

PRODUCT INFORMATION

Novacodone[®] modified release tablets (10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg)

NAME OF THE MEDICINE

Non-proprietary name: Oxycodone hydrochloride
Chemical name: 4,5 α -epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride
CAS No.: 124-90-3

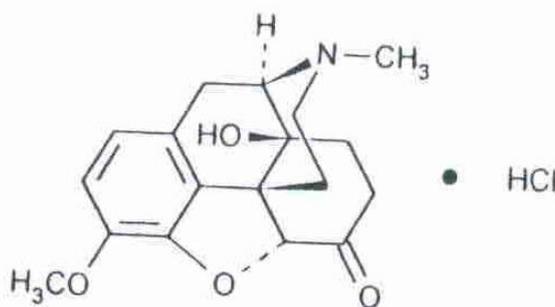
Molecular formula (anhydrous form): C₁₈H₂₁NO₄.HCl

Molecular weight (anhydrous form): 351.83

Molecular formula (monohydrate form): C₁₈H₂₁NO₄.HCl.H₂O

Molecular weight (monohydrate form): 369.84

Structural formula (anhydrous form):



DESCRIPTION

Oxycodone hydrochloride is a white, crystalline, odourless powder readily soluble in water, sparingly soluble in ethanol and nearly insoluble in ether.

Novacodone tablets are modified release tablets designed to provide delivery of oxycodone over 12 hours.

Novacodone 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg¹ and 80 mg tablets have been reformulated, and comprise a matrix formulation with a hydrogelling property (i.e. particles or whole tablets become highly viscous (gel-like) in water), intended to be crush-deterrent and to reduce the rapid release of oxycodone upon accidental or intentional misuse. The tablets have been heat-treated to increase the mechanical strength of the tablet.

The physical properties of the reformulated Novacodone tablets were examined following an extensive battery of physical manipulations. Beyond demonstrating that the reformulated Novacodone tablets are harder to crush than another controlled release oxycodone formulation, testing over the range of the reformulated Novacodone tablets fragment sizes showed that some of the controlled release properties were still retained. Hydrogelling properties continued to be demonstrated.

The inactive ingredients in the reformulated Novacodone 10 to 80 mg tablets are: polyethylene oxide and magnesium stearate. The tablets' film coating also contain:

10mg - Opadry White Y-5R-18024-A (ARPING No. 3585)

15mg - Opadry Grey 05B97512 (ARPING No. 12507)

20mg - Opadry Pink YS-1R-14518-A (ARPING No.109767)

30mg - Opadry Brown YS-1-16518-A (ARPING No. 12505)

40mg - Opadry Yellow YS-1R-12525-A. (ARPING No. 3587)

60mg - Opadry Red 15B25501 (ARPING No. 12506)

80mg - Opadry Green Y-5R-11167-A (ARPING No.3588)

PHARMACOLOGY

Actions

Oxycodone is a full opioid agonist with no antagonist properties whose principal therapeutic action is analgesia. It has an affinity for kappa, mu and delta opiate receptors in the brain and spinal cord. Oxycodone is similar to morphine in its action. Other pharmacological actions of oxycodone are in the central nervous system (CNS: respiratory depression, antitussive, anxiolytic, sedative and miosis), smooth muscle (constipation, reduction in gastric, biliary and pancreatic secretions, spasm of sphincter of Oddi and transient elevations in serum amylase) and cardiovascular system (release of histamine and/or peripheral vasodilatation, possibly causing pruritus, flushing, red eyes, sweating and/or orthostatic hypotension).

Pharmacokinetics

Absorption

Compared with morphine, which has an absolute bioavailability of approximately 30%, oxycodone has a high absolute bioavailability of up to 87% following oral administration.

The mean apparent half-life of Novacodone tablets is 6.5 hours and steady-state is achieved in about one day.

Release of oxycodone from Novacodone tablets is independent of pH under physiological conditions.

Novacodone tablets have an oral bioavailability comparable with immediate release oral oxycodone, but achieve maximal plasma concentrations at about three hours compared with 1-1.5 hours for immediate release oral oxycodone. Peak and trough concentrations of oxycodone from Novacodone tablets 10 mg administered 12-hourly are similar to those achieved from immediate release oxycodone 5 mg administered 6-hourly.

Dose proportionality has been established for the 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg and 80mg tablet strengths for both peak plasma concentrations (C_{max}) and extent of absorption (AUC).

Recent fasted and fed studies for Novacodone 10, 40 and 80 mg tablets indicate that food has no significant effect on the extent of absorption of oxycodone from Novacodone tablets.

Distribution

Following absorption, oxycodone is distributed throughout the entire body. Oxycodone has been found in breast milk (see **PRECAUTIONS**, Use in lactation).

Metabolism and Elimination

Oxycodone has an elimination half-life of approximately three hours and is metabolised in the liver to form noroxycodone, oxymorphone, noroxymorphone, 6 α and β oxycodol and conjugated glucuronides. CYP3A4 and CYP2D6 are involved in the formation of noroxycodone and oxymorphone, respectively (see **INTERACTIONS WITH OTHER MEDICINES**). The contribution of these metabolites to the analgesic effect is insignificant.

INDICATIONS

The management of moderate to severe chronic pain unresponsive to non-narcotic analgesia.

CONTRAINDICATIONS

Hypersensitivity to opioids or to any of the constituents of Novacodone tablets, acute respiratory depression, *cor pulmonale*, cardiac arrhythmias, acute asthma or other obstructive airways disease, suspected mechanical gastrointestinal obstruction (e.g. bowel obstruction, strictures) or any diseases/conditions that affect bowel transit (e.g. ileus of any type), suspected surgical abdomen, severe renal impairment (creatinine clearance < 10 mL/min), severe hepatic impairment (refer to Special Risk Groups), delayed gastric emptying, acute alcoholism, brain tumour, increased cerebrospinal or intracranial pressure, head injury (due to risk of raised intracranial pressure), severe CNS depression, convulsive disorders, *delirium tremens*, hypercarbia, concurrent administration of monoamine oxidase inhibitors or within two weeks of discontinuation of their use. Not recommended for pre-operative use or for the first 24 hours post-operatively. Pregnancy.

CLINICAL TRIALS

A double-blind, placebo-controlled, fixed-dose, parallel group, two-week study was conducted in 133 patients with persistent, moderate to severe pain, who were judged as having inadequate pain control with their current therapy. In this study, Novacodone 20 mg tablets, but not 10 mg tablets, was statistically significant in pain reduction compared with placebo (text from Novacodone US Prescribing Information dated April 2013).

PRECAUTIONS

The major risk of opioid excess is respiratory depression, including subclinical respiratory depression. As with all opioids, a reduction in dosage may be advisable in hypothyroidism. Use with caution in opioid-dependent patients and in patients with hypotension, hypovolaemia, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, prostatic hypertrophy, adrenocortical insufficiency (Addison's disease), toxic psychosis, chronic pulmonary, renal or hepatic disease, myxoedema and debilitated elderly or infirm patients or patients taking benzodiazepines, other CNS depressants (including alcohol) or MAO inhibitors. As with all opioid preparations, patients who are to undergo cordotomy or other pain-relieving surgical procedures should not receive Novacodone tablets for 24 hours before surgery. Pain in the immediate pre-operative period, and any symptoms of opioid withdrawal, should be managed

with short-acting analgesic agents. If further treatment with Novacodone tablets is then indicated the dosage should be adjusted to the new post-operative requirement.

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

As with all opioid preparations, Novacodone tablets should be used with caution following abdominal surgery as opioids are known to impair intestinal motility and should not be used until the physician is assured of normal bowel function. Should paralytic ileus be suspected or occur during use, Novacodone tablets should be discontinued immediately.

Use caution when prescribing Novacodone tablets for patients who have any underlying GI disorders that may predispose them to intestinal obstruction. Patients with underlying GI disorders such as oesophageal cancer or colon cancer with a small gastrointestinal lumen are at greater risk.

Novacodone tablets should not be taken by patients with difficulty in swallowing or who have been diagnosed with narrowing of the oesophagus. If patients experience swallowing difficulties (e.g. choking, gagging, discomfort, regurgitation, tablets stuck in the throat) after taking Novacodone tablets, they should be advised to seek immediate medical attention.

Opioids, such as oxycodone hydrochloride, 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 symptoms may manifest from these hormonal changes.

Use in chronic, non-malignant pain

The use of Novacodone tablets for the treatment of chronic pain which is not due to malignancy should be restricted to situations where:

- all other conservative non-pharmacological and pharmacological methods of analgesia have been tried and have failed or are insufficient
- the pain is having a significant impact on the patient's quality of life
- there is no psychological contraindication, drug-seeking behaviour or past and current personal or family history of alcohol, prescription/illicit drug abuse or misuse.

Opioids, where clinically indicated, should only be prescribed as one component of a comprehensive multimodal management approach to chronic, non-malignant pain. Appropriate patient selection is the key to successful treatment of moderate to severe chronic pain with opioid analgesics.

An initial comprehensive assessment should be conducted using a biopsychosocial approach to identify a cause for the pain and the appropriateness of opioid therapy - and to identify psychosocial factors that may exacerbate pain or magnify overall distress (e.g. depression, anxiety, post-traumatic stress disorder, borderline personality disorder, marked family stressors, history of sexual abuse). In the absence of a clear indication for a strong opioid analgesic, drug-seeking behaviour must be suspected and resisted, particularly in individuals with a history of, or propensity for, drug abuse. Factors that may put the patient at increased risk of opioid abuse/addiction include a personal/family history of substance, prescription medication and

alcohol abuse, and major psychosocial issues (e.g. psychological/psychiatric disorder). The use of opioids to treat predominant emotional distress should be avoided.

Generally, opioid analgesics are not initiated prior to a full initial clinical assessment and before consideration of other treatment options such as physiotherapy/exercise/rehabilitation approaches, psychosocial interventions such as CBT (cognitive-behavioural therapy) self-management approaches, involvement of a psychologist or psychiatrist to address psychological co-morbidities which may be impacting on pain coping and trials of other non-opioid pharmacotherapeutic or interventional strategies.

Prior to longer-term prescribing, a trial of Novacodone tablets or shorter-acting opioid should be undertaken. Longer-term administration of Novacodone tablets should only occur if this trial demonstrates that the pain is opioid sensitive. Opioid-naïve patients who require rapid dose escalation with no concomitant pain relief within the trial period should generally be considered inappropriate for longer-term therapy.

One doctor only should be responsible for the prescription and monitoring of the patient's opioid use. Prescribers should consult appropriate clinical guidelines on the use of opioid analgesics in such patients (e.g. those published by the Australian Pain Society in the Medical Journal of Australia 1997; 167: 30-4).

Drug dependence

As with other opioids, tolerance and physical dependence tend to develop upon repeated administration of oxycodone. There is potential for abuse of the drug and for development of strong psychological dependence. Novacodone tablets should therefore be prescribed and handled with a high degree of caution appropriate to the use of a drug with strong abuse potential.

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

Oxycodone should be used with caution and under close supervision in patients with pain not due to malignancy who have a prior history of substance abuse. In such cases, prior psychological assessment is essential and the prescribing doctor should consider whether the benefit of treatment outweighs the risk of abuse.

Drug abuse studies

Intranasal abuse

In a human abuse liability study, milled Novacodone 30 mg tablets produced subjective responses on each of the four established primary measures that were greater than placebo but significantly less than the responses for another, conventional finely crushed controlled release oxycodone tablets formulation 30 mg, or a fine powder of oxycodone 30 mg when administered intranasally in healthy recreational opioid users with a history of intranasal drug abuse/misuse (n=27). The primary measures were: 'Drug-liking 'at this moment''; 'Overall drug liking'; 'Subjective Drug Value'; 'Addiction Research Centre Inventory (ARCI) Morphine Benzodrine Group (MBG)' scales.

Objective measures of pupil diameter and other subjective measures were consistent with a lower opioid effect. Measurements of intranasal irritation showed increased irritation, particularly

related to nasal stuffiness, with Novacodone tablets compared with another conventional controlled release oxycodone tablets formulation or oxycodone powder.

In a tolerability and safety study with healthy subjects under fasting conditions, milled Novacodone tablets were shown to cause increased nasal discomfort, particularly related to increased nasal stuffiness, and a decrease in runny nose scores when compared with another finely milled controlled release oxycodone tablets formulation, when administered intranasally. Although total AUC was similar for all treatments, C_{max} was 67% for coarsely and 77.6% for finely milled Novacodone tablets (Ratio of metric means expressed as a percent, transformed back to the linear scale) compared with the other finely milled conventional controlled release oxycodone tablets formulation and T_{max} was later with Novacodone tablets.

An additional study was conducted to assess the administration site safety and tolerability of intranasally administered milled Novacodone tablets placebo vs another crushed conventional controlled release oxycodone tablets formulation placebo. Endoscopy photographs showed residual particles in the nasal cavity at 30 minutes following administration of Novacodone tablets placebo.

Accidental or Intentional Oral Misuse

A study in healthy subjects was conducted to characterize the impact of chewing intact and tampered tablets and subsequent swallowing, on the pharmacokinetics of Novacodone tablets under fasting conditions. The manufacturing process for Novacodone tablets imparts increased hardness to the tablets. Subjects were required to complete a chewing qualification assessment prior to receiving their initial study doses.

The results showed that under both normal and vigorous chewing conditions, Novacodone tablets retained some of their controlled release characteristics. Peak plasma levels of oxycodone (C_{max}) for Novacodone tablets were 13.5% lower when swallowed after vigorous chewing and 23.6% lower when swallowed after normal chewing (Ratio of metric means expressed as a percent, transformed back to the linear scale) when compared with another chewed conventional formulation of controlled release oxycodone tablets. The time to reach peak plasma levels (T_{max}) was also delayed for Novacodone tablets compared with the other conventional controlled release oxycodone tablet formulation, under both vigorous (1.5 vs 1.0 hours respectively) and normal (2.38 vs 1.13 hours respectively) chewing conditions.

Formulation

Novacodone tablets are intended for oral use only. The modified release tablets must be swallowed whole, and not broken, chewed or crushed. The administration of broken, chewed or crushed modified release oxycodone tablets leads to a rapid release and absorption of a potentially fatal dose of oxycodone. Parenteral venous injection of the tablet constituents can be expected to result in local tissue necrosis, pulmonary granulomas and serious adverse reactions which may be fatal.

Effects on fertility

In reproductive toxicology studies, no evidence of impaired fertility was seen in male or female rats at oral oxycodone doses of 8 mg/kg/day, with estimated exposure (plasma AUC) equivalent to 8 mg/day in men and 17 mg/day in women.

Despite these fertility studies in animals, prolonged use of opioids may result in impairment of reproductive function, including fertility and sexual dysfunction in both sexes, and irregular menses in women.

Use in pregnancy

Australian Pregnancy Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible.

Oxycodone used during pregnancy or labour may cause withdrawal symptoms and/or respiratory depression in the newborn infant. Oral administration of oxycodone during the period of organogenesis did not elicit teratogenicity or embryofetal toxicity in rats or rabbits at doses up to 8 mg/kg/day in rats (equivalent to 17 mg/day in women, based on estimated plasma AUC values) or 125 mg/kg/day in rabbits.

Oral administration of oxycodone to rats from early gestation to weaning did not affect postnatal development parameters at doses up to 6 mg/kg/day (equivalent to 9 mg/day in women, based on estimated AUC values). In a study designed specifically to investigate the effect of pre-natal oxycodone on the hypothalamic-pituitary-adrenal axis in adolescent rats, intravenous administration of oxycodone 0.8 mg/kg/day (equivalent to 11 mg/day in pregnant women, based on estimated AUC values) had no effect on the corticosterone response, but delayed and enhanced the peak ACTH response to corticotrophin releasing hormone in males, but not females. The clinical significance of this observation is unknown.

There are no adequate and well-controlled studies with oxycodone in pregnant women. Because animal reproduction studies are not always predictive of human responses, oxycodone should not be used during pregnancy unless clearly needed. Prolonged use of oxycodone during pregnancy can result in neonatal opioid withdrawal. Oxycodone is not recommended for use in women during or immediately prior to labour. Infants born to mothers who have received opioids during pregnancy should be monitored for respiratory depression.

Use in lactation

Oxycodone accumulates in human milk, with a median maternal milk:plasma ratio of 3:1 recorded in one study. Oxycodone (7.5 ng/mL) was detected in the plasma of one of forty-one infants 72 hours after Caesarean section. Opioids may cause respiratory depression in the newborn and withdrawal symptoms can occur in breastfeeding infants when maternal administration of an opioid analgesic is stopped. Novacodone tablets should not be used in breastfeeding mothers unless the benefits outweigh the risks. Breastfed infants should be monitored for respiratory depression, sedation, poor attachment and gastrointestinal signs.

Special Risk Groups

Use in renal and hepatic impairment

In renal and hepatic impairment, the administration of Novacodone tablets does not result in significant levels of active metabolites. However, the plasma concentration of oxycodone in this patient population may be increased compared with patients having normal renal or hepatic function. Therefore, initiation of dosing in patients with renal impairment ($\text{CrCl} < 60 \text{ mL/min}$) or hepatic impairment should be reduced to $\frac{1}{3}$ to $\frac{1}{2}$ of the usual dose with cautious titration.

Use in the elderly

The plasma concentrations of oxycodone are only nominally affected by age, being approximately 15% greater in elderly as compared with young subjects. There were no differences in adverse event reporting between young and elderly subjects.

Use in elderly, debilitated patients

As with other opioid initiation and titration, doses in elderly patients who are debilitated should be reduced to $\frac{1}{3}$ to $\frac{1}{2}$ of the usual doses.

Gender

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown. There were no significant male/female differences detected for efficacy or adverse events in clinical trials.

Genotoxicity

Oxycodone was not genotoxic in bacterial gene mutation assays but was positive in the mouse lymphoma assay. In assays of chromosomal damage, genotoxic effects occurred in the human lymphocyte chromosomal aberration assay *in vitro*, but not in the *in vivo* bone marrow micronucleus assay in mice.

Carcinogenicity

Studies of oxycodone in animals to evaluate its carcinogenic potential have not been conducted.

Driving and operating dangerous machinery

Oxycodone may modify patients' reactions to a varying extent depending on the dosage and individual susceptibility. If their ability is impaired, patients should not drive or operate machinery.

INTERACTIONS WITH OTHER MEDICINES

Anticholinergic agents

Concurrent use with oxycodone with anticholinergics or medications with anticholinergic activity (e.g. tricyclic antidepressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson medications) may result in increased anticholinergic adverse effects, including an increased risk of severe constipation and/or urinary retention.

Antihypertensive agents

Hypotensive effects of these medications may be potentiated when used concurrently with oxycodone, leading to increased risk of orthostatic hypotension.

CNS depressants (including non-benzodiazepines sedatives or hypnotics, general anaesthetics, phenothiazines, other tranquillisers, alcohol, other opioids, benzodiazepines and neuroleptic drugs, etc.)

Concurrent use with oxycodone may result in increased respiratory depression, hypotension, profound sedation, death or coma. Caution is recommended and the dosage of one or both agents should be reduced. Intake of alcoholic beverages while being treated with Novacodone tablets should be avoided because this may lead to more frequent undesirable effects such as somnolence and respiratory depression. Oxycodone hydrochloride containing products should be avoided in patients with a history of or present alcohol, drug or medicines abuse.

Coumarin derivatives

Although there is little substantiating evidence, opiate agonists have been reported to potentiate the anticoagulant activity of coumarin derivatives.

CYP2D6 and CYP3A4 inhibitors and inducers

Oxycodone is metabolised in part via the CYP2D6 and CYP3A4 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. Drugs that inhibit CYP2D6 activity, such as paroxetine and quinidine, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. Concurrent administration of quinidine does not alter the pharmacodynamic effects of oxycodone. CYP3A4 inhibitors such as macrolide antibiotics (e.g. clarithromycin), azole antifungal agents (e.g. ketoconazole), protease inhibitors (e.g. ritonavir) and grapefruit juice may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. Oxycodone metabolism may be blocked by a variety of drugs (e.g. cimetidine, certain cardiovascular drugs and antidepressants), although such blockade has not yet been shown to be of clinical significance with Novacodone tablets.

CYP3A4 inducers, such as rifampin, carbamazepine, phenytoin and St. John's wort, may induce the metabolism of oxycodone and cause increased clearance of the drug, resulting in a decrease in oxycodone plasma concentrations.

Oxycodone did not inhibit the activity of P450 isozymes 2D6, 3A4, 1A2, 2A6, 2C19 or 2E1 in human liver microsomes *in vitro*. Non-clinical data *in vitro* and *in vivo* indicate that oxycodone can act as a P-glycoprotein substrate and can induce overexpression of P-glycoprotein in rats.

Metoclopramide

Concurrent use with oxycodone may antagonise the effects of metoclopramide on gastrointestinal motility.

Monoamine Oxidase Inhibitors (MAOIs)

Non-selective MAOIs intensify the effects of opioid drugs which can cause anxiety, confusion and significant respiratory depression. Severe and sometimes fatal reactions have occurred in patients concurrently administered MAOIs and pethidine. Oxycodone should not be given to patients taking non-selective MAOIs or within 14 days of stopping such treatment. As it is unknown whether there is an interaction between selective MAOIs (e.g. selegiline) and oxycodone, caution is advised with this drug combination.

Neuromuscular blocking agents

Oxycodone may enhance the effects of neuromuscular blocking agents resulting in increased respiratory depression.

Opioid agonist analgesics (including morphine, pethidine)

Additive CNS depressant, respiratory depressant and hypotensive effects may occur if two or more opioid agonist analgesics are used concurrently.

Opioid agonist-antagonist analgesics (including pentazocine, butorphanol, buprenorphine)

Mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms.

ADVERSE EFFECTS

Adverse drug reactions are typical of full opioid agonists, and tend to reduce with time, with the exception of constipation. Anticipation of adverse drug reactions and appropriate patient management can improve acceptability.

Cardiac disorders

Uncommon bradycardia, chest pain, palpitations (as part of withdrawal syndrome), ST depression, supraventricular tachycardia

Ear and labyrinth disorders

Uncommon tinnitus, vertigo

Eye disorders

Uncommon miosis, visual impairment

Gastrointestinal disorders

Very common nausea, vomiting, constipation

Common abdominal pain, diarrhoea, dry mouth, dyspepsia, gastritis, hiccup

Uncommon colic, dental caries, dysphagia, eructation, flatulence, gastrointestinal disorder, ileus, stomatitis, regurgitation, retching

General disorders and administration site conditions

Common asthenia, fatigue, chills, fever

Uncommon accidental injury, drug tolerance, drug withdrawal syndrome (with or without seizures), facial flushing, lymphadenopathy, malaise, muscular rigidity, neck pain, oedema, peripheral oedema, pain, thirst

Not known drug withdrawal syndrome neonatal

Hepatobiliary disorders

Uncommon biliary spasm, cholestasis, hepatic enzyme increased

Immune system disorders

Uncommon allergic reaction, anaphylactic reaction, anaphylactoid reaction, hypersensitivity

Injury, poisoning and procedural complications

Uncommon medication struck in throat

Metabolism and nutrition disorders

Common decreased appetite

Uncommon increased appetite, dehydration, hyponatraemia

Nervous system disorders

Very common dizziness, headache, somnolence

Common faintness, sedation, twitching, tremor, lethargy

Uncommon amnesia, drowsiness, abnormal gait, convulsion, dysgeusia (taste perversion), hyperkinesia, hypertonia, hypoaesthesia, hypothermia, raised intracranial

pressure, muscle contractions involuntary, paraesthesia, seizures, speech disorder, stupor, syncope
Not Known hyperalgesia

Psychiatric disorders

Common abnormal dreams, anxiety, confusional state, insomnia, nervousness, thinking abnormal, depression
Uncommon affect lability, agitation, disorientation, drug dependence, dysphoria, euphoric mood, hallucination, libido decreased, mood altered, restlessness
Not known aggression

Renal and urinary disorders

Uncommon ureteric spasm, urinary abnormalities, urinary retention, urinary tract infection

Reproductive system and breast disorders

Uncommon amenorrhoea, erectile dysfunction, hypogonadism

Respiratory, thoracic and mediastinal disorders

Common bronchospasm, dyspnoea, pharyngitis, voice alteration
Uncommon respiratory depression, choking

Skin and subcutaneous tissue disorders

Very common pruritus
Common hyperhidrosis, rash
Uncommon dry skin, exfoliative dermatitis, urticaria and other skin rashes

Vascular disorders

Common orthostatic hypotension
Uncommon hypotension, migraine, vasodilatation

Key: *Very common* ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $< 1/1000$)

Very rare ($< 1/10,000$)

Not known (cannot be estimated from the available data)

If nausea and vomiting are troublesome, oxycodone may be combined with an antiemetic. Constipation must be treated with appropriate laxatives. Overdose may produce respiratory depression. Compared with other opioids, oxycodone is associated with low histamine release although urticaria and pruritus may occur.

Post-marketing

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.

There have been uncommon post-marketing reports of difficulty swallowing Novacodone 10 mg to 80 mg tablets, potentially due to the swelling and hydrogelling property of the tablets: choking, gagging, regurgitation, tablets stuck in the throat and difficulty swallowing the tablet.

DOSAGE AND ADMINISTRATION

Novacodone tablets 60 mg¹ and 80 mg should only be used in opioid-tolerant patients. These tablet strengths may cause fatal respiratory depression in patients not previously exposed to opioids (opioid naïve).

Novacodone tablets are to be swallowed whole, and are not to be cut, broken, chewed, crushed or dissolved. The tablets have been hardened to reduce the risk of being accidentally or intentionally broken, chewed or crushed. Taking cut, broken, chewed, crushed or dissolved Novacodone tablets could lead to the rapid release and absorption of a potentially fatal dose of oxycodone.

To avoid difficulty swallowing, Novacodone 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.

There are no data on rectal administration of Novacodone tablets, therefore rectal administration of Novacodone tablets is not recommended.

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

Alcoholic beverages should be avoided by patients while being treated with Novacodone tablets.

¹ Novacodone 60 mg tablets are not marketed in Australia.

Adults, elderly and children over 12 years

Prior to initiation and titration of doses, refer to the **PRECAUTIONS** section for information on special risk groups such as females and the elderly. Novacodone tablets should be taken at 12-hourly intervals. Appropriate pain management principles of careful assessment and ongoing monitoring should be followed at regular intervals, including reassessing the need for continued opioid therapy. The dosage is dependent on the severity of the pain, and the patient's previous history of analgesic requirements.

The usual starting dose for opioid-naïve patients or patients presenting with moderate to severe pain uncontrolled by weaker opioids (especially if they are receiving concurrent sedatives, muscle relaxants or other CNS medicines) is 10 mg 12-hourly.

The dose should then be carefully titrated with longitudinal patient monitoring, assessing whether the pain is opioid responsive and providing the patient significant pain relief.

Increasing severity of pain may require an increased dosage of Novacodone tablets to achieve a stable dose that provides acceptable pain relief. The correct dosage for any individual patient is that which controls the pain and is well tolerated, for a full 12 hours. If higher doses are necessary, increases should be made, where possible, in 25% - 50% increments.

Patients who experience breakthrough pain may require dosage adjustment or rescue medication. The need for rescue medication more than twice a day indicates that the patient should be reassessed and, only if appropriate, the dosage of Novacodone tablets should be increased. There

are no well-controlled clinical studies evaluating the safety and efficacy with dosing more frequently than every 12 hours.

Patients receiving oral morphine before Novacodone tablet therapy should have their daily dose based on the following ratio: 10 mg of oral oxycodone is equivalent to 20 mg of oral morphine. It is emphasised that this is a guide to the dose of Novacodone tablets required only. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

Controlled pharmacokinetic studies in elderly patients (aged over 65 years) have shown that compared with younger adults the clearance of oxycodone is only slightly reduced. No untoward adverse drug reactions were seen based on age, therefore adult doses and dosage intervals are appropriate.

Children under 12 years

Novacodone tablets are not recommended for children under 12 years of age.

Patients with renal or hepatic impairment

The dose initiation should follow a conservative approach in these patients. The recommended adult starting dose should be reduced by $\frac{1}{3}$ to $\frac{1}{2}$, and each patient should be titrated to adequate pain control according to their clinical situation (see **PRECAUTIONS**, Special Risk Groups).

Patients transferring from other opioid formulations

Patients receiving other oral oxycodone formulations may be transferred to Novacodone tablets at the same total daily dosage, equally divided into two 12-hourly Novacodone tablet doses. For patients who are receiving an alternative opioid, the “oral oxycodone equivalent” of the analgesic presently being used should be determined. Having determined the total daily dosage of the present analgesic, the following equivalence table can be used to calculate the approximate daily oral oxycodone dosage that should provide equivalent analgesia. The total daily oral oxycodone dosage should then be equally divided into two 12-hourly Novacodone tablet doses.

*Multiplication Factors for Converting the Daily Dose of Prior Opioids to the Daily Dose of Oral Oxycodone**

(mg/Day Prior Opioid x Factor = mg/Day Oral Oxycodone)

	Oral Prior Opioid	Parenteral Opioid
Oxycodone	1	--
Codeine	0.15	--
Fentanyl TTS	SEE BELOW**	SEE BELOW**
Hydromorphone	4	20
Pethidine	0.1	0.4
Methadone	1.5	3
Morphine	0.5	3

* To be used for conversion to oral oxycodone. For patients receiving high-dose parenteral opioids, a more conservative conversion is warranted. For example, for high-dose parenteral morphine, use 1.5 instead of 3 as a multiplication factor.

** Conversion from transdermal fentanyl to Novacodone tablets: 18 hours following the removal of the transdermal fentanyl patch, Novacodone tablets treatment can be initiated. Although there has been no systematic assessment of such conversion, a conservative oxycodone dose, approximately 10 mg 12-

hourly of Novacodone tablets, should be initially substituted for each 25 µg/hr fentanyl transdermal patch. The patient should be followed closely.

OVERDOSAGE

Symptoms

Acute overdosage with oxycodone can be manifested by respiratory depression (reduced respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, hypotonia, cold and/or clammy skin, miosis (dilated if hypoxia is severe), and sometimes bradycardia, hypotension, and death. Severe overdose may result in apnoea, pulmonary oedema, circulatory collapse and death. The features of overdose may be delayed with a sustained release product such as Novacodone tablets.

Treatment of oxycodone overdosage

Primary attention should be given to immediate supportive therapy with the establishment of adequate respiratory exchange through the provision of a patent airway and institution of assisted or controlled ventilation. Adequate body temperature and fluid balance should be maintained. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated, to manage the circulatory shock accompanying an overdose. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

Activated charcoal may reduce absorption of the drug if given within one to two hours after ingestion. Administration of activated charcoal should be restricted to patients who are fully conscious with an intact gag reflex or protected airway. A saline cathartic or sorbitol added to the first dose of activated charcoal may speed gastrointestinal passage of the product. In patients who are not fully conscious or have an impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

Whole bowel irrigation (e.g. 1 or 2 litres of polyethylene glycol solution orally per hour until rectal effluent is clear) may be useful for gut decontamination. Whole bowel irrigation is contraindicated in patients with bowel obstruction, perforation, ileus, haemodynamic instability or compromised, unprotected airways and should be used cautiously in debilitated patients and where the condition may be further compromised. Concurrent administration of activated charcoal and whole bowel irrigation may decrease the effectiveness of the charcoal (there may be competition for the charcoal binding site between the polyethylene glycol and the ingested drugs) but the clinical relevance is uncertain. Prolonged periods of observation (days) may be required for patients who have overdosed with long-acting oxycodone preparations.

If there are signs of clinically significant respiratory or cardiovascular depression, the use of an opioid antagonist should be considered. The opioid antagonist naloxone hydrochloride is a specific antidote for respiratory depression due to overdosage or as a result of unusual sensitivity to opioid. The usual intravenous adult dose of naloxone is 0.4 mg or higher (please refer to naloxone product information for further information). The onset of naloxone effect may be delayed by 30 minutes or more. 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, or an antagonist infusion established, to maintain adequate respiration.

In an individual physically dependent on, or tolerant to, opioids, the administration of the usual dose of opioid antagonist can precipitate an acute withdrawal syndrome. This may lead to agitation, hypertension, tachycardia and risk of vomiting with possible aspiration. The severity of this syndrome will depend on the degree of physical dependence and the dose of antagonist administered. The use of opioid antagonists in such individuals should be avoided if possible. If an opioid 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.

Toxicity

Oxycodone toxicity may result from overdosage but because of the great interindividual variation in sensitivity to opioids it is difficult to determine an exact dose of any opioid that is toxic or lethal. Crushing and taking the contents of a modified release dosage form leads to the release of oxycodone in an immediate fashion; this might result in a fatal overdose. The toxic effects and signs of overdosage may be less pronounced than expected, when pain and/or tolerance are manifest.

Please phone the Poisons Information Centre on 13 11 26 for advice on managing overdose.

PRESENTATION AND STORAGE CONDITIONS

Presentation

Novacodone[®] modified release tablets are available* as round, unscored bi-convex tablets embossed with letters and numerals in blister pack sizes of 20 and 28 and contain the following quantities of oxycodone hydrochloride:

Novacodone[®] 10 mg contains oxycodone hydrochloride 10 mg (white, embossed with ON on one side and 10 on the other)

Novacodone[®] 15 mg contains oxycodone hydrochloride 15 mg (grey, embossed with ON on one side and 15 on the other)

Novacodone[®] 20 mg contains oxycodone hydrochloride 20 mg (pink, embossed with ON on one side and 20 on the other)

Novacodone[®] 30 mg contains oxycodone hydrochloride 30 mg (brown, embossed with ON on one side and 30 on the other)

Novacodone[®] 40 mg contains oxycodone hydrochloride 40 mg (yellow, embossed with ON on one side and 40 on the other)

Novacodone[®] 60 mg contains oxycodone hydrochloride 60 mg (red, embossed with ON on one side and 60 on the other)

Novacodone[®] 80 mg contains oxycodone hydrochloride 80 mg (green, embossed with ON on one side and 80 on the other)

*Not all strengths and pack sizes are currently marketed in Australia

Storage Conditions

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Mundipharma Pty Limited

ABN 87 081 322 509

88 Phillip Street

SYDNEY, NSW 2000

Further information may be obtained from the Medical Information Department on 1800 726 369.

DISTRIBUTED BY:

Sandoz Pty Ltd
ABN 60 075 449 553.
54 Waterloo Road, Macquarie Park
NSW 2113, AUSTRALIA.

POISON SCHEDULE OF THE MEDICINE

S8

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

Novacodone[®] tablets 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg:
07 September 2015

DATE OF MOST RECENT AMENDMENT

08 August 2017

®: NOVACODONE is a registered trademark.

Orbis AU-4120