New Zealand Data Sheet

1 PRODUCT NAME

OXYCODONE CONTROLLED RELEASE TABLETS (MATRIX FORMULATION)
5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg & 80 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Oxycodone hydrochloride 5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg & 80 mg

Excipient with known effect: lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oxycodone Controlled Release Tablets **5 mg** – Light blue, round, biconvex, controlled release tablets with black imprint '5' on one side and a diameter of approx. 7.1 mm.

Oxycodone Controlled Release Tablets **10 mg** – White, round, biconvex, controlled release tablets with black imprint '10' on one side and a diameter of approx. 7.1 mm.

Oxycodone Controlled Release Tablets **15 mg*** – Grey, round, biconvex, controlled release tablets with a diameter of approx. 7.1 mm.

Oxycodone Controlled Release Tablets **20 mg** – Light pink, round, biconvex controlled release tablets with black imprint '20' on one side and a diameter of approx. 7.1 mm.

Oxycodone Controlled Release Tablets **30 mg*** – Brown, round, biconvex, controlled release tablets with a diameter of approx. 7.1 mm.

Oxycodone Controlled Release Tablets **40 mg** – Light orange to ochre, round, biconvex, controlled release tablets with black imprint '40' on one side and a diameter of approx. 7.1 mm.

Oxycodone Controlled Release Tablets **60 mg*** – Pink-red, round, biconvex, controlled release tablets with a diameter of approx. 8.8 mm.

Oxycodone Controlled Release Tablets **80 mg** – Green, round, biconvex, controlled release tablets with white imprint '80' on one side and a diameter of approx. 8.8 mm.

**Not available in New Zealand.*

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Dose and method of administration

Oxycodone Controlled Release Tablets 80 mg should only be used in opioid-tolerant patients. In patients not previously exposed to opioids (opioid naïve), this tablet strength may cause fatal respiratory depression.

Oxycodone Controlled Release Tablets are to be swallowed whole, and are not to be broken, chewed or crushed. Taking broken, chewed or crushed Oxycodone Controlled Release Tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone.

Alcoholic beverages should be avoided while the patient is being treated with Oxycodone Controlled Release Tablets.

Dose

Adults, elderly and children over 12 years:
Prior to initiation and titration of doses, refer to the section 4.4 Special warnings and precautions for use for information on special risk groups such as females and the elderly.

Oxycodone Controlled Release Tablets should be taken at 12-hourly intervals. The dosage is dependent on the severity of the pain, and the patient's previous history of analgesic requirements.

Increasing severity of pain will require an increased dosage of Oxycodone Controlled Release Tablets using the 5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg or 80 mg tablet strengths, either alone or in combination, to achieve pain relief. The correct dosage for any individual patient is that which controls the pain and is well tolerated, for a full 12 hours. There is no ceiling dose and patients should be titrated to pain relief unless unmanageable adverse drug reactions prevent this. If higher doses are necessary, increases should be made, where possible, in 25% - 50% increments. The need for escape medication more than twice a day indicates that the dosage of Oxycodone Controlled Release Tablets should be increased.

The usual starting dose for opioid-naïve patients or patients presenting with severe pain uncontrolled by weaker opioids is 10 mg 12-hourly, or 5 mg 12-hourly for patients with renal or hepatic impairment. The dose should then be carefully titrated, as frequently as once a day if necessary, to achieve pain relief.

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.

Patients transferring from other opioid formulations:

Patients receiving other oral oxycodone formulations may be transferred to Oxycodone Controlled Release Tablets at the same total daily dosage, equally divided into two 12- hourly Oxycodone Controlled Release Tablets doses.

Patients receiving oral morphine before Oxycodone Controlled Release Tablets 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 must be emphasised that this is only a guide to the dose of Oxycodone Controlled Release Tablets required. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

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 Oxycodone Controlled Release Tablets 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 Oxycodone Controlled Release Tablets: 18 hours following the removal of the transdermal fentanyl patch, Oxycodone Controlled Release Tablet treatment can be initiated. Although there has been no systematic assessment of such conversion, a conservative oxycodone dose, approximately 10 mg 12-hourly of Oxycodone Controlled Release Tablets, should be initially substituted for each 25 µg/hr fentanyl transdermal patch. The patient should be monitored closely.

Paediatric population

***Children under 12 years*:**

Not recommended.

Method of administration

Oxycodone Controlled Release Tablets consist of a dual-polymer matrix, intended for oral use only. The controlled release tablets must be swallowed whole, and not be broken, chewed or crushed. The administration of broken, chewed or crushed controlled release oxycodone tablets leads to a rapid release and absorption of a potentially fatal dose of oxycodone. Parenteral venous injection of the tablet constituents, especially talc, can be expected to result in local tissue necrosis, pulmonary granulomas and serious adverse reactions which may be fatal.

4.3 Contraindications

- Hypersensitivity to opioids or to any of the ingredients of Oxycodone Controlled Release Tablets listed in section 6.1
- Acute respiratory depression
- *Cor pulmonale*
- Cardiac arrhythmias
- Acute asthma or other obstructive airways disease
- Paralytic ileus
- Suspected surgical abdomen
- Severe hepatic impairment (refer to Special risk groups in section 4.4 Special warnings and precautions for use)
- 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
- Pregnancy
- Not recommended for pre-operative use or for the first 24 hours post-operatively.

4.4 Special warnings and precautions for use

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.

As with all opioid preparations, patients who are to undergo cordotomy or other pain-relieving surgical procedures should not receive Oxycodone Controlled Release 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 Oxycodone Controlled Release 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, Oxycodone Controlled Release 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, Oxycodone Controlled Release Tablets should be discontinued immediately.

Use with CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Oxycodone Controlled Release Tablets with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, medicines with antihistamine-sedating actions such as antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of medicine-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 Section 4.5 Interactions with other medicines and other forms of interaction].

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 Oxycodone Controlled Release Tablets are 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 Section 4.5 Interactions with other medicines and other forms of interaction].

Use in chronic, non-malignant pain

The use of Oxycodone Controlled Release Tablets for the treatment of chronic pain which is not due to malignancy should be restricted to situations where:

- all other conservative methods of analgesia have been tried and have failed
- the pain is having a significant impact on the patient's quality of life
- there is no psychological contraindication, drug-seeking behaviour or history of drug misuse.

Opioids, where clinically indicated, are one component of, and should be integrated into, a comprehensive management approach to chronic, non-malignant pain. Appropriate patient selection is the key to successful treatment of moderate to severe 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 long-term prescribing, a trial of Oxycodone Controlled Release Tablets or shorter-acting opioid should be undertaken. Long-term administration of Oxycodone Controlled Release 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 long-term therapy.

One doctor only should be responsible for the prescribing 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 medicine and for development of strong psychological dependence. Oxycodone Controlled Release Tablets should therefore be prescribed and handled with a high degree of caution appropriate to the use of a medicine 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 medicine 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. However, in such cases, prior psychological assessment is essential and the prescribing doctor should consider whether the benefit of treatment outweighs the risk of abuse.

Formulation

Oxycodone Controlled Release Tablets contain lactose.

Oxycodone Controlled Release Tablets consist of a dual-polymer matrix, intended for oral use only. The controlled release tablets must be swallowed whole, and not be broken, chewed or crushed. The administration of broken, chewed or crushed controlled release oxycodone tablets leads to a rapid release and absorption of a potentially fatal dose of oxycodone. Parenteral venous injection of the tablet constituents, especially talc, can be expected to result in local tissue necrosis, pulmonary granulomas and serious adverse reactions which may be fatal.

Special risk groups

Renal and hepatic impairment

In renal and hepatic impairment, the administration of Oxycodone Controlled Release 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 (CLcr < 60 mL/min) or hepatic impairment should be reduced to ⅓ to ½ of the usual dose with cautious titration.

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.

Elderly, debilitated patients

As with other opioid initiation and titration, doses in elderly patients who are debilitated should be reduced to ⅓ to ½ 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.

Paediatric population

Not recommended for children under 12 years.

4.5 Interaction with other medicines and other forms of interaction

Anticholinergic agents

Concurrent use of 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 sedatives or hypnotics, general anaesthetics, phenothiazines, other tranquillisers, alcohol, other opioids and neuroleptic medicines, etc.).

Concurrent use with oxycodone may result in increased respiratory depression, hypotension, profound sedation or coma. Caution is recommended and the dosage of one or both agents should be reduced. Intake of alcoholic beverages while being treated with Oxycodone Controlled Release 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.

Benzodiazepines and other Central Nervous System (CNS) Depressants	
Clinical Impact	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.
Intervention	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 Section 4.4 Special warnings and precautions for use].
Examples	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, drugs with antihistamine-sedating actions such as antipsychotics, other opioids, alcohol.

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 medicines (e.g. cimetidine, certain cardiovascular drugs and antidepressants), although such blockade has not yet been shown to be of clinical significance with oxycodone tablets.

CYP3A4 inducers, such as rifampicin, 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*. Nonclinical 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 medicines 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 medicine 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.

Paediatric population

Not recommended for children under 12 years.

4.6 Fertility, pregnancy and lactation

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 foetus 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 embryofoetal 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 syndrome. 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.

Breastfeeding

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. Oxycodone Controlled Release 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.

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.

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

a. Summary of the safety profile

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.

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.

b. Tabulated summary of adverse reactions

Key:		
	Very common	*(≥ 1/10)*
	Common	*(≥ 1/100 to < 1/10)*
	Uncommon	*(≥ 1/1,000 to < 1/100)*
	Rare	*(≥ 1/10,000 to < 1/1,000)*
	Very rare	*(< 1/10,000)*
	Not known	*(cannot be estimated from the available data)*

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, lacrimation disorder

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

Rare

gum bleeding, tarry stool, tooth staining and damage

General disorders and administration site conditions

Common

sweating, 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

Rare

weight changes (increase or decrease), cellulitis

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

Metabolic and nutritional disorders

Common

anorexia, decreased appetite

Uncommon

increased appetite, dehydration, hyponatraemia

Nervous system disorders

Very common

dizziness, headache, somnolence

Common

faintness, asthenia, sedation, twitching, tremor

Uncommon

amnesia, drowsiness, abnormal gait, convulsion, dysgeusia (taste perversion), hyperkinesia, hypertonia, hypoaesthesia, hypothermia, raised intracranial pressure, involuntary muscle contractions, paraesthesia, seizures, speech disorder, stupor, syncope, coordination disturbances

Rare

seizures, in particular in epileptic patients or patients with tendency to convulsions, muscle spasm

Not known

hyperalgesia

Psychiatric disorders

Common

abnormal dreams, anxiety, confusional state, insomnia, nervousness, thinking abnormal, depression, lethargy

Uncommon

affect emotional lability, agitation, disorientation, drug dependence, dysphoria, euphoric mood, hallucination, libido decreased, mood altered, restlessness, hyperacousis, depersonalisation

Not known

aggression

Renal and urinary disorders

Common

Micturition disturbances (increased urge to urinate)

Uncommon

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

Reproductive system and breast disorders

Uncommon

amenorrhoea, erectile dysfunction, hypogonadism, impotence

Respiratory, thoracic and mediastinal disorders

Common

bronchospasm, dyspnoea, pharyngitis, voice alteration

Uncommon

respiratory depression

Skin and subcutaneous tissue disorders

Very common

pruritus

Common

hyperhidrosis, rash

Uncommon

dry skin, exfoliative dermatitis, urticaria and other skin rashes

Rare

herpes simplex, urticaria

Vascular disorders

Common

orthostatic hypotension

Uncommon

hypotension accompanied by secondary symptoms such as palpitations & syncope, migraine, vasodilatation

c. Description of selected adverse reactions

No information held by the sponsor.

d. Paediatric population

Not recommended for children under 12 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Symptoms

Acute overdosage with oxycodone can be manifested by respiratory depression (reduced respiratory rate and/or tidal volume, 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 Oxycodone Controlled Release 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 Data Sheet 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 inter-individual 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 may 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.

Paediatric population

No information held by the sponsor. Not recommended for children under 12 years.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids

ATC-Code: N02A A05

Mechanism of action

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).

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 symptoms may be manifest from these hormonal changes.

Paediatric population

Not recommended for children under 12 years.

5.2 Pharmacokinetic properties

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 absorption of oxycodone from Oxycodone Controlled Release Tablets is biphasic, with an initial absorption of approximately 40% of the active medicine ($t_{1/2}$ = 0.6 h) providing onset of analgesia within one hour in most patients, followed by a more controlled absorption, which determines the 12-hour duration of action ($t_{1/2}$ = 6.2 h). The mean apparent half-life of Oxycodone Controlled Release Tablets is 6.5 hours and steady-state is achieved in about one day. The initial absorption occurs from the surface of the tablet, following dissolution of the film coat. The remaining drug substance is absorbed from the matrix either by dissolution or diffusion from or through the tablet matrix.

Release of oxycodone from Oxycodone Controlled Release Tablets is independent of pH under physiological conditions.

The relative bioavailability of oxycodone controlled release tablets is comparable to that of rapid release oxycodone with maximum plasma concentrations being achieved after approximately 3 to 4.5 hours after intake of the controlled-release tablets compared to 1 to 1.5 hours. Peak plasma concentrations and oscillations of the concentrations of oxycodone from the controlled-release and rapid-release formulations are comparable when given at the same daily dose at intervals of 12 and 6 hours, respectively.

Earlier bioequivalence studies indicated that ingestion of a standard high-fat meal does not alter the peak oxycodone concentration or the extent of oxycodone absorption from oxycodone controlled release tablets, however, two later studies on the lowest (5 mg) and highest (160 mg not registered in New Zealand) oxycodone controlled release tablet strengths suggested that a high-fat meal increased the AUC by up to 20% and the Cmax by up to 29%.

The tablets must not be broken, crushed or chewed as this leads to rapid oxycodone release and absorption of a potentially fatal dose of oxycodone due to the damage of the prolonged release properties.

Distribution

In steady state, the volume of distribution of oxycodone amounts to 2.6 L/kg and plasma protein binding to 38 - 45%; the elimination half-life to 4 to 6 hours and plasma clearance to 0.8 L/min.

Biotransformation

Oxycodone hydrochloride 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 **Section 4.5 Interaction with other medicines and other forms of interaction**). The contribution of these metabolites to the analgesic effect is insignificant.

Elimination

Oxycodone has an elimination half-life of approximately three hours and is metabolised principally to noroxycodone and oxymorphone. Oxymorphone has some analgesic activity but is present in plasma in low concentrations and is not considered to contribute to oxycodone's pharmacological effect.

Oxycodone and its metabolites are excreted via urine and faeces. Oxycodone crosses the placenta and is found in breast milk.

The elimination half-life of oxycodone from controlled-release tablets is 4 to 5 hours with steady state values being achieved after a mean of 1 day.

Linearity/non-linearity

Across the 5 - 80 mg dose range of controlled release oxycodone tablets, linearity of plasma concentrations was demonstrated in terms of rate and extent of absorption.

5.3 Preclinical safety data

Carcinogenicity

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

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Oxycodone Controlled Release Tablets contain the following excipients: lactose monohydrate, ammonio methacrylate copolymer Type B, povidone, talc, triacetin, stearyl alcohol, magnesium stearate, hypromellose, macrogol 400, titanium dioxide, brilliant blue FCF (5 mg tablets only), iron oxide black (15 mg and 30 mg tablets only), iron oxide brown (30 mg tablets only), iron oxide red (20 mg, 40 mg and 60 mg tablets only), iron oxide yellow (40 mg and 80 mg tablets only), erythrosine (60 mg tablets only), indigo carmine (80 mg tablets only) and printing ink (5 mg, 10 mg, 20 mg, 40 mg and 80 mg tablets only).

6.2 Incompatibilities

Nil

6.3 Shelf life

5 mg tablets:	2 years
10 mg/15 mg/20 mg/30 mg/40 mg/60 mg/80 mg tablets:	3 years

6.4 Special precautions for storage

Store below 25°C

6.5 Nature and contents of container

Blister packs of 20, 60 and 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Controlled Drug B3

8 SPONSOR

BNM Group
39 Anzac Road
Browns Bay
Auckland 0753

Phone 0800 565 633

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:

03 September 2015

10 DATE OF REVISION OF TEXT

06 July 2017

Summary table of changes

Section changed	Summary of new information
All sections	Text reformatted into new Medsafe data sheet format
4.4 Special warnings and precautions for use	Information included on warnings for use with Central Nervous System (CNS) Depressants
4.5 Interaction with other medicines and other forms of interaction	Information included on interactions between Benzodiazepines and other Central Nervous System (CNS) Depressants
4.8 Undesirable effects	Inclusion of an additional undesirable effect under Psychiatric disorders