PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[N] SUPEUDOL®
Oxycodone Hydrochloride USP
Tablets 5 mg and 10 mg

[N] SUPEUDOL®
Oxycodone Hydrochloride
Suppositories 10 mg and 20 mg

Therapeutic Classification

Opioid Analgesic

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TABLE OF CONTENTS

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Immediate Release Tablets 5 and 10 mg	Dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, microcrystalline cellulose and aluminium blue lake FD&C for 5 mg only.
	Suppository 10 and 20 mg	hard fat

INDICATIONS AND CLINICAL USE

Adults

Supeudol (oxycodone hydrochloride) tablets and suppository is indicated for the relief of moderate to severe pain.

Supeudol (oxycodone hydrochloride) tablets and suppository is not indicated as an as-needed (prn) analgesic.

Geriatrics (> 65 years of age)

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

Pediatrics (< 18 years of age)

The safety and efficacy of oxycodone hydrochloride has not been studied in the pediatric population. Therefore the use of Supeudol is not recommended in patients under 18 years of age.

CONTRAINDICATIONS

- Patients who are hypersensitive to the active substance (oxycodone) or other opioid analgesics or to any ingredient in the formulation. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.
- In patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction or strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).
- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis).
- Patients with mild pain that can be managed with other pain medications.
- Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus.
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood and cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).
- Women who are breast-feeding, and during pregnancy or during labour and delivery (see Serious Warnings and Precautions, and Warnings and Precautions).

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

<u>Limitations of Use</u>
Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the risks of overdose and death with immediate release opioid formulations, Supeudol (oxycodone hydrochloride) tablets or suppositories 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 DOSAGE AND ADMINISTRATION).

<u>Addiction, Abuse, and Misuse</u>
Supeudol 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 Supeudol, and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS). Supeudol 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 Supeudol. 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 Supeudol or following a dose increase.

Supeudol tablets must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving Supeudol tablets or suppository can lead to dangerous adverse events including death (see WARNINGS AND PRECAUTIONS). Further, instruct patients of the hazards related to taking opioids including fatal overdose.

Accidental Exposure

Accidental ingestion of even one dose of Supeudol, especially by children, can result in a fatal overdose of oxycodone (see DOSAGE AND ADMINISTRATION, Disposal, for instructions on proper disposal).

Neonatal Opioid Withdrawal Syndrome

Prolonged maternal use of Supeudol during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see WARNINGS AND PRECAUTIONS).

Interaction with Alcohol

The co-ingestion of alcohol with Supeudol should be avoided as it may result in dangerous additive effects, causing serious injury or death (see WARNINGS AND PRECAUTIONS and DRUG 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 WARNINGS AND PRECAUTIONS, Neurologic and DRUG INTERACTIONS).

- **Reserve concomitant prescribing of Supeudol and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

General

Patients should be instructed not to give Supeudol (oxycodone hydrochloride) tablets or suppository to anyone other than the patient for whom it was prescribed, as such

inappropriate use may have severe medical consequences, including death. Supeudol should be stored securely to avoid theft or misuse.

Supeudol should only be prescribed by persons knowledgeable in the continuous administration of potent opioids, in the management of patients receiving potent opioids for the treatment of pain, and in the detection and management of respiratory depression, including the use of opioid antagonists.

Patients should be cautioned not to consume alcohol while taking Supeudol as it may increase the chance of experiencing serious adverse events, including death.

Hyperalgesia that will not respond to a further dose increase of oxycodone can occur at particularly high doses. An oxycodone dose reduction or change in opioid may be required.

Abuse and Misuse

Like all opioids, Supeudol is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, Supeudol should be prescribed and handled with caution.

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

Supeudol tablets is intended for oral use only. The tablets should be swallowed whole, and not chewed or crushed. Abuse of oral dosage forms can be expected to result in serious adverse events, including death.

Carcinogenesis and Mutagenesis

See TOXICOLOGY section.

Cardiovascular

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 drugs such as phenothiazines and other tranquilizers, sedative/hypnotics, tricyclic antidepressants or general anesthetics. These patients should be monitored for signs of hypotension after initiating or titrating the dose of Supeudol.

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

Dependence/Tolerance

As with other opioids, tolerance and physical dependence may develop upon repeated administration of oxycodone and there is a potential for development of psychological 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 ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage).

Use in Drug and Alcohol Addiction

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

Endocrine

Adrenal Insufficiency: Cases of adrenal insufficiency have been reported with opioid use, 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 Effects

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 (see **CONTRAINDICATIONS**).

Neonatal Opioid Withdrawal Syndrome (NOWS)

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

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

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

Neurologic

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

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (see 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 Supeudol 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 DRUG INTERACTIONS).

Supeudol should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see CONTRAINDICATIONS and ADVERSE REACTIONS, Sedation, and DRUG INTERACTIONS).

Severe pain antagonizes the subjective and respiratory depressant actions of opioid analgesics.

Should pain suddenly subside, these effects may rapidly become manifest.

Serotonin Syndrome: Supeudol could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs (e.g. anti-depressants, migraine medications). Treatment with the serotonergic drug should be discontinued if such events (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated. Supeudol should not be used in combination with MAO inhibitors or serotonin-precursors (such as L-tryptophan, oxitriptan) and should be used with caution in combination with other serotonergic drugs (triptans, certain tricyclic antidepressants, lithium, tramadol, St. John's Wort) due to the risk of serotonergic syndrome (see DRUG INTERACTIONS).

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 must be used with extreme caution and only if it is judged essential (see CONTRAINDICATIONS)**.**

Peri-Operative Considerations

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

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

Supeudol 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.

Psychomotor Impairment
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, sedative/hypnotics and alcohol.

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. Oxycodone should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia (see CONTRAINDICATIONS).

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

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

To reduce the risk of respiratory depression, proper dosing and titration of Supeudol are essential. Overestimating the Supeudol dose when converting patients from another opioid product can result in a fatal overdose with the first dose. In these patients, the use of non-opioid analgesics should be considered, if feasible (see WARNINGS AND PRECAUTIONS, Special Populations, Special Risk Groups, and DOSAGE AND ADMINISTRATION).

Use in Patients with Chronic Pulmonary Disease: Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression for respiratory depression, particularly when initiating therapy and titrating with Supeudol, as in these patients, even usual therapeutic doses of Supeudol 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 Supeudol is contraindicated in Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see CONTRAINDICATIONS).

Patient Counselling Information
A patient information sheet should be provided when Supeudol are dispensed to the patient.

Patients receiving Supeudol 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 Supeudol contains oxycodone, an opioid pain medicine.

3. Patients should be advised that oxycodone tablets should only be taken as directed. The dose of Supeudol should not be adjusted without consulting with a physician.

4. Supeudol tablets must be swallowed whole (not cut, broken, chewed, dissolved or crushed) due to the risk of fatal oxycodone overdose.

5. Patients should be advised to report episodes of pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.

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

7. Patients should be advised to consult their physician or pharmacist if other medications are being used or will be used with Supeudol.

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

9. Patients should be advised that the most common adverse reactions that may occur while taking Supeudol are asthenia, constipation, dizziness, dry mouth, fatigue, headache, lethargy, nausea, pruritus, somnolence, sweating and vomiting.

10. Patients should be advised that Supeudol may cause drowsiness, dizziness, or lightheadedness and may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery). Patients started on Supeudol 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 Supeudol.

11. Patients should be advised that oxycodones a potential drug of abuse. They should protect it from theft or misuse.

12. Patients should be advised that Supeudol should never be given to anyone other than the individual for whom it was prescribed.

13. Women of childbearing potential who become or are planning to become pregnant should be advised to consult a physician prior to initiating or continuing therapy with Supeudol. Women who are breast-feeding or pregnant should not use Supeudol.

Sexual Function / Reproduction

Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (see ADVERSE REACTIONS, Post-Marketing Experience).

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.

Pregnant Women: Studies in humans have not been conducted. Supeudol crosses the placental barrier and is contraindicated in pregnant women.While animal reproduction studies have revealed no evidence of harm to the fetus due to oxycodone (see TOXICOLOGY, Teratogenicity), oxycodone does cross the placental barrier. Thus, Supeudol should not be administered to pregnant women unless in the judgment of the physician, potential benefits outweigh the risks (see CONTRAINDICATIONS).

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

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

Labour, Delivery and Nursing Women: Since opioids can cross the placental barrier and are excreted in breast milk, Supeudol is contraindicated in nursing women and during labour and delivery. Life-threatening respiratory depression can occur in the infant if opioids are administered to the mother. Naloxone, a drug that counters the effects of opioids, should be readily available if Supeudol is used in this population.

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

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

Patients with 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 Supeudol to patients with any degree of hepatic impairment. Initiate these patients at a reduced dose followed by careful titration (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Patients with Renal Impairment: In a pharmacokinetic study, patients with mild to severe renal impairment (creatinine clearance <60 mL/min) had approximately 50% higher plasma concentrations of oxycodone and its metabolites than subjects with normal renal function. Caution should be exercised when prescribing Supeudol to patients with any degree of renal impairment. Initiate these patients at a reduced dose followed by careful titration (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse effects of oxycodone hydrochloride 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 Supeudol are asthenia, constipation, dizziness, dry mouth, headache, fatigue, hyperhidrosis, lethargy, nausea, pruritus, somnolence and vomiting.

Sedation: Sedation is a common side effect of opioid analgesics, especially in opioid naïve individuals. Sedation may also occur partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Most patients develop tolerance to the sedative effects of opioids within three to five days and, if the sedation is not severe, will not require any treatment except reassurance. If excessive sedation persists beyond a few days, the dose of the opioid should be reduced and alternate causes investigated. Some of these are: concurrent CNS depressant medication, hepatic or renal dysfunction, brain metastases, hypercalcemia and respiratory failure. If it is necessary to reduce the dose, it can be carefully increased again after three or four days if it is obvious that the pain is not being well controlled. Dizziness and unsteadiness may be caused by postural hypotension, particularly in elderly or debilitated patients, and may be alleviated if the patient lies down.

Nausea and Vomiting: Nausea is a common side effect on initiation of therapy with opioid analgesics and is thought to occur by activation of the chemoreceptor trigger zone, stimulation of the vestibular apparatus and through delayed gastric emptying. The prevalence of nausea declines following continued treatment with opioid analgesics. When instituting therapy with an opioid for chronic pain, the routine prescription of an antiemetic should be considered. In the cancer patient, investigation of nausea should include such causes as constipation, bowel obstruction, uremia, hypercalcemia, hepatomegaly, tumor invasion of celiac plexus and concurrent use of drugs with emetogenic properties. Persistent nausea which does not respond to dosage reduction may be caused by opioid-induced gastric stasis and may be accompanied by

other symptoms including anorexia, early satiety, vomiting and abdominal fullness. These symptoms respond to chronic treatment with gastrointestinal prokinetic agents.

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

The following adverse effects occur less frequently with opioid analgesics and include those reported in clinical trials of oxycodone, whether related or not to oxycodone.

Cardiovascular: chest pain, faintness, hypotension, migraine, orthostatic hypotension, palpitation, ST depression, syncope, tachycardia and vasodilatation

Dermatologic: dry skin, exfoliative dermatitis, edema, other skin rashes and urticaria

Gastrointestinal: abdominal pain, biliary spasm, cholestasis, decreased appetite, dental caries, diarrhea, dysgeusia, dyspepsia, dysphagia, eructation, flatulence, gastritis, gastrointestinal disorder, hiccups, ileus, increased appetite and stomatitis

General and CNS: abnormal dreams, abnormal gait, agitation, amnesia, anaphylactic reaction, anaphylactoid reaction, anxiety, confusional state, convulsion, delirium, depersonalization, depression, disorientation, drug dependence, drug tolerance, drug withdrawal syndrome, dysphoria, edema peripheral, affect lability, euphoric mood, hallucinations, hypertonia, hypoaesthesia, hypotonia, insomnia, miosis, muscle contractions involuntary, nervousness, paresthesia, speech disorder, thinking abnormal, tinnitus, tremor, twitching, vertigo and visual impairment

Genitourinary: amenorrhea, antidiuretic effects, erectile dysfunction, libido decreased, dysuria, hematuria, polyuria, urinary retention or hesitancy.

Other: chills, dehydration, fever, hypersensitivity, hypoglycemia, increased hepatic enzymes, lymphadenopathy, malaise, thirst and weight loss

Respiratory: bronchitis, bronchospasm, cough, dyspnea, pharyngitis, pneumonia, respiratory depression, sinusitis and yawning

Post-marketing Experience

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.

Hyperalgesia, hypogonadism and pulmonary edema have been reported during post-marketing experience with oxycodone.

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

DRUG INTERACTIONS

Overview

Interaction with Benzodiazepines and Other Central Nervous System (CNS) Depressants: Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants (e.g. other opioids, sedatives/hypnotics, antidepressants, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, phenothiazines, neuroleptics, antihistamines, antiemetics, and alcohol) and beta-blockers, increases the risk of respiratory depression, profound sedation, coma, and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see WARNINGS AND PRECAUTIONS, Neurologic, Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol) and Psychomotor Impairment). Supeudol tablets should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

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 coadministered drugs or dietary elements. Oxycodone doses may need to be adjusted.

Inhibitors of CYP3A4: Since the CYP3A4 isoenzyme plays a major role in the metabolism of oxycodone hydrochloride tablets, drugs that inhibit CYP3A4 activity, such as macrolide antibiotics (e.g., clarithromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir) and grapefruit juice may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. A published study showed that the co-administration of the antifungal drug, voriconazole, increased oxycodone AUC and 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 oxycodone hydrochloride tablets is necessary, caution is advised when initiating therapy with, currently taking, or discontinuing CYP450 inhibitors. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved.

Inducers of CYP3A4: CYP450 inducers, such as rifampin, carbamazepine phenytoin, and St. John's wort, may induce the metabolism of oxycodone and, therefore, may cause increased clearance of the drug which could lead to a decrease in oxycodone plasma concentrations, lack of efficacy or possibly the development of an abstinence syndrome in a patient who had developed physical dependence to oxycodone. A published study showed that the co-administration of rifampin, a drug metabolizing enzyme inducer, decreased oxycodone (oral) AUC and Cmax by 86% and 63% respectively. If co-administration with oxycodone hydrochloride tablets 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.

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.

MAO Inhibitors: MAO Inhibitors intensify the effects of opioid drugs which can cause anxiety, confusion and decreased respiration. Oxycodone hydrochloride tablets is contraindicated in patients receiving MAO Inhibitors or who have used them within the previous 14 days (see CONTRAINDICATIONS).

Serotonergic Agents: Coadministration of oxycodone with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor or a Serotonin Norepinephrine Re-uptake Inhibitor, may increase the risk of serotonin syndrome, a potentially life-threatening condition (see WARNINGS AND PRECAUTIONS, Neurologic).

Drug-Food Interactions

Food has no significant effect on the extent of absorption of oxycodone from oxycodone hydrochloride tablets.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions
The concomitant use of alcohol should be avoided (see WARNINGS AND PRECAUTIONS, General).

DOSAGE AND ADMINISTRATION

Supeudol should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics).

Supeudol tablets must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving Supeudol can lead to dangerous adverse events including death (see WARNINGS AND PRECAUTIONS).

For acute pain, it is recommended that Supeudol be used for a maximum of 7 days at the lowest dose that provides adequate pain relief.

All doses of opioids carry an inherent risk of fatal or non-fatal adverse events. This risk is increased with higher doses. For the management of chronic non-cancer, non-palliative pain, it is recommended that 60 mg (90 morphine milligram equivalent) per day of Supeudol not be exceeded. Each patient should be assessed for their risk prior to prescribing Supeudol 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 Supeudol (see DOSAGE AND ADMINISTRATION, Adjustment or reduction of Dosage).

Dosing Considerations
Supeudol (oxycodone hydrochloride) tablets / suppository should be used with caution within 12 hours pre-operatively and within the first 12-24 hours post-operatively (see WARNINGS AND PRECAUTIONS, Peri-operative Considerations).

Supeudol tablets is not indicated for rectal administration

Supeudol tablets may be taken with or without food, with a glass of water.

Recommended Dose and Dosage Adjustment
Adults: Individual dosing requirements vary considerably based on each patient's age, weight, severity and cause of pain, and medical and analgesic history.

Patients Not Receiving Opioids at the Time of Initiation of Oxycodone Hydrochloride Treatment tablets: The usual initial adult dose of oxycodone hydrochloride for patients who have not previously received opioid analgesics is 5 or 10 mg, orally, every 6 hours.

Treatment suppository: 1 suppository 3 or 4 times a day, or as required.
Remove suppository from packaging and insert into the rectum.

Patients Currently Receiving Opioids: For patients who are receiving an alternate opioid, the "oral oxycodone equivalent" of the analgesic presently being used, should be determined. Having determined the total daily dosage of the present analgesic, Table 1 can be used to calculate the approximate daily oral oxycodone dosage that should provide equivalent analgesia. It is usually appropriate to treat a patient with only one opioid at a time. Further dose reductions should be considered due to incomplete cross-tolerance between opioids.

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/d
Codeine	0.15	6.67	600 mg/d
Hydromorphone	5	0.2	18 mg/d
Oxycodone	1.5	0.667	60 mg/d
Tapentadol	0.3-0.4	2.5-3.33	300 mg/d
Tramadol	0.1-0.2	6	***
Methadone	Morphine dose equivalence is not reliably established		

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

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

Patients with Hepatic and Renal Impairment: In patients with any degree of hepatic or renal impairment, the dose initiation should follow a conservative approach. The recommended adult starting dose in these patients should be at 1/3 to 1/2 the usual starting dose followed by careful dose titration to adequate pain control according to their clinical situation (see WARNINGS AND PRECAUTIONS, Special Populations and ACTION AND CLINICAL PHARMACOLOGY).

Geriatrics: Respiratory depression has occurred in the elderly following administration of large initial doses of opioids to patients who were not opioid-tolerant or when opioids were co-administered with other agents that can depress respiration. Supeudol should be initiated at a low dose and slowly titrated to effect (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY).

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. Supeudol can be safely used concomitantly with usual doses of other non-opioid analgesics.

Dose Titration:
Dose titration is the key to success with opioid analgesic therapy. **Proper optimization of doses scaled to the relief of the individual's pain should aim at administration of the lowest dose which will achieve the overall treatment goal of satisfactory pain relief with acceptable side effects.**

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

Adjustment or Reduction of Dosage: Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including Supeudol. Withdrawal (abstinence) symptoms may occur following abrupt discontinuation of therapy. These symptoms may include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning

Following successful relief of moderate to severe pain, periodic attempts to reduce the opioid dose should be made. Smaller doses or complete discontinuation may become feasible due to a change in the patient's condition or mental state. 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 WARNINGS AND PRECAUTIONS). Tapering should be individualised and carried out under medical supervision.

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

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

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.

Disposal

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

Supeudol should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired Supeudol should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets. Supeudol 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.

OVERDOSAGE

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

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, and sometimes bradycardia and hypotension. Severe overdose may result in apnea, circulatory collapse, cardiac arrest, pulmonary edema and death.

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

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

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

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

ACTION AND CLINICAL PHARMACOLOGY

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 CO_2, 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.

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 (see DETAILED PHARMACOLOGY, Pharmacodynamics).

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 CO_2 tension and to electrical stimulation.

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

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

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.

Cardiovascular System: Oxycodone may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral

vasodilatation may include pruritus, flushing, red eyes, hyperhidrosis and/or orthostatic hypotension.

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.

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.

Pharmacokinetics

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

Distribution: Following intravenous administration, the steady-state volume of distribution (V_{ss}) 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 DRUG INTERACTIONS, Drug-Drug Interactions).

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

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

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

Excretion: 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: Individuals under 18 years of age should not take Supeudol tablets or suppositories.

Geriatrics: The plasma concentrations of oxycodone are 15% greater in elderly as compared to young subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Gender: Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis.

Hepatic Impairment: Data from a study involving 24 patients with mild to moderate hepatic impairment show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, than subjects with normal hepatic function. The AUC values were 95% and 65% higher, respectively. Oxymorphone peak plasma concentrations and AUC values were lower by 30% and 40%. These differences are accompanied by increases in some, but not other, drug effects. The mean elimination half-life for oxycodone increased by 2.3 hours.

Renal Impairment: Data from a pharmacokinetic study involving 13 patients with mild to severe renal impairment showed peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, and AUC values for oxycodone, noroxycodone, and oxymorphone 60%, 50%, and 40% higher than normal subjects, respectively. This was accompanied by an

increase in sedation but not by differences in respiratory rate, pupillary constriction, or several other measures of drug effect. The mean elimination half-life for oxycodone increased by 1 hour.

STORAGE AND STABILITY

Tablets: Store between 15 and 30°C. Protect from light. Protect from moisture.

Suppository: Store below 25°C.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Supeudol tablets 5 mg are blue, round tablets, scored on one side and printed "5 in V" on the other side. Each tablet contains: oxycodone hydrochloride 5 mg. Non-medicinal Ingredients: dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, microcrystalline cellulose and aluminium blue lake FD&C. Supeudol tablets are available in polyethylene bottles of 100 tablets.

Supeudol tablets 10 mg are white, round tablets, scored on one side and printed "10 in V" on the other side. Each tablet contains: oxycodone hydrochloride 10 mg. Non-medicinal Ingredients: dibasic calcium phosphate, croscarmellose sodium, magnesium stearate and microcrystalline cellulose. Supeudol tablets are available in polyethylene bottles of 100 tablets.

Supeudol Suppositories 10 mg are ivory white conical shaped suppositories. Each suppository contains: oxycodone hydrochloride 10 mg. Non-medicinal Ingredients: hard fat. Supeudol Suppositories are available in blister boxes of 12.

Supeudol Suppositories 20 mg are ivory white conical shaped suppositories. Each suppository contains: oxycodone hydrochloride 20 mg. Non-medicinal Ingredients: hard fat. Supeudol Suppositories are available in blister boxes of 12.

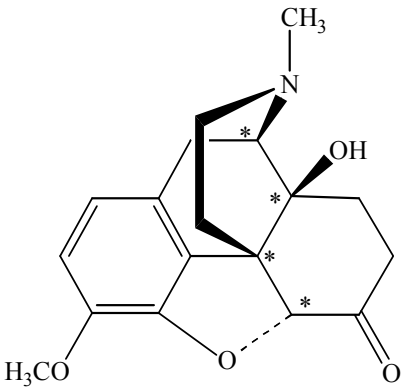
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name : Oxycodone Hydrochloride USP

Structural formula :



Chemical names: 1) Morphinan-6-one, 4,5-epoxy-14-hydroxy-3-methoxy-17-methyl, hydrochloride, (5α)-
2) 4,5α-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride

Molecular formula: $C_{18}H_{21}NO_4$ •HCl

Molecular weight: 351.83 g/mol

Melting Point: 218 - 223°C

Description: White to off-white, odourless, hygroscopic crystals.

Solubility: Soluble in water, slightly soluble in alcohol.

CLINICAL TRIALS

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

DETAILED PHARMACOLOGY

Pharmacodynamics: 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 2-4 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.

TOXICOLOGY

The LD_{50} after subcutaneous administration of oxycodone in mice was 275 - 340 mg/kg. The lowest lethal dose has been reported to be 200 mg/kg after subcutaneous administration in mice. These values are similar to those obtained for morphine. In a preliminary 12 day study in rabbits, no drug related toxic effects were discernible at 5 mg/kg. Doses of 25, 75 and 150 mg/kg were associated with variable and transient pharmacotoxic effects typical of high dose opioid treatment in animals (decreased activity, decreased or absent defecation and convulsions).

Teratogenicity: Oxycodone had no effect on fertility or early embryonic development in male and female rats at doses as high as 8 mg/kg/day. Also, oxycodone did not induce any malformations in rats at doses as high as 8 mg/kg/day or in rabbits at doses as high as 125 mg/kg/day. Dose-related increases in developmental variations (increased incidences of extra (27) presacral vertebrae and extra pairs of ribs) were observed in rabbits when the data for individual fetuses were analyzed. However, when the same data were analyzed using litters as

opposed to individual fetuses, there was no dose-related increase in developmental variations although the incidence of extra presacral vertebrae remained significantly higher in the 125 mg/kg/day group compared to the control group. Since this dose level was associated with severe pharmacotoxic effects in the pregnant animals, the fetal findings may have been a secondary consequence of severe maternal toxicity.

In a study of peri- and postnatal development 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.

Mutagenicity: Oxycodone was not mutagenic in the following assays: *Ames Salmonella* and *E. coli t*est with and without metabolic activation at doses of up to 5000 mcg, chromosomal aberration test in human lymphocytes in the absence of metabolic activation at doses of up to 1500 mcg/mL and with activation 48 hours after exposure at doses of up to 5000 mcg/mL, and in the *in vivo* bone marrow micronucleus test in mice at plasma levels of up to 48 mcg/mL.

Mutagenic results occurred in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 mcg/mL) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 mcg/mL or greater with metabolic activation and at 400 mcg/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.

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

Supeudol

Oxycodone Hydrochloride USP

Tablets 5 mg and 10 mg

Supeudol

Oxycodone Hydrochloride

Suppositories 10 mg and 20 mg

Read this carefully before you start taking Supeudol 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 Supeudol.

Serious Warnings and Precautions

- **Even if you take Supeudol as prescribed you are at a risk for opioid addiction, abuse and misuse. This can lead to overdose and death.**
- **When you take Supeudol tablets it must be swallowed whole. Do not cut, break, crush, chew the tablets or dissolve the tablet or suppository. This can be dangerous and can lead to death or seriously harm you.**
- **You may get life-threatening breathing problems while taking Supeudol. This is less likely to happen if you take it as prescribed by your doctor. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.**
- **You should never give anyone your Supeudol. They could die from taking it. If a person has not been prescribed Supeudol, taking even one dose can cause a fatal overdose. This is especially true for children.**
- **If you took Supeudol 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 Supeudol 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 Supeudol used for?
Supeudol is a medicine used to treat moderate to severe pain.

How does Supeudol work?
Supeudol contains oxycodone which is a pain medication belonging to the class of drugs known as opioid which includes codeine, fentanyl, hydromorphone and morphine. It relieves pain by acting on specific nerve cells of the spinal cord and brain.

What are the ingredients in Supeudol?
Medicinal ingredients: Oxycodone Hydrochloride

Tablets
Non-medicinal ingredients: dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, microcrystalline cellulose and aluminium blue lake FD&C for 5 mg only.
Suppository
Non-medicinal ingredients: Hard fat.

Supeudol comes in the following dosage forms:
Supeudol Immediate Release Tablets: 5 and 10 mg.
Supeudol Suppository: 10 and 20 mg.

Do not use Supeudol if:
- your doctor did not prescribe it for you
- you are allergic to oxycodone, opioids or any other ingredient in the Supeudol tablets or suppository (see What are the ingredients in Supeudol?)
- you can control your pain by the occasional use of other pain medications. This includes those available without a prescription
- you have severe asthma, trouble breathing, or other breathing problems
- you have any heart problems
- you have bowel blockage or narrowing of the stomach or intestines
- you have severe pain in your abdomen
- you have a head injury
- you are at risk for seizures
- you have a brain tumor
- you suffer from alcoholism
- you are taking or have taken within the past 2 weeks a Monoamine Oxidase inhibitor (MAOi) (such as phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline)
- you are going to have, or recently had, a planned surgery

- you are pregnant or planning to become pregnant or you are in labour
- you are breastfeeding

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Supeudol. Talk about any health conditions or problems you may have, including if you:

- have a history of illicit or prescription drug or alcohol abuse
- have severe kidney, liver or lung disease
- have heart disease
- have low blood pressure
- have past or current depression
- suffer from chronic or severe constipation
- have problems with your adrenal or prostate gland
- have, or had in the past hallucinations or other severe mental problems
- suffer from migraines
- are planning to become pregnant

Other warnings you should know about?

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

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

If you are pregnant and are taking Supeudol, 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 doctor will monitor and guide you on how to slowly stop taking Supeudol. 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 Supeudol. Supeudol can cause:

- drowsiness
- dizziness or
- light headedness

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

Disorder of the adrenal gland: You may develop a disorder of the adrenal gland called adrenal insufficiency. This means that your adrenal gland is not making enough of certain hormones. You may experience symptoms such as:

- nausea, vomiting
- feeling tired, weak or dizzy

- decreased appetite

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

Serotonin Syndrome: Supeudol can cause Serotonin Syndrome, 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 Syndrome if you take Supeudol with certain anti-depressants or migraine medications.

Serotonin Syndrome 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.

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

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

The following may interact with Supeudol:

- Alcohol. This includes prescription and non-prescription medications that contain alcohol.
  Do not drink alcohol while you are taking Supeudol. It can lead to:
  - drowsiness
  - unusually slow or weak breathing
  - serious side effects or
  - a fatal overdose
- other sedative drugs which may enhance the drowsiness caused by Supeudol
- other opioid analgesics (drugs used to treat pain)
- general anesthetics (drugs used during surgery)
- benzodiazepines (drugs used to help you sleep or that help reduce anxiety)
- antidepressants (for depression and mood disorders). **Do not** take Supeudol with MAO inhibitors (MAOi) or if you have taken MAOi's in the last 14 days.
- drugs used to treat serious mental or emotional disorders (such as schizophrenia)
- antihistamines (drugs used to treat allergies)
- anti-emetics (drugs used for the prevention of vomiting)
- drugs used to treat muscle spasms and back pain
- anti-retroviral drugs (used to treat viral infections)
- anti-fungal drugs (used to treat fungal infections)

- antibiotic drugs (used to treat bacterial infections)
- anticonvulsants (used to treat seizures)
- some heart medication (such as beta blockers)
- drugs used to treat migraines (e.g. triptans)
- St. John's Wort

How to take Supeudol?
Tablets:
Supeudol is usually taken every 6 hours with water. Supeudol tablets is for oral use. Your doctor may prescribe a different dose, if this is necessary for you. The dose of Supeudol varies based on each patient's weight, age, severity and cause of pain, as well as medical and pain medication history.

Swallow whole. Do not cut, break, crush, chew or dissolve the tablet. This can be dangerous and can lead to death or seriously harm you.

Suppository:
1 suppository 3 or 4 times a day, or as required.
Remove suppository from packaging and insert into the rectum.

Usual Adult Starting Dose:
Your dose is tailored/personalized just for you. Be sure to follow your doctor's dosing instructions exactly. Do not increase or decrease your dose without consulting your doctor.

Your doctor will prescribe the lowest dose that works to control your pain. It is recommended that you only take Supeudol for up to 7 days. If you need to take Supeudol for longer, your doctor will determine the best dose for you to lower the risk of side effects and overdose. Higher doses can lead to more side effects and a greater chance of overdose.

Review your pain regularly with your doctor to determine if you still need Supeudol. Be sure to use Supeudol only for the condition for which it was prescribed.

If your pain increases or you develop any side effect as a result of taking Supeudol, tell your doctor immediately.

Stopping your Medication:
If you have been taking Supeudol for more than a few days you should not stop taking it all of a sudden. Your doctor will monitor and guide you on how to slowly stop taking Supeudol. You should do it slowly to avoid uncomfortable symptoms such as having:
- body aches
- diarrhea
- goosebumps
- loss of appetite
- nausea
- feeling nervous or restless
- runny nose

- sneezing
- tremors or shivering
- stomach cramps
- rapid heart rate (tachycardia)
- having trouble sleeping
- an unusual increase in sweating
- heart palpitations
- an unexplained fever
- weakness
- yawning

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

Refilling your Prescriptions for Supeudol:
A new written prescription is required from your doctor each time you need more Supeudol. Therefore, it is important that you contact your doctor before your current supply runs out.

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

Overdose:

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

Signs of overdose may include:
- unusually slow or weak breathing
- dizziness
- confusion
- extreme drowsiness

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

What are possible side effects from using Supeudol?
These are not all the possible side effects you may feel when taking Supeudol. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:
- Drowsiness

- Insomnia
- Dizziness
- Fainting
- Nausea, vomiting, or a poor appetite
- Dry mouth
- Headache
- Problems with vision
- Weakness, uncoordinated muscle movement
- Itching
- Sweating
- Constipation
- Low sex drive, impotence (erectile dysfunction), infertility

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

Serious side effects and what to do about them				
Symptom / effect		Talk with your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Rare	**Overdose:** hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone, cold and clammy skin**.**			✓
	Respiratory Depression: slow, shallow or weak breathing.			✓
	Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
	Bowel Blockage (impaction): abdominal pain, severe constipation, nausea			✓
	Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating.		✓	
	Fast, Slow or Irregular Heartbeat: heart palpitations.		✓	
	Low Blood Pressure: dizziness, fainting, light-headedness.	✓		

Serious side effects and what to do about them			
Symptom / effect	Talk with your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Serotonin Syndrome: agitation or restlessness, loss of muscle control or muscle twitching, tremor, diarrhea			✓

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

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect: https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html
- By calling 1-866-234-2345 (toll-free);
- By completing a Patient Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Patient Side Effect Reporting Form are available at MedEffect (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html).

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

Storage:

- **Keep unused or expired Supeudol in a secure place to prevent theft, misuse or accidental exposure.**
- Store tablets between 15 and 30°C. Protect from light. Protect from moisture.
- Store suppository below 25°C.
- Keep Supeudol 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 Supeudol, get emergency help right away.

Disposal:

Supeudol 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 would like more information about Supeudol:

- talk with 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.sandoz.ca or by calling 1-800-361-3062.

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