PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

^{N}OxyNEO®

Oxycodone Hydrochloride Controlled Release Tablets

Tablets, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg and 80 mg, Oral

Purdue Pharma Standard

Opioid Analgesic

N02AA05

Purdue Pharma

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, General, Addiction, Abuse and Misuse	07/2022
7 WARNINGS AND PRECAUTIONS, Neurologic, Serotonin Toxicity / Serotonin Syndrome	08/2020
7 WARNINGS AND PRECAUTIONS, Neurologic, Opioid-induced hyperalgesia	07/2022
7 WARNINGS AND PRECAUTIONS, Respiratory, Sleep Apnea	08/2020

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Sections or subsections that are not applicable at the time of authorization are not listed .

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

OxyNEO (oxycodone hydrochloride controlled release tablets) is indicated for:

- the management of pain severe enough to require daily, continuous, long-term opioid treatment, and:
  - that is opioid-responsive; and
  - for which alternative options are inadequate.

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

1.1 Pediatrics

- Pediatrics (<18 years of age): The safety and efficacy of OxyNEO 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): In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or other drug therapy (see 4 DOSAGE AND ADMINISTRATION).

2 CONTRAINDICATIONS

OxyNEO 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 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction, 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, intermittent or short duration pain that can be managed with other pain medications.
- The management of acute pain.
- 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 breastfeeding, pregnant, or during labour and delivery (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, 7.1.1 Pregnant Women, 7.1.2 Breast-feeding, and 7 WARNINGS AND PRECAUTIONS, Reproductive Health: Male and Female Potential, Teratogenic Risk, Neonatal Opioid Withdrawal Syndrome).

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 greater risks of overdose and death with controlled release opioid formulations, OxyNEO 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 DOSAGE AND ADMINISTRATION).

- Addiction, Abuse, and Misuse

  OxyNEO 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 OxyNEO, and all patients should be monitored regularly for the development of these behaviours or conditions (see 7 WARNINGS AND PRECAUTIONS, General, Addiction, Abuse and Misuse). OxyNEO 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 OxyNEO. 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 OxyNEO or following a dose increase (see 7 WARNINGS AND PRECAUTIONS, Respiratory, Respiratory Depression).

  OxyNEO must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving OxyNEO can lead to rapid release and absorption of a potentially fatal dose of oxycodone (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 OxyNEO, 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 OxyNEO during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see 7 WARNINGS AND PRECAUTIONS, Reproductive Health: Male and Female Potential, Teratogenic Risk, Neonatal Opioid Withdrawal Syndrome).

- Interaction with Alcohol

  The co-ingestion of alcohol with OxyNEO 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).

  - Reserve concomitant prescribing of OxyNEO 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

- **OxyNEO should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, or not tolerated, or would be otherwise inadequate to provide appropriate management of pain.**
- **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 OxyNEO not be exceeded. Each patient should be assessed for their risk prior to prescribing OxyNEO, 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 OxyNEO (see 4.2 Recommended Dose and Dosage Adjustment, Adjustment or Reduction of Dosage).**
- **OxyNEO tablets must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving OxyNEO can lead to rapid release and absorption of a potentially fatal dose of oxycodone (see 7 WARNINGS AND PRECAUTIONS, General, Addiction, Abuse and Misuse).**
- **There have been post-marketing reports of difficulty swallowing OxyNEO tablets. These reports include choking, gagging, regurgitation and tablets stuck in the throat. If patients experience such swallowing difficulties or pain after taking OxyNEO tablets, they are advised to seek immediate medical attention. To avoid difficulty swallowing OxyNEO, tablets should not be pre-soaked, licked or otherwise wetted prior to placing in the mouth and should be taken one tablet at a time with enough water to ensure complete swallowing immediately after placing it in the mouth (see Patient Counselling Information). OxyNEO should not be taken by patients with difficulty in swallowing or who have been diagnosed with narrowing of the esophagus.**
- **Do not administer OxyNEO via nasogastric, gastric or other feeding tubes as it may cause obstruction of feeding tubes.**

- **The tablets have been hardened by a unique process to reduce the risk of being broken, chewed or crushed.**
- **OxyNEO 60 mg and 80 mg tablets, or a single dose greater than 40 mg, are for use in opioid tolerant patients only. A single dose greater than 40 mg, or total daily doses greater than 80 mg, may cause fatal respiratory depression when administered to patients who are not tolerant to the respiratory depressant effects of opioids.**
- OxyNEO 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.
- OxyNEO is not indicated for rectal administration.

4.2 Recommended Dose and Dosage Adjustment

- Pediatrics (<18 years of age)

  Health Canada has not authorized an indication for pediatric use (see 1.1 Pediatrics).

- 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. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with OxyNEO.

- Patients Not Receiving Opioids at the Time of Initiation of OxyNEO Treatment

  The usual initial adult dose of OxyNEO for patients who have not previously received opioid analgesics is 10 mg every 12 hours.

  Use of higher starting doses in patients who are not opioid tolerant may cause fatal respiratory depression.

- Patients Currently Receiving Opioids

  Patients currently receiving other oral oxycodone formulations may be transferred to OxyNEO tablets at the same total daily oxycodone dosage, equally divided into two 12 hourly OxyNEO doses.

  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. This total daily oral oxycodone dose should then be equally divided into two 12 hourly OxyNEO doses. 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 who are receiving 1 to 5 tablets/capsules per day of a fixed-dose combination opioid/non-opioid containing 5 mg of oxycodone or 30 mg codeine should be started on 10 mg to 20 mg OxyNEO q12h. For patients receiving 6 to 9 tablets/capsules per day of a fixed-dose combination opioid/non-opioid containing 5 mg of oxycodone or 30 mg codeine, a starting dose of 20 mg to 30 mg q12h should be used and for patients receiving 10 to 12 tablets/capsules per day of a fixed-dose combination opioid/non-opioid containing 5 mg of oxycodone or 30 mg codeine, a starting dose of 30 mg to 40 mg q12h is suggested. For those receiving >12 tablets/ capsules per day of a fixed-dose combination opioid/non-opioid containing 5 mg of oxycodone or 30 mg codeine, conversions should be based on the total daily opioid dose.

- Patients with Hepatic and Renal Impairment

  The dose initiation should follow a conservative approach in these patients. 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 Special Populations, Hepatic Impairment, 7.1 Special Populations Renal Impairment, 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency, and 10.3 Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency).

- 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. OxyNEO 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 regular administration of the lowest dose of controlled release oxycodone (OxyNEO) 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 patients receiving OxyNEO, the dose may be titrated at intervals of 24 to 36 hours to that which provides satisfactory pain relief without unmanageable side effects. OxyNEO is designed to allow 12 hourly dosing.

If pain repeatedly occurs at the end of the dosing interval it is generally an indication for a dosage increase rather than more frequent administration of controlled release oxycodone (OxyNEO).

- Adjustment or Reduction of Dosage

  Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including OxyNEO. 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 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, 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

OxyNEO 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 and hypotension. Severe overdosage 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 i.v. 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	Controlled Release Tablets with Tamper Resistance Properties / 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg and 80 mg	Butylated hydroxytoluene (BHT), hypromellose, polyethylene glycol, polyethylene oxide, magnesium stearate, titanium dioxide and hydroxypropyl cellulose (10 mg, 80 mg), iron oxide (15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg), polysorbate 80 (20 mg, 30 mg, 40 mg, 60 mg), silicon dioxide and FD&C Blue No. 2 (80 mg)

- Dosage Forms

  OxyNEO has been formulated with features intended to be tamper-resistant. The tablets consist of a polymer matrix, utilizing polyethylene oxide, with hydrogelling properties (i.e., particles or whole tablets become highly viscous (gel-like) in water). The tablets have been hardened through a unique recrystallization process, HTR Technology™, and are designed to be resistant to crushing. Testing over the range of OxyNEO tablet fragment sizes showed that some of the controlled release properties were still retained (see 10.3 Pharmacokinetics, Tamper-resistance Properties).

  OxyNEO 10 mg are round, unscored, white, biconvex tablets imprinted with 'ON' on one side and 10 on the other.

  OxyNEO 15 mg are round, unscored, grey, biconvex tablets imprinted with 'ON' on one side and 15

on the other.

OxyNEO 20 mg are round, unscored, pink, biconvex tablets imprinted with 'ON' on one side and 20 on the other.

OxyNEO 30 mg are round, unscored, brown, biconvex tablets imprinted with 'ON' on one side and 30 on the other.

OxyNEO 40 mg are round, unscored, yellow, biconvex tablets imprinted with 'ON' on one side and 40 on the other.

OxyNEO 60 mg are round, unscored, red, biconvex tablets imprinted with 'ON' on one side and 60 on the other.

OxyNEO 80 mg are round, unscored, green, biconvex tablets imprinted with 'ON' on one side and 80 on the other.

- Composition

  OxyNEO 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg and 80 mg tablets contain the following ingredients:

  Tablet core: butylated hydroxytoluene, polyethylene oxide, magnesium stearate and silicon dioxide.

  Tablet coating: hypromellose, polyethylene glycol, titanium dioxide. Additional coating ingredients specific to each strength are as follows:

  - 10 mg: hydroxypropyl cellulose
  - 15 mg: red, yellow and black iron oxide
  - 20 mg: polysorbate 80 and red iron oxide
  - 30 mg: polysorbate 80, red, yellow and black iron oxide
  - 40 mg: polysorbate 80 and yellow iron oxide
  - 60 mg: polysorbate 80, red and black iron oxide
  - 80 mg: hydroxypropyl cellulose, yellow iron oxide and FD&C Blue No. 2

- Packaging

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

7 WARNINGS AND PRECAUTIONS

General

OxyNEO must be swallowed whole and should not be chewed, dissolved or crushed. Taking cut, broken, chewed, dissolved or crushed OxyNEO tablets could lead to the rapid release and absorption of a potentially fatal dose of oxycodone.

There have been post-marketing reports of difficulty swallowing OxyNEO tablets. These reports include choking, gagging, regurgitation and tablets stuck in the throat. If patients experience such swallowing difficulties or pain after taking OxyNEO tablets, they are advised to seek immediate medical attention. To avoid difficulty swallowing OxyNEO, tablets should not be pre-soaked, licked or otherwise wetted prior to placing in the mouth and must be taken one tablet at a time with enough water to ensure

complete swallowing immediately after placing it in the mouth. OxyNEO should not be taken by patients with difficulty in swallowing or who have underlying GI disorders such as narrowing of the esophagus, that may predispose them to obstruction.

Do not administer OxyNEO via nasogastric, gastric or other feeding tubes as it may cause obstruction of feeding tubes.

OxyNEO 60 mg and 80 mg tablets, or a single dose greater than 40 mg are for use in opioid tolerant patients only (see 4 DOSAGE AND ADMINISTRATION). A single dose greater than 40 mg of oxycodone, or total daily doses greater than 80 mg of oxycodone, may cause fatal respiratory depression when administered to patients who are not tolerant to the respiratory depressant effects of opioids (see 7 WARNINGS AND PRECAUTIONS, Respiratory, Respiratory Depression and 9 DRUG INTERACTIONS).

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

Patients should be cautioned not to consume alcohol while taking OxyNEO, 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, may occur at particularly high doses. An oxycodone dose reduction or change in opioid may be required.

- Addiction, Abuse and Misuse

  Like all opioids, OxyNEO is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, OxyNEO should be prescribed and handled with caution. This risk is increased if OxyNEO is taken with alcohol or other CNS depressants.

  Tamper-resistance properties do not render OxyNEO less addictive.

  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 OxyNEO, 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.

  OxyNEO 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 OxyNEO tablets are dispensed to them.

  Patients receiving OxyNEO should be given the following instructions by the physician:

  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 OxyNEO contains oxycodone, an opioid pain medicine.
3. Patients should be advised that OxyNEO should only be taken as directed. The dose of OxyNEO should not be adjusted without consulting with a physician.
4. OxyNEO must be swallowed whole (not cut, broken, chewed, dissolved or crushed) due to the risk of fatal oxycodone overdose.
5. To avoid difficulty swallowing, patients should be advised to take OxyNEO tablets one at a time. Tablets should not be pre-soaked, licked or otherwise wetted prior to placing in the mouth. Each tablet should be taken with enough water to ensure complete swallowing immediately after placing in the mouth. If patients experience difficulty in swallowing or pain after taking OxyNEO, they should seek immediate medical attention.
6. 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.
7. Patients should not combine OxyNEO with alcohol or other central nervous system depressants (sleep aids, tranquilizers) because dangerous additive effects may occur, resulting in serious injury or death.
8. Patients should be advised to consult their physician or pharmacist if other medications are being used or will be used with OxyNEO.
9. Patients should be advised that if they have been receiving treatment with OxyNEO and cessation of therapy is indicated, it may be appropriate to taper OxyNEO dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms.
10. Patients should be advised that the most common adverse reactions that may occur while taking OxyNEO are asthenia, constipation, dizziness, dry mouth, headache, nausea, pruritus, somnolence, sweating and vomiting.
11. Patients should be advised that OxyNEO 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 OxyNEO 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 OxyNEO.
12. Patients should be advised that OxyNEO is a potential drug of abuse. They should protect it from theft or misuse.
13. Patients should be advised that OxyNEO should never be given to anyone other than the individual for whom it was prescribed.
14. Patients should be advised that OxyNEO 60 mg and 80 mg tablets or a single dose greater than 40 mg are for use only in individuals tolerant to the effect of opioids.
15. Women of childbearing potential who become or are planning to become pregnant should be advised to consult a physician prior to initiating or continuing therapy with OxyNEO. Women who are breast-feeding or pregnant should not use OxyNEO.

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 or certain anesthetics.

Dependence/Tolerance

As with other opioids, tolerance and physical dependence may develop upon repeated administration of OxyNEO and there is a potential for development of psychological dependence. OxyNEO should therefore be prescribed and handled with the degree of caution appropriate to the use of a drug with abuse potential.

Tamper-resistance properties do not affect the development of tolerance and/or dependence.

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 addictive disorder or abuse.

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

  OxyNEO 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 OxyNEO; extreme caution and awareness is warranted to mitigate the risk.

- In Vitro Dissolution Studies of Interaction with Alcohol

  Among readily available drugs with the established potential to pharmacologically augment the CNS depressant effect of opioids, ethanol also has the potential to chemically interact with the pharmaceutical formulation to accelerate the release of opioids from the dosage form. Given the larger doses of opioids in controlled release opioid formulations on average, the occurrence of such a formulation effect can further augment the risk of serious and unintended respiratory depression. A method to assess the potential for ethanol to accelerate the release of opioids from a pharmaceutical formulation requires the use of in vitro dissolution studies using simulated gastric fluid and 40% ethanol.

  With OxyNEO, increasing concentrations of alcohol in the dissolution medium (from 0% to 40% v/v), resulted in a slight decrease in the rate of release of oxycodone from intact tablets. Additional in vitro dissolution testing in ethanol (40% v/v), conducted with OxyNEO tablet fragments over a range of particles sizes, showed that dose dumping did not occur with the particle sizes tested.

Driving and Operating Machinery

Oxycodone 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

There have been rare post-marketing cases of intestinal obstruction, and exacerbation of diverticulitis, some of which have required medical intervention to remove the tablet. Patients with underlying GI disorders such as esophageal cancer or colon cancer with a small gastrointestinal lumen are at greater risk of developing these complications.

Use caution when prescribing OxyNEO for patients who have difficulty swallowing or any underlying GI disorders that may predispose them to obstruction.

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, appendicitis and pancreatitis. Monitor patients with biliary tract disease for worsening symptoms (see 2 CONTRAINDICATIONS, 8.1 Adverse Reactions Overview, ADVERSE REACTIONS, Nausea and Vomiting, and 8.1 Adverse Reactions Overview, Constipation).

Hepatic/Biliary/Pancreatic

When compared to normal subjects, patients with mild to severe hepatic dysfunction may have higher plasma concentrations of oxycodone and noroxycodone, and lower plasma concentrations of oxymorphone. There may be an increase in the elimination half-life of oxycodone, and this may be accompanied by an increase in drug effects.

Neurologic

- Interactions with CNS Depressants (including benzodiazepines and alcohol)

  OxyNEO 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, centrally-active anti-emetics and other CNS depressants. Respiratory depression, hypotension and profound sedation, coma or death may result. When such combination therapy is

contemplated, a substantial reduction in the dose of one or both agents should be considered and patients should be carefully monitored. OxyNEO should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects (see 9 DRUG INTERACTIONS).

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 DRUG INTERACTIONS). 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 OxyNEO 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 DRUG INTERACTIONS).

OxyNEO 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 Reactions 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.

- Use in Patients with Convulsive or Seizure Disorders

  The oxycodone hydrochloride in OxyNEO may aggravate convulsions in patients with convulsive disorders and may induce or aggravate seizures in some clinical settings. Therefore, OxyNEO should not be used in these patients (see 2 CONTRAINDICATIONS).

- Serotonin Toxicity / Serotonin Syndrome

  Serotonin toxicity also known as serotonin syndrome is a potentially life-threatening condition and has been reported with oxycodone, including OxyNEO, 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 OxyNEO and other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (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).

- 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

OxyNEO 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 OxyNEO for at least 24 hours before the operation and OxyNEO should not be used in the immediate post-operative period.

Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. Thereafter, if OxyNEO 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 healthcare providers 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.

OxyNEO 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.

Renal

When compared to normal subjects, patients with mild to severe renal dysfunction (creatinine clearance <60 mL/min) may have higher plasma concentrations of oxycodone and its metabolites. There may be an increase in the elimination half-life of oxycodone, and this may be accompanied by an increase in drug effects.

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).

- **Teratogenic 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 OxyNEO 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 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 OxyNEO, 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 OxyNEO and following dose increases.

  To reduce the risk of respiratory depression, proper dosing and titration of OxyNEO are essential (see 4 DOSAGE AND ADMINISTRATION). Overestimating the OxyNEO dose when converting patients from another opioid product can result in a fatal overdose with the first dose.

- 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 OxyNEO, as in these patients, even usual therapeutic doses of OxyNEO 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 OxyNEO is contraindicated in patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (2 CONTRAINDICATIONS).

- Sleep Apnea

  Opioids can cause sleep-related breathing disorders such as sleep apnea syndromes (including central sleep apnea [CSA]) and hypoxia (including sleep-related hypoxia). 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 these patients, consider reducing 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 or urethral stricture.

  The administration of opioid analgesics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

- Hepatic Impairment

  In a pharmacokinetic study, patients with mild to moderate hepatic impairment had greater plasma concentrations of oxycodone and noroxycodone than subjects with normal hepatic function. Caution should be exercised when prescribing OxyNeo to patients with any degree of hepatic impairment. Initiate these patients at a reduced dose followed by careful titration (see 4 DOSAGE AND ADMINISTRATION and 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency).

- Renal Impairment

  In a pharmacokinetic study, patients with mild to severe renal impairment had approximately 50% higher plasma concentrations of oxycodone and its metabolites than subjects with normal renal function. Caution should be exercised when prescribing OxyNeo to patients with any degree of renal impairment. Initiate these patients at a reduced dose followed by careful titration (see 4 DOSAGE AND ADMINISTRATION and 10.3 Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency).

7.1.1 Pregnant Women

Animal reproduction studies have revealed no evidence of harm to the fetus due to oxycodone, however, as studies in humans have not been conducted, OxyNEO is contraindicated in patients who are pregnant (see 2 CONTRAINDICATIONS).

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening (see 7 WARNINGS AND PRECAUTIONS, Reproductive Health: Male and Female Potential, Teratogenic Risk, Neonatal Opioid Withdrawal Syndrome).

7.1.2 Breast-feeding

OxyNEO 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 may occur in the infant if opioids are administered to the mother. Naloxone, a drug that counters the effect of opioids, should be readily available if OxyNEO is used in this population. Respiratory depression may occur in the infant if opioids are administered during labour. Therefore, OxyNEO should not be used during or immediately prior to labour or in nursing mothers.

7.1.3 Pediatrics

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

7.1.4 Geriatrics

Geriatrics (>65 years of age): In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see 4 DOSAGE AND ADMINISTRATION and 10.3 Pharmacokinetics, Special Populations and Conditions, Geriatrics).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Adverse effects of OxyNEO 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 OxyNEO are asthenia, constipation, dizziness, dry mouth, headache, hyperhidrosis, 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, tumour 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 OxyNEO 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, dental caries
- General Disorders and Administration Site Conditions:
  - Common: asthenia, fatigue, fever, hypotonia
  - Uncommon: abnormal gait, chest pain, chills, drug withdrawal syndrome, edema, edema peripheral, malaise, thirst, drug tolerance
  - Not known: drug withdrawal syndrome neonatal
- Hepatobiliary Disorders:
  - Uncommon: increased hepatic enzyme
  - Not known: cholestasis
- Immune System Disorders:
  - Uncommon: hypersensitivity
  - Not known: anaphylactic reaction, anaphylactoid reaction
- Investigations:
  - Uncommon: weight loss
- Metabolism and Nutrition Disorders:
  - Common: decreased appetite
  - Uncommon: dehydration, hypoglycemia
  - 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, speech disorder, syncope
  - Not known: obstructive sleep apnea syndrome, hyperalgesia
- Psychiatric Disorders:
  - Common: abnormal dreams, anxiety, confusional state, depression, insomnia, nervousness, thinking abnormal
  - Uncommon: affect lability, agitation, depersonalization, euphoric mood, hallucination, libido decreased, drug dependence
  - Rare: dysphoria
  - Not known: aggression, delirium
- Renal and Urinary Disorders:
  - Uncommon: dysuria, hematuria, polyuria, urinary retention or hesitancy
- Reproductive System and Breast Disorders
  - Uncommon: erectile dysfunction, hypogonadism
  - Not known: amenorrhea
- Respiratory, Thoracic and Mediastinal Disorders:
  - Common: dyspnea
  - Uncommon: bronchitis, cough, pharyngitis, respiratory depression, yawning
  - Rare: sinusitis
  - Not known: bronchospasm, pneumonia
- Skin and Subcutaneous Tissue Disorders:
  - Very common: pruritus
  - Common: hyperhidrosis, rash
  - Uncommon: dry skin, exfoliative dermatitis
  - Rare: urticaria
- Vascular Disorders:
  - Uncommon: vasodilatation
  - Rare: hypotension, orthostatic hypotension

8.5 Post-Market Adverse Reactions

In addition to the events listed above, the following have been reported during post-marketing experience with OxyNEO, potentially due to the swelling and hydrogelling property of the tablet: choking, gagging, regurgitation, tablets stuck in the throat and dysphagia (difficulty swallowing the tablet). Hyperalgesia, hypogonadism and pulmonary edema have been reported during post-marketing experience with oxycodone.

There have also been post-marketing reports off Neonatal Opioid Withdrawal Syndrome (NOWS) in patients treated with oxycodone (see 7 WARNINGS AND PRECAUTIONS, Reproductive Health: Male and Female Potential, Teratogenic Risk, Neonatal Opioid Withdrawal Syndrome).

- 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.

- Serotonin syndrome

  Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

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 OxyNEO 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. OxyNEO 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)

  OxyNEO should be dosed with caution and started in a reduced dosage (1/3 to 1/2 of the usual dosage) in patients who are currently taking other central nervous system depressants (e.g., other opioids, sedatives, gabapentinoids such as pregabalin, baclofen, hypnotics, anti-depressants, phenothiazines, neuroleptics, anti-histamines, anti-emetics) and beta-blockers, as they may enhance the CNS-depressant effect (e.g., respiratory depression) of OxyNEO. OxyNEO 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, which may alter plasma oxycodone concentrations. Oxycodone doses may need to be adjusted accordingly.

- Inhibitors of CYP3A4

  Since the CYP3A4 isoenzyme plays a major role in the metabolism of OxyNEO, drugs that inhibit CYP3A4 activity, such as macrolide antibiotics (e.g., erythromycin, 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 C_{max} 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 OxyNEO 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 C_{max} by 86% and 63% respectively. If co-administration with OxyNEO 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. OxyNEO 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

  Coadministration of oxycodone hydrochloride 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

Administration of OxyNEO with food results in an increase in peak plasma oxycodone concentration of up to 1.5-fold but has no significant effect on the extent of absorption of oxycodone.

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 vasodilatation. 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 (CO2) 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.

- 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.

  The dose of OxyNEO must be individualized (see 4 DOSAGE AND ADMINISTRATION) because the effective analgesic dose for some patients will be too high to be tolerated by other patients.

10.3 Pharmacokinetics

The activity of OxyNEO is primarily due to the parent drug oxycodone. OxyNEO is designed to provide delivery of oxycodone over 12 hours.

Cutting, breaking, chewing, crushing or dissolving OxyNEO impairs the controlled release delivery mechanism and could lead to the rapid release and absorption of a potentially fatal dose of oxycodone.

A range of in vitro dissolution studies in different media have shown that oxycodone release from OxyNEO is pH independent. The oral bioavailability of oxycodone is 60% to 87%. Upon repeated dosing with OxyNEO in healthy subjects in pharmacokinetic studies, steady-state levels were achieved within 36 hours. Oxycodone is extensively metabolized and eliminated primarily in the urine as both conjugated and unconjugated metabolites. The mean apparent elimination half-life of oxycodone following administration of 10 mg to 80 mg OxyNEO was 5.1 to 7.1 hours.

- Tamper-resistance Properties

  Abuse of OxyNEO can lead to overdose and death (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX).

  OxyNEO is formulated with ingredients and manufacturing processes intended to reduce misuse and abuse. The following studies show that OxyNEO has physicochemical properties (i.e., resistant to crushing and hydrogelling) that may make the product difficult to misuse or abuse and less rewarding by intranasal and intravenous routes of administration. Abuse potential for other routes is not addressed. Abuse by any route remains possible. These studies have not been shown to predict the actual real-world abuse of OxyNEO.

- In Vitro Testing

  In vitro physical and chemical tablet manipulation studies were performed to evaluate the success of different extraction methods in defeating the controlled release formulation. Results support that, relative to OxyContin, there is an increase in the ability of OxyNEO to resist crushing, breaking and dissolution using a variety of tools and solvents. The results of these studies also support this finding for OxyNEO relative to an immediate release oxycodone. Testing over a range of OxyNEO tablet fragment sizes showed that some of the controlled release properties were still retained. When subjected to a small volume of water, OxyNEO fragments transition to a viscous hydrogel, a property that is expected to make abuse via injection difficult. Dose dumping was not associated with OxyNEO in in vitro studies.

- In Vivo Testing

  A clinical study was conducted to evaluate the intranasal abuse potential of OxyNEO. Subjects that received OXYNEO tablet fragments experienced less drug liking than those that received the finely crushed controlled release oxycodone or the immediate release oxycodone formulation. Subjective and objective measures, however, remained higher for OxyNEO than for placebo. Abuse by this route remains possible.

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.

- Plasma Oxycodone Concentration over Time

  Dose proportionality has been established for OxyNEO 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg and 80 mg tablet strengths for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) (see Table 3). Steady-state plasma concentrations of oxycodone are achieved within 36 hours of initiation of dosing with OxyNEO.

Table 3 – Pharmacokinetic Parameters (Mean ± SD)

	Dosage Form	AUC (ng•hr/mL)[a]	C_{max}	T_{max}
Single dose[b]	10 mg	136 ± 37.3	11.5 ± 3.06	5.11 ± 1.05
	15 mg	196 ± 54.9	16.8 ± 4.91	4.59 ± 0.89
	20 mg	248 ± 61.1	22.7 ± 5.73	4.63 ± 1.03
	30 mg	377 ± 91.2	34.6 ± 7.43	4.61 ± 0.86
	40 mg	497 ± 133	47.4 ± 14.0	4.40 ± 0.95
	60 mg	705 ± 157	64.6 ± 15.2	4.15 ± 1.06
	80 mg	908 ± 190	87.1 ± 25.6	4.27 ± 1.12

a. for single-dose studies AUC = $AUC_{0\text{-inf}}$
b. data obtained while subjects received naltrexone which can enhance absorption

In a series of single-dose, randomized, cross-over bioavailability studies under both fasting and fed conditions, OxyNEO was shown to be bioequivalent to equivalent doses of OxyContin®.

- Food Effects

  In controlled studies in healthy volunteers, administration of OxyNEO with a high fat meal resulted in a 1.3- to 1.5-fold increase in peak plasma oxycodone concentration but had no significant effect on the extent of absorption of oxycodone.

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 into 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):**

  OxyNEO has not been studied in children and is not indicated for patients less than 18 years of age.

- **Geriatrics (>65 years of age):**

  Plasma concentrations of oxycodone are increased by approximately 15% in elderly subjects receiving OxyNEO. 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.

- **Genetic Polymorphism:**

  No data available.

- **Ethnic Origin**:

  No data available.

- **Hepatic Insufficiency**:

  Patients with mild to moderate hepatic dysfunction showed peak plasma oxycodone and noroxycodone concentrations approximately 50% and 20% higher, respectively, than normal subjects. AUC values were approximately 95% and 75% higher, respectively. Oxymorphone peak plasma concentrations and AUC values were lower by 15% to 50%. The t1/2 elimination for oxycodone increased by 2.3 hours.

  Plasma concentrations of oxycodone are increased by approximately 2-fold in patients with hepatic cirrhosis.

- **Renal Insufficiency:**

  Patients with mild to severe renal dysfunction 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. There was an increase in mean elimination t1/2 for oxycodone of 1 hour.

11 STORAGE, STABILITY AND DISPOSAL

- Storage

  Store OxyNEO at room temperature (15°C - 30°C). Keep in a dry place.

- Disposal

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

  Unused or expired OxyNEO should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets. OxyNEO 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

OxyNEO 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. OxyNEO should not be used in front of children, since they may copy these actions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

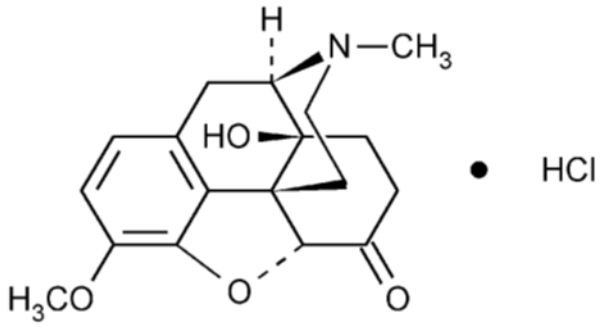
Drug Substance

Proper name: Oxycodone hydrochloride

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

Molecular formula and molecular mass: $C_{18}H_{21}NO_4 \bullet HCl$, 351.83

Structural formula:



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

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 controlled release (CR) oxycodone hydrochloride tablets and immediate release (IR) oxycodone hydrochloride 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 a single dose analgesic assay, the peak effect of CR oxycodone (20 mg and 30 mg) was greater than that of 10 mg CR oxycodone and was equivalent to that of two tablets of oxycodone (5 mg) plus acetaminophen (325 mg), or 15 mg of immediate release oxycodone but with a longer duration of action. In patients with pain due to osteoarthritis, CR oxycodone q12h was more effective than placebo in decreasing pain and in improving quality of life, mood and sleep. In patients with cancer pain, CR oxycodone administered q12h produced equivalent analgesia to IR oxycodone administered four times per day. In patients with low back pain, CR oxycodone q12h and IR oxycodone given four times per day were equally effective. In patients with neuropathic pain, studies with CR oxycodone have demonstrated clinically important analgesia, with significant benefits in functionality, quality of life and sleep, relative to placebo.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

The LD_{50} after subcutaneous administration of oxycodone in mice was 275 mg/kg to 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 discernable at 5 mg/kg. Doses of 25 mg/kg, 75 mg/kg 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).

- 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.

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:

Reproductive and Developmental Toxicology:

- Teratogenicity

  Oxycodone has 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 presacral vertebrae and extra pairs of ribs) were observed in rabbits when the data for individual foetuses 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 peri- 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}OxyNEO®

Oxycodone Hydrochloride Controlled Release Tablets

Read this carefully before you start taking **OxyNEO** 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 **OxyNEO**.

Serious Warnings and Precautions

- Even if you take OxyNEO as prescribed you are at risk for opioid addiction, abuse, and misuse that 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 OxyNEO it must be swallowed whole. Do not cut, break, crush, chew, or dissolve the tablets. This can be dangerous and can lead to death or seriously harm you.
- Life-threatening breathing problems can happen while taking OxyNEO, 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 OxyNEO. They could die from taking it. If a person has not been prescribed OxyNEO, taking even one dose can cause a fatal overdose. This is especially true for children.
- If you took OxyNEO 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 OxyNEO 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 OxyNEO used for?

OxyNEO is used in adults to manage long-term pain, when:

- the pain is severe enough to require daily, around-the-clock pain medication; and
- the healthcare professional determines that other treatment options are not able to effectively manage your pain.

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

How does OxyNEO work?

OxyNEO 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 OxyNEO?

Medicinal ingredient: oxycodone hydrochloride.

Non-medicinal ingredients: butylated hydroxytoluene (BHT), hypromellose, magnesium stearate, polyethylene glycol, polyethylene oxide, silicon dioxide, and titanium dioxide.

The tablet coatings contain the following additional ingredients:

- 10 mg: hydroxypropyl cellulose.
- 15 mg: black iron oxide, red iron oxide, yellow iron oxide.
- 20 mg: polysorbate 80, and red iron oxide.
- 30 mg: black iron oxide, polysorbate 80, red iron oxide, yellow iron oxide.
- 40 mg: polysorbate 80, and yellow iron oxide.
- 60 mg: black iron oxide, polysorbate 80, red iron oxide.
- 80 mg: FD&C Blue No. 2, hydroxypropyl cellulose, and yellow iron oxide.

OxyNEO comes in the following dosage forms:

Controlled Release Tablets: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg of oxycodone hydrochloride.

Do not use OxyNEO if:

- your healthcare professional did not prescribe it for you.
- you are allergic to oxycodone hydrochloride, or any of the other ingredients of OxyNEO.
- you have mild or short-term 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 lung 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.
- you have increased pressure in your skull, a head injury.
- you have or have a history with epilepsy.

- you suffer from alcoholism or alcohol withdrawal.
- 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 pregnant or plan to become pregnant, or you are in labour and delivery.
- you are breastfeeding.
- you are going to have a surgery or operation, or have had a surgery in the last 24 hours.
- you have any heart problems.
- you have severe CNS depression (nervous system slows down).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take OxyNEO. 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 problems.
- have liver 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 past or current depression.
- have problems with your thyroid, adrenal, or prostate gland.
- suffer from chronic or severe constipation.
- have or have had problems with your mood (such as depression or anxiety), hallucinations, or other mental health problems.
- have gastrointestinal (GI) problems.
- are planning to breastfeed.
- are planning on drinking alcohol. Drinking alcohol while taking OxyNEO may cause dangerous side effects, including death. Do not drink alcohol while taking OxyNEO.
- have a condition that causes weakness or frailty.
- have difficulty swallowing (e.g., narrowing of the throat).
- have difficulty urinating.
- are 65 years of age and older.

Other warnings you should know about:

Taking OxyNEO 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 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 OxyNEO.

- **Serotonin toxicity (also known as serotonin syndrome):** OxyNEO 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 OxyNEO 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.

Opioid dependence and addiction: There are important differences between physical dependence and addiction. It is important that you talk to your healthcare professional if you have questions or concerns about abuse, addiction, or physical dependence

Pregnancy, nursing, labour, and delivery: Do not use OxyNEO while pregnant, nursing, during labour or delivery. Opioids can be transferred to your baby through breast milk, or while still in the womb. OxyNEO can then cause life-threatening breathing problems in your unborn baby or nursing infant.

If you are pregnant and are taking OxyNEO, 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 OxyNEO. 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 OxyNEO. OxyNEO can cause:

- drowsiness,
- dizziness, or
- light headedness.

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

Sexual function and 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.

Worsening 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 OxyNEO.

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 OxyNEO 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);
  - 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 OxyNEO. 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 OxyNEO with MAOIs or if you have taken MAOI's in the last 14 days.

The following may interact with OxyNEO:

- anticoagulants used to thin the blood and prevent blood clots (e.g., warfarin and coumadin).
- 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., erythromycin, clarithromycin, 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.

How to take OxyNEO:

- Take OxyNEO exactly as prescribed by your healthcare professional.
- OxyNEO must be taken orally, by mouth. Do **NOT** administer the OxyNEO tablets via any other route (e.g., via nasogastric, gastric, or other feeding tubes, or rectally) as this can cause serious harm, including death.
- OxyNEO can be taken with or without food.
- **Swallow the whole tablet. Do not cut, break, chew, dissolve, or crush OxyNEO tablets. This can be dangerous and can lead to death or seriously harm you.**
- **To reduce the chances of having difficulties swallowing:**
  - **Take one OxyNEO tablet at a time;**
  - **Do NOT pre-soak, lick, or otherwise wet the tablet prior to placing it in your mouth;**
  - **Take each tablet with enough water to ensure complete swallowing immediately after placing it in your mouth.**
- If you experience difficulty swallowing or pain after taking OxyNEO, seek immediate medical attention as you may require medical assistance to remove the tablet.
- The OxyNEO 60 mg and 80 mg strength tablets will only be prescribed if you are "opioid tolerant". Your healthcare professional will tell you when you are "opioid tolerant" to a certain dose of OxyNEO.
- Review your pain regularly with your healthcare professional to determine if you still need OxyNEO. Be sure to use OxyNEO 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 OxyNEO 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 OxyNEO. 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 with 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 OxyNEO

Refilling Prescriptions for OxyNEO: A new written prescription is required from your healthcare professional each time you need more OxyNEO. 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 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).

If you think you, or a person you are caring for, have taken too much OxyNEO, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no 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 OxyNEO?

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

Side effects may include:

- constipation. Talk with your healthcare professional about ways to prevent constipation when you start using OxyNEO;
- dizziness;
- drowsiness;
- dry mouth;
- headache;
- itching;
- weakness, uncoordinated muscle movement;
- nausea, vomiting, or poor appetite;
- sweating;
- insomnia;
- 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			
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.			✓
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.			✓
Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, or sweating.		✓	
Fast, slow or irregular heartbeat: heart palpitations.		✓	
Hypotension (low blood pressure): dizziness, fainting, or light-headedness.	✓		
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.			✓

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	
UNKNOWN FREQUENCY			
Sleep apnea: stop breathing for short periods during your normal nightly sleep.		✓	
Disorder of the adrenal gland: nausea, vomiting, anorexia, fatigue, weakness, dizziness, or low blood pressure.			✓

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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:

- Store OxyNEO at room temperature (15° - 30°C). Keep in a dry place.
- Keep unused or expired OxyNEO 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 OxyNEO, get emergency help right away.
- OxyNEO 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 OxyNEO:

- 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.

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