINDICATIONS; 8.1 Adverse Reaction Overview, Sedation, and 9.3 Drug-Behavioural Interactions).

  Severe pain antagonizes the subjective and respiratory depressant actions of opioid analgesics. Should pain suddenly subside, these effects may rapidly become manifest.

- **Serotonin Toxicity / Serotonin Syndrome:** Serotonin toxicity also known as serotonin syndrome is a

potentially life-threatening condition and has been reported with oxycodone, including Oxy•IR, particularly during combined use with other serotonergic drugs (see 9.4 Drug-Drug Interactions, Serotonergic Agents).

Serotonin toxicity is characterised by neuromuscular excitation, autonomic stimulation (e.g. tachycardia, flushing, labile blood pressure, hyperthermia), and altered mental state (e.g. anxiety, agitation, hypomania). In accordance with the Hunter Criteria, serotonin toxicity diagnosis is likely when, in the presence of at least one serotonergic agent, one of the following is observed:

- Spontaneous clonus
- Inducible clonus or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature >38°C and ocular clonus or inducible clonus.

If concomitant treatment with Oxy•IR and other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see 9.4 Drug-Drug Interactions, Serotonergic Agents). If serotonin toxicity is suspected, discontinuation of the serotonergic agents should be considered.

- **Head Injury:** The respiratory depressant effects of oxycodone, and the capacity to elevate cerebrospinal fluid pressure, may be greatly increased in the presence of an already elevated intracranial pressure produced by trauma. Also, oxycodone may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, oxycodone should not be used (see 2 CONTRAINDICATIONS).
- **Use in Patients with Convulsive or Seizure Disorders:** The oxycodone hydrochloride in Oxy•IR may aggravate convulsions in patients with convulsive disorders and may induce or aggravate seizures in some clinical settings. Therefore, Oxy•IR should not be used in these patients (see 2 CONTRAINDICATIONS).
- **Opioid-induced hyperalgesia:** Opioid induced hyperalgesia (OIH) is a paradoxical response to an opioid in which there is an increase in pain perception despite stable or increased opioid exposure. It differs from tolerance, in which higher opioid doses are required to achieve the same analgesic effect or treat recurring pain. Clinically, OIH may be associated with high opioid doses, long term opioid treatment, and intra-operative opioid use. OIH may manifest as an unexplained increase in pain, more diffuse pain than pre-existing, or as pain from ordinary (i.e., non-painful) stimuli (allodynia) in the absence of disease progression. When OIH is suspected, the dose of opioid should be reduced or tapered off, if possible. It is reasonable to consider opioid rotation, or the use of a non-opioid strategy for pain control. There is currently no well-established treatment for OIH.

Peri-Operative Considerations

Oxy•IR is not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative pain).

In the case of planned chordotomy or other pain-relieving operations, patients should not be treated with Oxy•IR for at least 24 hours before the operation and Oxy•IR should not be used in the immediate post-operative period.

Health professionals should individualize treatment, moving from parenteral to oral analgesics as appropriate. Thereafter, if Oxy•IR is to be continued after the patient recovers from the post-operative

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.

The administration of analgesics in the peri-operative period should be managed by health professionals with adequate training and experience (e.g., by an anesthesiologist).

Oxycodone and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common post-operative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in post-operative patients receiving opioids. Standard supportive therapy should be implemented.

Oxy•IR should not be used in the early post-operative period (12 to 24 hours post-surgery) unless the patient is ambulatory and gastrointestinal function is normal.

Reproductive Health: Female and Male Potential

- **Fertility**

  Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (see 8.5 Post-Market Adverse Reactions, Androgen deficiency).

- **Teratogenic Risk**

  - **Neonatal Opioid Withdrawal Syndrome (NOWS):** Prolonged maternal use of Oxy•IR during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance, Neonatal Opioid Withdrawal Syndrome (NOWS)).

    Use of Oxy•IR is contraindicated in pregnant women (see 2 CONTRAINDICATIONS).

Respiratory

- **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. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. Oxycodone hydrochloride should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia (see 2 CONTRAINDICATIONS).

  While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of Oxy•IR, 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 Oxy•IR and following dose increases.

  Life-threatening respiratory depression is more likely to occur in the elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

  To reduce the risk of respiratory depression, proper dosing and titration of Oxy•IR are essential. Overestimating the Oxy•IR dose when converting patients from another opioid product can result in a fatal overdose with the first dose. In these patients, the use of non-opioid analgesics should be

considered, if feasible (see WARNINGS AND PRECAUTIONS, Special Populations, Special Risk Groups, and DOSAGE AND ADMINISTRATION).

- **Use in Patients with Chronic Pulmonary Disease:** Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression for respiratory depression, particularly when initiating therapy and titrating with Oxy•IR, as in these patients, even usual therapeutic doses of Oxy•IR may decrease respiratory drive to the point of apnea. In these patients, use of alternative non-opioid analgesics should be considered, if possible. The use of Oxy•IR is contraindicated in patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see 2 CONTRAINDICATIONS).

- **Sleep related breathing disorder:** Opioids can cause sleep-related breathing disorders such as sleep apnea syndromes (including central sleep apnea [CSA]) and hypoxemia (including sleep-related hypoxemia). Opioid use increases the risk of CSA in a dose-dependent fashion. Evaluate patients on an ongoing basis for the onset of a new sleep apnea, or a worsening of an existing sleep apnea. In patients who present with CSA, consider decreasing the total opioid dosage or stopping the opioid treatment if appropriate, using best practices for tapering of opioids (see 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance and 4.2 Recommended Dose and Dosage Adjustment, Adjustment or Reduction of Dosage).

7.1 Special Populations

- **Special Risk Groups:**

  Oxycodone should be administered with caution to patients with a history of alcohol and drug abuse and in a reduced dosage to debilitated patients, and in patients with severely impaired pulmonary function, Addison's disease, hypothyroidism, myxedema, toxic psychosis, prostatic hypertrophy, urethral stricture or diseases of the biliary tract.

  Opioid analgesics, including oxycodone, should also be used with caution in patients about to undergo surgery of the biliary tract, since it may cause spasm of the sphincter of Oddi.

  Patients with Hepatic and Renal Impairment:

  Oxycodone should be administered with caution to patients with any degree of hepatic or renal impairment, the dose initiation and titration should follow a conservative approach (see 4 DOSAGE AND ADMINISTRATION and 10.3 Pharmacokinetics, Special Populations and Conditions).

7.1.1 Pregnant Women

Studies in humans have not been conducted. Oxy•IR crosses the placental barrier and is contraindicated in pregnant women (see 2 CONTRAINDICATIONS).

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal Opioid Withdrawal Syndrome (NOWS), unlike opioid withdrawal syndrome in adults, can be life-threatening (see 7 WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome (NOWS)).

Pregnant women using opioids should not discontinue their medication abruptly as this can cause pregnancy complications such as miscarriage or still-birth. Tapering should be slow and under medical supervision to avoid serious adverse events to the fetus.

7.1.2 Breast-feeding

Oxy•IR is contraindicated during labour, delivery, pregnancy and in nursing mothers. Oxycodone can cross the placental barrier and is also excreted in breast milk. Life threatening respiratory depression can occur in the infant if opioids are administered to the mother. Naloxone, a drug that counters the effects of opiates, should be readily available if Oxy•IR is used in this population.

7.1.3 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of Oxy•IR has not been studied in the pediatric population. Therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range and titrated slowly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see 4.2 Recommended Dose and Dosage Adjustment, Geriatrics and 10.3 Pharmacokinetics, Special Populations and Conditions, Geriatrics).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Adverse effects of Oxy•IR tablets are similar to those of other opioid analgesics and represent an extension of pharmacological effects of the drug class. The major hazards of opioids include respiratory and central nervous system depression and to a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest.

The most frequently observed adverse effects of Oxy•IR are asthenia, constipation, dizziness, dry mouth, headache, fatigue, hyperhidrosis, lethargy, nausea, pruritus, somnolence and vomiting.

- **Sedation:** Sedation is a common side effect of opioid analgesics, especially in opioid naïve individuals. Sedation may also occur partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Most patients develop tolerance to the sedative effects of opioids within three to five days and, if the sedation is not severe, will not require any treatment except reassurance. If excessive sedation persists beyond a few days, the dose of the opioid should be reduced and alternate causes investigated. Some of these are: concurrent CNS depressant medication, hepatic or renal dysfunction, brain metastases, hypercalcemia and respiratory failure. If it is necessary to reduce the dose, it can be carefully increased again after three or four days if it is obvious that the pain is not being well controlled. Dizziness and unsteadiness may be caused by postural hypotension, particularly in elderly or debilitated patients, and may be alleviated if the patient lies down.
- **Nausea and Vomiting:** Nausea is a common side effect on initiation of therapy with opioid analgesics and is thought to occur by activation of the chemoreceptor trigger zone, stimulation of the vestibular apparatus and through delayed gastric emptying. The prevalence of nausea declines following continued treatment with opioid analgesics. When instituting therapy with an opioid for

chronic pain, the routine prescription of an antiemetic should be considered. In the cancer patient, investigation of nausea should include such causes as constipation, bowel obstruction, uremia, hypercalcemia, hepatomegaly, tumor invasion of celiac plexus and concurrent use of drugs with emetogenic properties. Persistent nausea which does not respond to dosage reduction may be caused by opioid-induced gastric stasis and may be accompanied by other symptoms including anorexia, early satiety, vomiting and abdominal fullness. These symptoms respond to chronic treatment with gastrointestinal prokinetic agents.

- **Constipation:** Practically all patients become constipated while taking opioids on a persistent basis. In some patients, particularly the elderly or bedridden, fecal impaction may result. It is essential to caution the patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged opioid therapy. Stimulant laxatives, stool softeners, and other appropriate measures should be used as required. As fecal impaction may present as overflow diarrhea, the presence of constipation should be excluded in patients on opioid therapy prior to initiating treatment for diarrhea.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The following adverse effects occur with opioid analgesics and include those reported in Oxy•IR clinical trials. The reactions are categorized by body system and frequency according to the following definitions: Very common (≥ 1/10); Common (≥ 1/100 to <1/10); Uncommon (≥ 1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (< 1/10,000), Not known (cannot be estimated from the available data).

- **Blood and Lymphatic System Disorders:**

  Not known: lymphadenopathy

- **Cardiac Disorders:**

  Uncommon: palpitations, tachycardia

  Not known: ST depression

- **Ear and Labyrinth Disorders:**

  Uncommon: vertigo, tinnitus

- **Eye Disorders:**

  Uncommon: miosis, visual impairment

- **Gastrointestinal Disorders:**

  Very common: constipation, nausea, vomiting

  Common: abdominal pain, diarrhea, dry mouth, dyspepsia

  Uncommon: dysphagia, eructation, flatulence, gastritis, hiccups, ileus, stomatitis

  Not known: biliary spasm

- **General Disorders and Administration Site Conditions:**

  Common: asthenia, fatigue, fever, hypotonia

  Uncommon: abnormal gait, chest pain, chills, edema, edema peripheral, malaise, thirst
  Not known: opioid tolerance, opioid withdrawal syndrome

- **Immune System Disorders:**

  Uncommon: hypersensitivity

- **Investigations**

  Uncommon: weight loss

- **Metabolism and Nutrition Disorders:**

  Common: decreased appetite

  Uncommon: dehydration

  Rare: increased appetite

- **Nervous System Disorders:**

  Very common: dizziness, headache, somnolence

  Common: tremor, lethargy

  Uncommon: amnesia, convulsion, dysgeusia, hypertonia, hypoaesthesia, migraine, muscle contractions involuntary, paresthesia, seizure, speech disorder, syncope

- **Psychiatric Disorders:**

  Common: abnormal dreams, anxiety, confusional state, depression, insomnia, nervousness, thinking abnormal

  Uncommon: affect lability, agitation, depersonalization, euphoric mood, hallucination, libido decreased
  Rare: dysphoria

  Not known: delirium, drug dependence

- **Renal and Urinary Disorders:**

  Uncommon: dysuria, hematuria, polyuria, urinary retention or hesitancy

- **Reproductive System and Breast Disorders:**

  Uncommon: erectile dysfunction

  Not known: amenorrhea

- **Respiratory, Thoracic, and Mediastinal Disorders:**

  Common: dyspnea

  Uncommon: bronchitis, cough, pharyngitis, yawning

  Rare: sinusitis

  Not known: bronchospasm, obstructive sleep apnea syndrome, pneumonia

- **Skin and Subcutaneous Tissue Disorders:**

  Very common: pruritus

  Common: hyperhidrosis, rash

  Uncommon: dry skin, exfoliative dermatitis

  Rare: urticaria

- **Vascular Disorders:**

  Common: orthostatic hypotension

  Uncommon: vasodilatation

  Rare: hypotension

8.5 Post-Market Adverse Reactions

The following relevant adverse reactions have been identified from post-approval use of Oxy•IR. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- **Adrenal insufficiency:** Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Adrenal Insufficiency).
- **Androgen deficiency:** Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.
- **Hypoglycemia:**
  Cases of hypoglycemia have been reported in patients taking opioids. Most reports were in patients with at least one predisposing risk factor (e.g., diabetes)
- **Serotonin syndrome:** Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Aggression, anaphylactic reaction and anaphylactoid reaction, central sleep apnea syndrome, cholestasis, dental caries, drug withdrawal syndrome neonatal, hyperalgesia, hypogonadism, increased hepatic enzyme, pulmonary edema, respiratory depression and Sphincter of Oddi dysfunction have been reported during post-marketing experience with oxycodone.

There have also been reported post-marketing cases of Neonatal Opioid Withdrawal Syndrome (NOWS) in patients treated with oxycodone (see 7 WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal

Syndrome (NOWS)).

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- Risks from concomitant use of opioids and benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see 7 WARNINGS AND PRECAUTIONS, Neurologic, Interactions with CNS Depressants (including benzodiazepines and alcohol))
    - Reserve concomitant prescribing of Oxy•IR and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate
    - Consider dose reduction of CNS depressants in situations of concomitant prescribing
    - Follow patients for signs and symptoms of respiratory depression and sedation
- MAO inhibitors intensify the effects of opioid drugs which can cause anxiety, confusion and decreased respiration. Oxy•IR is contraindicated in patients receiving MAO inhibitors or who have used them within the previous 14 days.

9.2 Drug Interactions Overview

- **Interactions with CNS Depressants (including benzodiazepines and alcohol):** Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants (e.g. other opioids, sedatives, gabapentinoids such as pregabalin, baclofen, hypnotics, antidepressants, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, phenothiazines, neuroleptics, antihistamines, antiemetics and alcohol) and beta-blockers, increases the risk of respiratory depression, profound sedation, coma, and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see 7 WARNINGS AND PRECAUTIONS, Neurologic, Interactions with CNS Depressants (including benzodiazepines and alcohol)). Oxy•IR should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.
- **Interactions with Anticholinergics:** Concomitant administration of oxycodone with anticholinergics or medications with anticholinergic activity (e.g., tricyclic antidepressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects.

9.3 Drug-Behavioural Interactions

The concomitant use of alcohol should be avoided (see 7 WARNINGS AND PRECAUTIONS, General).

9.4 Drug-Drug Interactions

- **Drugs Metabolized by Cytochrome P450 Isozymes:** Oxycodone is metabolized in part by cytochrome P450 2D6 and cytochrome P450 3A4 pathways. The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs or dietary elements.

Oxycodone doses may need to be adjusted.

- **Inhibitors of CYP3A4:** Since the CYP3A4 isoenzyme plays a major role in the metabolism of Oxy•IR, drugs that inhibit CYP3A4 activity, such as macrolide antibiotics (e.g., clarithromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir) and grapefruit juice may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. A published study showed that the co-administration of the antifungal drug, voriconazole, increased oxycodone AUC and Cmax by 3.6- and 1.7-fold, respectively. Although clinical studies have not been conducted with other CYP3A4 inhibitors, the expected clinical results would be increased or prolonged opioid effects. If co-administration with Oxy•IR is necessary, caution is advised when initiating therapy with, currently taking, or discontinuing CYP450 inhibitors. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved.
- **Inducers of CYP3A4:** CYP450 inducers, such as rifampin, carbamazepine, phenytoin, and St. John's wort, may induce the metabolism of oxycodone and, therefore, may cause increased clearance of the drug which could lead to a decrease in oxycodone plasma concentrations, lack of efficacy or possibly the development of an abstinence syndrome in a patient who had developed physical dependence to oxycodone. A published study showed that the co-administration of rifampin, a drug metabolizing enzyme inducer, decreased oxycodone (oral) AUC and Cmax by 86% and 63% respectively. If co-administration with Oxy•IR is necessary, caution is advised when initiating therapy with, currently taking or discontinuing CYP3A4 inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved.
- **Inhibitors of CYP2D6:** Oxycodone is metabolized in part to oxymorphone via cytochrome CYP2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone, and quinidine as well as polycyclic antidepressants), such blockade has not been shown to be of clinical significance during oxycodone treatment.
- **Administration with Mixed Activity Agonist/Antagonist Opioids:** Mixed agonist/antagonist opioid analgesics (i.e., pentazocine, nalbuphine, butorphanol, and buprenorphine) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as oxycodone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients.
- **MAO Inhibitors:** MAO Inhibitors intensify the effects of opioid drugs which can cause anxiety, confusion and decreased respiration. Oxy•IR is contraindicated in patients receiving MAO Inhibitors or who have used them within the previous 14 days (see 2 CONTRAINDICATIONS).
- **Warfarin and Other Coumarin Anticoagulants:** Clinically relevant changes in International Normalized Ratio (INR or Quick-value) in both directions have been observed in individuals when oxycodone and coumarin anticoagulants are co-administered.
- **Serotonergic Agents:** Co-administration of oxycodone with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI), may increase the risk of serotonin syndrome, a potentially life-threatening condition (see 7

WARNINGS AND PRECAUTIONS, Neurologic, Serotonin Toxicity/Serotonin Syndrome).

9.5 Drug-Food Interactions

Food has no significant effect on the extent of absorption of oxycodone from Oxy•IR.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Oxycodone is a semi-synthetic opioid analgesic which exerts an agonist effect at specific, saturable opioid receptors in the CNS and other tissues. In man, oxycodone produces a variety of effects including analgesia, constipation from decreased gastrointestinal motility, suppression of the cough reflex, respiratory depression from reduced responsiveness of the respiratory center to CO2, nausea and vomiting via stimulation of the chemoreceptor trigger zone, changes in mood including euphoria and dysphoria, sedation, mental clouding, and alterations of the endocrine and autonomic nervous systems.

10.2 Pharmacodynamics

Oxycodone retains at least one-half of its analgesic activity when administered orally and with acute dosing is approximately twice as potent as orally administered morphine.

There is no intrinsic limit to the analgesic effect of oxycodone; like morphine, adequate doses will relieve even the most severe pain. Clinically however, dosage limitations are imposed by the adverse effects, primarily respiratory depression, nausea and vomiting, which can result from high doses.

Oxycodone and related μ-agonist opioids produce their major effects on the CNS and the bowel by acting at specific saturable opioid receptors in the CNS and other tissues. The effects include analgesia, drowsiness, changes in mood, respiratory depression, cough suppression, decreased gastrointestinal motility, nausea, vomiting, and alterations of the endocrine and autonomic nervous systems.

Oxycodone receptor selectivity has not been extensively studied or characterized, and there appears to be a discrepancy between its weak affinity for opioid receptors and its potent antinociceptive activity.

Oxycodone has been shown to be 2 to 4 times more potent than morphine after both subcutaneous and intraperitoneal administration in rats. In clinical studies in patients with acute post-operative pain, oxycodone has been demonstrated to be twice as potent as morphine.

- **Cardiovascular System**

  Oxycodone may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus,

flushing, red eyes, hyperhidrosis and/or orthostatic hypotension.

- **Central Nervous System**

  Oxycodone produces respiratory depression by direct action on brain stem respiratory centres. The respiratory depression involves both a reduction in the responsiveness of the brain stem centres to increases in carbon dioxide (CO_2) tension and to electrical stimulation.

  Oxycodone depresses the cough reflex by direct effect on the cough centre in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

  Oxycodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of oxycodone overdose.

- **Endocrine System:** Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may be manifest from these hormonal changes.

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

- **Hepatobiliary System:**
  Opioids may induce biliary spasm.

- **Immune System:** In vitro and animal studies indicate that opioids have a variety of effects on immune functions, depending on the context in which they are used. The clinical significance of these findings is unknown.

- **Concentration – Efficacy Relationships:** Studies in normal volunteers and patients reveal predictable relationships between oxycodone dosage and plasma oxycodone concentrations, as well as between concentration and certain expected opioid effects, such as papillary constriction, sedation, overall subjective “drug effect”, analgesia and feelings of “relaxation”.

  The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. As a result, patients must be treated with individualized titration of dosage to the desired effect. The minimum effective analgesic concentration of oxycodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance.

- **Concentration – Adverse Reaction Relationship:** There is a significant relationship between increasing oxycodone plasma concentrations and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related

side effects.

10.3 Pharmacokinetics

Absorption

About 60% to 87% of an oral dose of oxycodone reaches the central compartment in comparison to a parenteral dose. The high oral bioavailability is due to low pre-systemic and/or first-pass metabolism.

Distribution:

Following intravenous administration, the steady-state volume of distribution (Vss) for oxycodone was 2.6 L/kg. Oxycodone binding to plasma protein at 37°C and a pH of 7.4 was about 45%. Once absorbed, oxycodone is distributed to skeletal muscle, liver, intestinal tract, lungs, spleen, and brain. Oxycodone has been found in breast milk.

Metabolism:

Oxycodone is extensively metabolized by multiple metabolic pathways to produce noroxycodone, oxymorphone and noroxymorphone, which are subsequently glucuronidated. Noroxycodone and noroxymorphone are the major circulating metabolites. CYP3A mediated N-demethylation to noroxycodone is the primary metabolic pathway of oxycodone with a lower contribution from CYP2D6 mediated O-demethylation to oxymorphone. Therefore, the formation of these and related metabolites can, in theory, be affected by other drugs (see 9.4 Drug-Drug Interactions).

Noroxycodone exhibits very weak anti-nociceptive potency compared to oxycodone, however, it undergoes further oxidation to produce noroxymorphone, which is active at opioid receptors. Although noroxymorphone is an active metabolite and is present at relatively high concentrations in circulation, it does not appear to cross the blood-brain barrier to a significant extent.

Oxymorphone has been shown to be active and possessing analgesic activity but its contribution to analgesia following oxycodone administration is thought to be clinically insignificant. Other metabolites (α- and β-oxycodol, noroxycodol and oxymorphol) may be present at very low concentrations and demonstrate limited penetration in to the brain as compared to oxycodone. The enzymes responsible for keto-reduction and glucuronidation pathways in oxycodone metabolism have not been established.

Oxycodone has an elimination half-life of approximately 3 hours.

Elimination

Oxycodone and its metabolites are excreted in both urine and feces. The amounts measured in the urine have been reported as follows: free and conjugated oxycodone 8.9%, free noroxycodone 23%, free oxymorphone less than 1%, conjugated oxymorphone 10%, free and conjugated noroxymorphone 14%, reduced free and conjugated metabolites up to 18%. The total plasma clearance was approximately 1.4 L/min in adults.

Special Populations and Conditions

- **Pediatrics (<18 years of age):** Oxy•IR has not been studied in children and is not indicated for patients less than 18 years of age.
- **Geriatrics (>65 years of age):** The plasma concentrations of oxycodone are 15% greater in elderly as compared to young subjects. 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, and of concomitant disease or other drug therapy.

- **Sex:** Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis.
- **Hepatic Insufficiency:** Data from a study involving 24 patients with mild to moderate hepatic impairment show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, than subjects with normal hepatic function. The AUC values were 95% and 65% higher, respectively. Oxymorphone peak plasma concentrations and AUC values were lower by 30% and 40%. These differences are accompanied by increases in some, but not other, drug effects. The mean elimination half-life for oxycodone increased by 2.3 hours.
- **Renal Insufficiency:** Data from a pharmacokinetic study involving 13 patients with mild to severe renal impairment showed peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, and AUC values for oxycodone, noroxycodone, and oxymorphone 60%, 50%, and 40% higher than normal subjects, respectively. This was accompanied by an increase in sedation but not by differences in respiratory rate, pupillary constriction, or several other measures of drug effect. The mean elimination half-life for oxycodone increased by 1 hour.

11 STORAGE, STABILITY AND DISPOSAL

- **Storage:** Store Oxy•IR tablets at room temperature (15° - 30°C). Keep in a dry place.
- **Disposal:** Oxy•IR should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired Oxy•IR should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets. Oxy•IR should not be shared with others and steps should be taken to protect it from theft or misuse. The patient should speak to their pharmacist about temporary storage options, if required, until the medication can be returned to the pharmacy for safe disposal.

12 SPECIAL HANDLING INSTRUCTIONS

Oxy•IR should be kept in a safe place, such as under lock and out of the sight and reach of children before, during and after use. Oxy•IR should not be used in front of children since they may copy these actions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

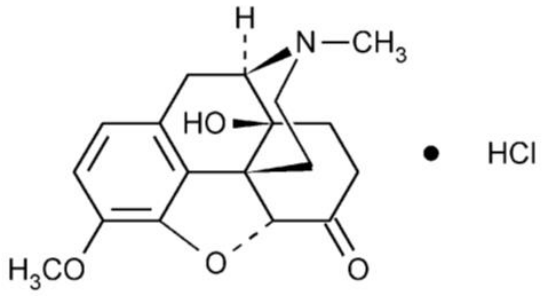
Drug Substance

Proper name: Oxycodone hydrochloride

Chemical name: 4,5αEpoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride

Molecular formula and molecular mass: $C_{18}H_{21}NO_4$•HCl / 351.83

Structural formula:



Product Characteristics

Physicochemical properties: Oxycodone is a semi-synthetic derivative of the naturally occurring opium alkaloid, thebaine.

Appearance: White to off-white, odourless, crystalline powder.

Solubility: Soluble in water, slightly soluble in alcohol.

Melting Point: 218° to 223°C

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Studies with immediate release (IR) oxycodone hydrochloride tablets and controlled release (CR) oxycodone tablets in normal volunteers and patients demonstrate a consistent relationship between oxycodone dosage and plasma oxycodone concentrations, as well as between concentration and pharmacodynamic effects. In patients with cancer pain, IR oxycodone administered four times per day produced equivalent analgesia to controlled release oxycodone tablets administered q12h. In patients with low back pain, IR oxycodone given four times per day and controlled release oxycodone tablets administered q12h, were equally effective. Titration to analgesic effect was achieved as easily with IR oxycodone as with controlled release oxycodone tablets.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: The LD50 after subcutaneous administration of oxycodone in mice was 275 – 340 mg/kg. The lowest lethal dose has been reported to be 200 mg/kg after subcutaneous administration in mice. These values are similar to those obtained for morphine. In a preliminary 12-day study in rabbits, no drug related toxic effects were discernible at 5 mg/kg. Doses of 25, 75 and 150 mg/kg were associated with variable and transient pharmacotoxic effects typical of high dose opioid treatment in animals (decreased activity, decreased or absent defecation and convulsions).

Carcinogenicity: Studies of oxycodone in animals to evaluate its carcinogenic potential have not been conducted owing to the length of clinical experience with the drug substance.

Genotoxicity:

- **Mutagenicity:** Oxycodone was not mutagenic in the following assays: Ames Salmonella and E. coli

test with and without metabolic activation at doses of up to 5,000 µg, chromosomal aberration test in human lymphocytes in the absence of metabolic activation at doses of up to 1,500 µg/mL and with activation 48 hours after exposure at doses of up to 5,000 µg/mL, and in the in vivo bone marrow micronucleus test in mice at plasma levels of up to 48 µg/mL.

Mutagenic results occurred in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1,250 µg/mL) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 µg/mL or greater with metabolic activation and at 400 µg/mL or greater without metabolic activation. The data from these tests indicate that the genotoxic risk to humans may be considered low.

Reproductive and Developmental Toxicology:

- **Teratogenicity:** Oxycodone had no effect on fertility or early embryonic development in male and female rats at doses as high as 8 mg/kg/day. Also, oxycodone did not induce any malformations in rats at doses as high as 8 mg/kg/day or in rabbits at doses as high as 125 mg/kg/day. Dose-related increases in developmental variations (increased incidences of extra (27) presacral vertebrae and extra pairs of ribs) were observed in rabbits when the data for individual fetuses were analyzed. However, when the same data were analyzed using litters as opposed to individual fetuses, there was no dose-related increase in developmental variations although the incidence of extra presacral vertebrae remained significantly higher in the 125 mg/kg/day group compared to the control group. Since this dose level was associated with severe pharmacotoxic effects in the pregnant animals, the fetal findings may have been a secondary consequence of severe maternal toxicity.

  In a study of prenatal and postnatal development study in rats, maternal body weight and food intake parameters were reduced for doses ≥2 mg/kg/day compared to the control group. Body weights were lower in the F1 generation from maternal rats in the 6 mg/kg/day dosing group. There were no effects on physical, reflexological, or sensory developmental parameters or on behavioural and reproductive indices in the F1 pups (the NOEL for F1 pups was 2 mg/kg/day based on body weight effects seen at 6 mg/kg/day). There were no effects on the F2 generation at any dose in the study.

  There are no adequate and well-controlled studies in pregnant women, and no studies on fertility or the post-natal effects of intrauterine exposure have been carried out.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

^{N}Oxy•IR®

Oxycodone Hydrochloride Immediate Release Tablets

Read this carefully before you start taking **Oxy•IR** 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 **Oxy•IR**.

Serious Warnings and Precautions

- Even if you take Oxy•IR as prescribed you are at a risk for opioid addiction, abuse, and misuse. This can lead to overdose and death. To understand your risk of opioid addiction, abuse, and misuse you should speak to your healthcare professional.
- When you take Oxy•IR it must be swallowed whole. Do not cut, break, crush, chew, dissolve the tablet. This can be dangerous and can lead to death or seriously harm you.
- Life-threatening breathing problems can happen while taking Oxy•IR, especially if not taken as directed. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.
- Never give anyone your Oxy•IR. They could die from taking it. If a person has not been prescribed Oxy•IR, taking even one dose can cause a fatal overdose. This is especially true for children.
- If you took Oxy•IR while you were pregnant, whether for short or long periods of time or in small or large doses, your baby can suffer life-threatening withdrawal symptoms after birth. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has any of the following symptoms:
    - has changes in their breathing (such as weak, difficult or fast breathing);
    - is unusually difficult to comfort;
    - has tremors (shakiness);
    - has increased stools, sneezing, yawning, vomiting, or fever.

  Seek immediate medical help for your baby.
- Taking Oxy•IR with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.

What is Oxy•IR used for?

Oxy•IR is used in adults to manage moderate to severe pain.

It is NOT used “as-needed” to treat pain that you only have once in a while.

How does Oxy•IR work?

Oxy•IR is a painkiller belonging to the class of medicines known as opioids. It relieves pain by acting on specific nerve cells of the spinal cord and brain.

What are the ingredients in Oxy•IR?

Medicinal ingredient: oxycodone hydrochloride.

Non-medicinal ingredients: crospovidone, lactose, microcrystalline cellulose, and stearic acid. In addition, the tablet coating contains the following: hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol, and titanium dioxide.

Oxy•IR comes in the following dosage forms:

Immediate Release Tablets: 5 mg, 10 mg, and 20 mg of oxycodone hydrochloride.

Do not use Oxy•IR if:

- your healthcare professional did not prescribe it for you.
- you are allergic to oxycodone hydrochloride, or any of the other ingredients in Oxy•IR.
- you have mild pain that can be controlled by the occasional use of painkillers including those available without a prescription.
- you have severe asthma, trouble breathing, or other breathing problems.
- you have any heart problems.
- you have bowel blockage or narrowing of the stomach or intestines.
- you have a condition where the bowel does not work properly (ileus) or you have severe pain in your abdomen (for example from appendicitis or pancreatitis).
- you have increased pressure in your skull or a head injury.
- you have severe central nervous system (CNS) depression (nervous system slows down).
- you have or have a history with epilepsy.
- you suffer from alcoholism or alcohol withdrawal.
- you are being treated for narcotic withdrawal.
- you are opioid-dependent (need to keep taking opioids to avoid withdrawal symptoms).
- you have severe kidney problems.
- you are taking or have taken within the past 2 weeks a Monoamine Oxidase Inhibitor (MAOI) (such as phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline).
- you are going to have a surgery or operation, or have had a surgery in the last 24 hours.
- you are pregnant or planning to become pregnant or you are in labour and delivery.
- you are breastfeeding.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Oxy•IR. 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 kidney, liver, or lung problems.
- have been told you are at risk of having heart problems or seizures.
- have low blood pressure.
- have a sleep disorder which causes pauses in breathing or shallow breathing while sleeping (sleep apnea).
- have or have had problems with your mood (such as depression or anxiety), hallucinations, or other mental health problems.
- suffer from chronic or severe constipation.
- have problems with your thyroid, adrenal, or prostate gland.
- have circulatory problems (e.g., body does not get enough oxygen and nutrients to function properly due to lack of blood flow).
- have a history of pancreas or gall bladder problems.
- have a condition that causes weakness or frailty.
- have gastrointestinal (GI) problems.
- have difficulty urinating.
- are planning on drinking alcohol. Drinking alcohol while taking Oxy•IR may cause dangerous side effects, including death. Do not drink alcohol while taking Oxy•IR.
- are planning to breastfeed.
- are 65 years of age or older.
- have been told that you are "opioid tolerant". Ask your healthcare professional if you are unsure.
- have diabetes.

Other warnings you should know about:

Taking Oxy•IR can cause the following serious side effects:

- **Disorder of the adrenal gland:** You may develop a disorder of the adrenal gland called adrenal insufficiency. This means that your adrenal gland is not making enough of certain hormones. You may experience symptoms such as:
    - nausea, vomiting
    - feeling tired, weak or dizzy
    - decreased appetite

  You may be more likely to have problems with your adrenal gland if you have been taking opioids for longer than one month. Your healthcare professional may do tests, give you another medication, and slowly take you off Oxy•IR.

- **Serotonin toxicity (also known as serotonin syndrome):** Oxy•IR can cause serotonin toxicity, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop serotonin toxicity if you take Oxy•IR with certain anti-depressants or migraine medications.

  Serotonin toxicity symptoms include:

    - fever, sweating, shivering, diarrhea, nausea, vomiting;
    - muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
    - fast heartbeat, changes in blood pressure;

    - confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.
- **Sleep Apnea:** Opioids can cause a problem called sleep apnea (stopping breathing from time to time while sleeping). Tell your healthcare professional if you have a history of sleep apnea or if anyone notices that you stop breathing from time to time while sleeping.

See the **Serious side effects and what to do about them** table below for more information on these and other serious side effects.

Drug addiction, dependence, and tolerance: Like any opioid, if you use Oxy•IR for a long time, it may cause mental and physical dependence. Oxycodone hydrochloride also has the potential to cause addiction. There are important differences between physical dependence and addiction. If you use opioids for a long time, you may develop tolerance. This means that you may need higher doses of Oxy•IR to feel the same level of pain relief. It is important that you talk to your healthcare professional if you have questions or concerns about addiction, physical dependence, or tolerance. Your healthcare professional should prescribe and administer Oxy•IR with the same degree of caution appropriate to the use of other oral opioid medications. It is not recommended to use these products for a long period of time.

Pregnancy, nursing, labour and delivery: Do not use Oxy•IR while pregnant, nursing, during labour or delivery. Opioids can be transferred to your baby through breast milk, or while still in the womb. Oxy•IR can then cause life-threatening breathing problems in your unborn baby or nursing infant. If you become pregnant while taking Oxy•IR, tell your healthcare professional right away.

If you are pregnant and are taking Oxy•IR, it is important that you don't stop taking your medication all of a sudden. If you do, it can cause a miscarriage or a still-birth. Your healthcare professional will monitor and guide you on how to slowly stop taking Oxy•IR. This may help avoid serious harm to your unborn baby.

Driving and using machines: Before you do tasks which may require special attention, you should wait until you know how you react to Oxy•IR. Oxy•IR can cause:

- drowsiness,
- dizziness, or
- light headedness.

This can usually occur after you take your first dose and when your dose is increased.

Sexual function/reproduction: Long term use of opioids may lead to a decrease in sex hormone levels. It may also lead to low libido (desire to have sex), erectile dysfunction or being infertile.

Worsened pain: Taking opioids for pain can sometimes have the unintended effect of making your pain feel worse (opioid-induced hyperalgesia) even though your opioid dose has been unchanged or increased. This can also include feeling pain in new places in your body, or feeling pain from something that would not normally hurt, for example, feeling pain from clothing touching your skin. Tell your healthcare professional if you notice a change like this in your pain while you are taking Oxy•IR.

Testing and check-ups: Your healthcare professional will regularly monitor your health. This includes monitoring for signs of:

- misuse and abuse;
- sleep apnea (a sleep disorder which causes pauses in breathing or shallow breathing while sleeping);
- respiratory depression and sedation (e.g., slow, shallow, or weak breathing).

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

Serious Drug Interactions

Serious drug interactions with Oxy•IR include:

- benzodiazepines used to help you sleep or that help reduce anxiety.
- central nervous system (CNS) depressants used to slow down the nervous system. These can include:
  - other opioids and mixed opioid agonists/antagonists used to relieve pain (e.g., pentazocine, nalbuphine, butorphanol, and buprenorphine);
  - hypnotics used to help with sleeping;
  - antidepressants used for depression and mood disorders (e.g., tricyclic antidepressants; serotonin norepinephrine re-uptake inhibitors (SNRIs); and selective serotonin re-uptake inhibitors (SSRIs) such as St. John's Wort);
  - anxiolytics, tranquilizers, and phenothiazines used to treat mental or emotional disorders;
  - muscle relaxants used to treat muscle spasms and back pain (e.g., baclofen);
  - general anaesthetics used during surgery;
  - antipsychotics and neuroleptics used to treat mental health disorders;
  - antihistamines used to treat allergies;
  - antiemetics used to prevent nausea or vomiting;
  - sedatives which may enhance the drowsiness;
  - pregabalin, used to treat nerve pain;
  - gabapentin, used to prevent and control seizures in the treatment of epilepsy
  - beta blockers used to lower blood pressure;
  - alcohol. This includes prescription and non-prescription medications that contain alcohol. Do not drink alcohol while you are taking Oxy•IR. It can lead to drowsiness, unusually slow or weak breathing, serious side effects, or a fatal overdose.
- monoamine oxidase inhibitors (MAOIs) used to treat depression. Do not take Oxy•IR with MAOIs or if you have taken MAOI's in the last 14 days.

The following may also interact with Oxy•IR:

- anticoagulants used to thin the blood and prevent blood clots (e.g., warfarin).
- medicines that can affect the heart (e.g., amiodarone and quinidine).
- medicines used to treat Parkinson's Disease.
- antibiotics used to treat bacterial infections (e.g., clarithromycin and rifampin).
- antifungals used to treat fungal infections (e.g., ketoconazole and voriconazole).
- antiretrovirals used to treat viral infections (e.g., ritonavir).
- anticonvulsants used to treat seizures (e.g., carbamazepine, phenytoin).
- grapefruit juice.
- drugs used to treat migraines (e.g., triptans).

How to take Oxy•IR:

- Take Oxy•IR exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- Oxy•IR must be taken orally, by mouth. Do NOT administer the Oxy•IR tablets via any other route as this can cause serious harm, including death.

- **Swallow the whole tablet. Do not cut, break, crush, chew or dissolve Oxy•IR tablets. This can be dangerous and can lead to death or seriously harm you.**
- Oxy•IR can be taken with or without food.
- Review your pain regularly with your healthcare professional to determine if you still need Oxy•IR. Be sure to use Oxy•IR only for the condition for which it was prescribed.

Usual dose:

Your dose is tailored/personalized just for you. Take it exactly as your healthcare professional has told you to. Do not increase or decrease your dose without consulting your healthcare professional. Taking higher doses can lead to more side effects and a greater chance of overdose.

Stopping your Medication

If you have been taking Oxy•IR for more than a few days, you should not stop taking it all of a sudden. Your healthcare professional will monitor and guide you on how to slowly stop taking Oxy•IR. You should do it slowly to avoid uncomfortable symptoms such as having:

- body aches,
- diarrhea,
- goosebumps,
- loss of appetite,
- nausea,
- feeling nervous or restless,
- runny nose,
- sneezing,
- tremors or shivering,
- stomach cramps,
- rapid heart rate (tachycardia),
- having trouble sleeping,
- an unusual increase in sweating,
- heart palpitations,
- an unexplained fever,
- weakness,
- yawning.

By reducing or stopping your opioid treatment, your body will become less used to opioids. If you start treatment again, you will need to start at the lowest dose. You may overdose if you restart at the last dose you took before you slowly stopped taking Oxy•IR.

Refilling your Prescription for Oxy•IR

A new written prescription is required from your healthcare professional each time you need more Oxy•IR. Therefore, it is important that you contact your healthcare professional before your current supply runs out.

Only obtain prescriptions for this medicine from the healthcare professional in charge of your treatment. Do not seek prescriptions from other healthcare professionals unless you switch to another healthcare professional for your pain management.

Overdose:

Signs of overdose with Oxy•IR may include:

- unusually slow or weak breathing,
- dizziness,
- confusion,
- extreme drowsiness,
- shrinking of pupils,
- floppy muscles/low muscle tone,
- cold and clammy skin,
- toxic leukoencephalopathy (a brain disorder affecting the brain's white matter),
- slow heart rate,
- low blood pressure,
- sleep apnea (a sleep disorder which causes pauses in breathing or shallow breathing while sleeping),
- cardiac arrest (heart stops beating suddenly),
- pulmonary edema (build-up of fluid in the lungs),
- hypoglycemia (low blood sugar).

If you think you, or a person you are caring for, have taken too much Oxy•IR, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

It is important that you do not miss any doses. If you miss:

- **One dose:** Skip the missed dose and take your next dose as scheduled. Do not take two doses at once to make-up for the missed dose.
- **Several doses in a row:** Talk to your healthcare professional before restarting your medication.

What are possible side effects from using Oxy•IR?

These are not all the possible side effects you may have when taking Oxy•IR. If you experience any side effects not listed here, tell your healthcare professional.

Side effects with Oxy•IR may include:

- drowsiness,
- insomnia,
- dizziness,
- nausea, vomiting, or a poor appetite,
- dry mouth,
- headache,
- weakness, uncoordinated muscle movement,
- itching,
- sweating,
- constipation. Talk with your healthcare professional about ways to prevent constipation when you start using Oxy•IR.
- abdominal pain,

- fever,
- diarrhea,
- indigestion,
- tremor,
- abnormal dreams or thoughts,
- anxiety,
- confusion,
- depression,
- nervousness,
- rash,
- difficulty breathing,
- low sex drive, impotence (erectile dysfunction), infertility.

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**	
UNCOMMON			
Hallucinations: seeing or hearing things that are not there.			✓
Seizures (fit): uncontrollable shaking with or without loss of consciousness.			✓
RARE			
Allergic reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing.			✓
Bowel blockage (impaction): abdominal pain, severe constipation, or nausea.			✓
Fast, slow or irregular heartbeat: heart palpitations.		✓	
Hypotension (low blood pressure): dizziness, fainting, or light-headedness.	✓		
Overdose: hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone, or cold and clammy skin.			✓
Respiratory depression: slow, shallow or weak breathing.			✓

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**	
Serotonin toxicity (also known as serotonin syndrome): a reaction which may cause feelings of agitation or restlessness, flushing, muscle twitching, involuntary eye movements, heavy sweating, high body temperature (>38°C), or rigid muscles.			✓
Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, or sweating.		✓	
UNKNOWN FREQUENCY			
Disorder of the adrenal gland: nausea, vomiting, anorexia, fatigue, weakness, dizziness, or low blood pressure.			✓
Sleep apnea: stop breathing for short periods during your normal nightly sleep.		✓	

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

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store Oxy•IR at room temperature (15° - 30°C). Keep in a dry place.
- Keep unused or expired Oxy•IR in a secure place to prevent theft, misuse, or accidental exposure. It should be kept under lock, out of sight and reach of children and pets.
- Never take medicine in front of small children as they will want to copy you. Accidental ingestion by a child is dangerous and may result in death. If a child accidentally takes Oxy•IR, get emergency help

right away.

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

If you want more information about Oxy•IR:

- 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: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.purdue.ca, or by calling 1-800-387-4501.

This leaflet was prepared by Purdue Pharma.

Last Revised FEB 27, 2025

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