

# New Zealand Data sheet

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## 1 PRODUCT NAME

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OXYCODONE SANDOZ® modified release tablets

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## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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Oxycodone Sandoz 5mg tablets – each tablet contains Oxycodone hydrochloride 5mg  
Oxycodone Sandoz 10mg tablets – each tablet contains Oxycodone hydrochloride 10mg  
Oxycodone Sandoz 20mg tablets – each tablet contains Oxycodone hydrochloride 20mg  
Oxycodone Sandoz 40mg tablets – each tablet contains Oxycodone hydrochloride 40mg  
Oxycodone Sandoz 80mg tablets – each tablet contains Oxycodone hydrochloride 80mg

Excipient with known effect: lactose monohydrate

For full list of excipients, see section 6.1

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## 3 PHARMACEUTICAL FORM

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Modified release tablets.

Oxycodone Sandoz 5mg – round, blue, biconvex, modified release tablets

Oxycodone Sandoz 10mg – round, white, biconvex, modified release tablets

Oxycodone Sandoz 20mg – round, pink, biconvex, modified release tablets

Oxycodone Sandoz 40mg – round, yellow, biconvex, modified release tablets

Oxycodone Sandoz 80mg – round, green, biconvex, modified release tablets

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## 4 CLINICAL PARTICULARS

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### 4.1 Therapeutic indications

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

### 4.2 Dose and method of administration

Oxycodone Sandoz tablets 80 mg should only be used in opioid-tolerant patients. In patients not previously exposed to opioids (opioid naïve), these tablet strengths may cause fatal respiratory depression.

Oxycodone Sandoz tablets are to be swallowed whole, and are not to be broken, chewed or crushed. Taking broken, chewed or crushed Oxycodone Sandoz 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 Sandoz tablets.

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### **Adults, elderly and children over 12 years:**

Prior to initiation and titration of doses, refer to section 4.4 for information on *special risk groups* such as females and the elderly. Oxycodone Sandoz 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 Sandoz tablets using the 5 mg, 10 mg, 20 mg, 40 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 Sandoz tablets should be increased.

The usual starting dose for opioid-naive 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.

Patients receiving oral morphine before Oxycodone Sandoz 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 must be emphasised that this is only a guide to the dose of Oxycodone Sandoz tablets required. 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:**

Not recommended.

### **Patients transferring from other opioid formulations:**

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

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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 Sandoz tablets: 18 hours following the removal of the transdermal fentanyl patch, Oxycodone Sandoz 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 Sandoz tablets, should be initially substituted for each 25µg/hr fentanyl transdermal patch. The patient should be followed closely.

### **Duration of treatment**

Oxycodone should not be used for longer than necessary.

If long-term treatment is necessary due to the type and severity of the illness careful and regular monitoring is required to determine whether and to what extent treatment should be continued.

### **Discontinuation of treatment**

When a patient no longer requires therapy with oxycodone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

### **4.3 Contraindications**

Hypersensitivity to opioids or to any of the constituents of Oxycodone Sandoz tablets, acute respiratory depression with hypoxia and/or hypercarbia, cor pulmonale, cardiac arrhythmias, acute asthma or other obstructive airways disease, paralytic ileus, suspected surgical abdomen, severe hepatic impairment (refer to section 4.4), 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, elevated carbon dioxide levels in the blood (hypercarbia), concurrent administration of monoamine oxidase inhibitors or within two weeks of discontinuation of their use. Not

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recommended for pre-operative use or for the first 24 hours post-operatively. Pregnancy (see section 4.6).

### **4.4 Special warnings and precautions for use**

#### **Respiratory depression and sedation**

The major risk of opioid excess is respiratory depression, including subclinical respiratory depression. Profound sedation, respiratory depression, coma, and death may result from the concomitant use of OXYCONTIN 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 OXYCONTIN 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 Section 4.5 Interactions with other medicines and other forms of interaction).

#### **Effects on hypothalamic-pituitary-adrenal or gonadal axes**

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. As with all opioids, a reduction in dosage may be advisable in hypothyroidism.

#### **General**

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, debilitated elderly or infirm patients, or patients taking benzodiazepines, other CNS depressants (including alcohol) or MAO inhibitors.

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### **Pre and post-operative use**

As with all opioid preparations, patients who are to undergo cordotomy or other pain-relieving surgical procedures should not receive OXYCONTIN 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 OXYCONTIN tablets is then indicated the dosage should be adjusted to the new post-operative requirement. As with all opioid preparations, OXYCONTIN 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, OXYCONTIN tablets should be discontinued immediately.

Oxycodone is not recommended for use in children below the age of 12 years due to insufficient data on safety and efficacy.

### **Hyperalgesia**

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.

### **Use in chronic, non-malignant pain**

The use of Oxycodone Sandoz 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.

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Prior to long-term prescribing, a trial of Oxycodone Sandoz tablets or shorter-acting opioid should be undertaken. Long-term administration of Oxycodone Sandoz 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 Sandoz 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. 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 Sandoz 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.

### **Special Risk Groups**

#### *Use in renal and hepatic impairment*

In renal and hepatic impairment, the administration of Oxycodone Sandoz 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 (CL<sub>Cr</sub><60mL/min) or hepatic impairment should be reduced to  $\frac{1}{3}$  to  $\frac{1}{2}$  of the usual dose with cautious titration.

#### *Use in 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.

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## 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.

## Other risk patients

Risk patients, for example patients with low body weight or slow metabolism of medicinal products, should initially receive half the recommended adult dose if they are opioid naïve. Therefore the lowest recommended dose in the SmPC, i.e. 10 mg, may not be suitable as a starting dose. Dose titration should be performed in accordance with the individual clinical situation.

## **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, benzodiazepines, general anaesthetics, phenothiazines, other tranquillisers, alcohol, other opioids non-benzodiazepine sedatives, antidepressants, 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 Sandoz 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.

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).

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Examples	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, drugs with antihistamine-sedating actions such as antipsychotics, other opioids, alcohol.
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### **Coumarin derivatives**

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

A clinically relevant decrease or increase of INR (International Normalised Ratio, Quick's test) has been observed in individual cases in simultaneous use of oxycodone and coumarin anticoagulants.

### **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 Sandoz 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*. 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.



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### **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.

## **4.6 Fertility, pregnancy and lactation**

### **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 foetus or neonate without causing malformations. These effects may be reversible.

Oxycodone passes the placenta.

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.

### **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 breast feeding infants when maternal administration of an opioid analgesic is stopped. Oxycodone Sandoz tablets should not be used in breast feeding mothers unless the benefits outweigh the risks. Breastfed infants

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should be monitored for respiratory depression, sedation, poor attachment and gastrointestinal signs.

### 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 8mg/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. This is particularly likely at the initiation of treatment with oxycodone, after dose increase or product rotation and if oxycodone combined with other CNS depressant agents. Patients stabilised on a specific dose will not necessarily be restricted. Therefore, the physician should decide whether the patient is allowed to drive or use machines.

### 4.8 Undesirable 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.

Tabulated summary of adverse reactions

	Very Common (≥ 1/10)	Common (1/100 to <1/10)	Uncommon (1/1,000 to <1/100)	Not known
<b>Immune system disorders</b>			allergic reaction, anaphylactic reaction, anaphylactoid reaction, hypersensitivity	
<b>Metabolic and nutritional disorders</b>		decreased appetite	increased appetite, dehydration, hyponatraemia	
<b>Psychiatric disorders</b>		abnormal dreams, anxiety, confusional state, insomnia, nervousness, thinking abnormal, depression	affect lability, agitation, disorientation, drug dependence, dysphoria, euphoric mood, hallucination, libido decreased, mood altered, restlessness	
<b>Nervous system disorders</b>	dizziness, headache, somnolence	faintness, sedation, twitching, tremor, lethargy	amnesia, drowsiness, abnormal gait, convulsion, dysgeusia (taste perversion), hyperkinesia, hypertonia, hypoaesthesia, hypothermia, raised intracranial pressure, muscle contractions involuntary, paraesthesia, seizures, speech disorder, stupor, syncope	hyperalgesia
<b>Eye disorders</b>			miosis, visual impairment	
<b>Ear and labyrinth disorders</b>			tinnitus, vertigo	
<b>Cardiac disorders</b>			bradycardia, chest pain, palpitations (as part of withdrawal syndrome), ST depression, supraventricular tachycardia	
<b>Vascular disorders</b>		orthostatic hypotension	hypotension, migraine, vasodilatation	

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	Very Common (≥ 1/10)	Common (1/100 to <1/10)	Uncommon (1/1,000 to <1/100)	Not known
<b>Respiratory, thoracic and mediastinal disorders</b>		bronchospasm, dyspnoea, pharyngitis, voice alteration	respiratory depression	
<b>Gastrointestinal disorders</b>	nausea, vomiting, constipation	abdominal pain, diarrhoea, dry mouth, dyspepsia, gastritis, hiccup	colic, dental caries, dysphagia, eructation, flatulence, gastrointestinal disorder, ileus, stomatitis	
<b>Hepatobiliary disorders</b>			biliary spasm, cholestasis, hepatic enzyme increased	
<b>Skin and subcutaneous tissue disorders</b>	pruritus	hyperhidrosis, rash	dry skin, exfoliative dermatitis, urticaria and other skin rashes	
<b>Renal and urinary disorders</b>			ureteric spasm, urinary abnormalities, urinary retention, urinary tract infection	
<b>Reproductive system and breast disorders</b>			amenorrhoea, erectile dysfunction, hypogonadism	
<b>General disorders and administration site conditions</b>		asthenia, fatigue, chills, fever	accidental injury, drug tolerance, drug withdrawal syndrome (with or without seizures), facial flushing, lymphadenopathy, malaise, muscular rigidity, neck pain, oedema, peripheral oedema, pain, thirst	drug withdrawal syndrome neonatal

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.

### Reporting of suspected adverse reactions

Reporting suspected adverse reaction 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 of intoxication

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 Sandoz tablets.

### Therapy of intoxication

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.

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The opioid antagonist naloxone hydrochloride is a specific antidote for respiratory depression due to overdose or as a result of unusual sensitivity to opioid.

Contact the Poisons Information Centre on (telephone 0800 POISON or 0800 764766) for advice on management of overdose.

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### 5 PHARMACOLOGICAL PROPERTIES

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#### 5.1 Pharmacodynamic properties

*Pharmacotherapeutic group: Natural opium alkaloids ATC code: N02A A05*

Non-proprietary name: Oxycodone hydrochloride

Chemical name: 4,5 $\alpha$ -epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride

CAS NO.: 124-90-3

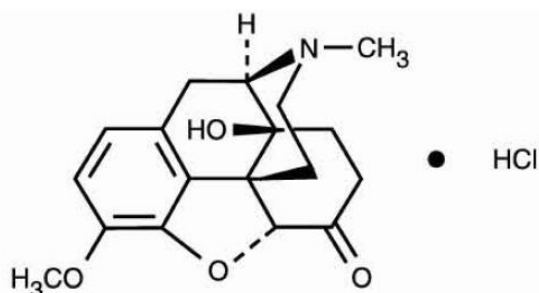
Molecular formula (anhydrous form): C<sub>18</sub>H<sub>21</sub>NO<sub>4</sub>HCl

Molecular weight (anhydrous form): 351.83

Molecular formula (monohydrate form): C<sub>18</sub>H<sub>21</sub>NO<sub>4</sub>HCl.H<sub>2</sub>O

Molecular weight (monohydrate form): 369.84

Structural formula:



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

#### 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).

#### CLINICAL TRIALS

A recent study assessed the effects of a standard high-fat meal on the pharmacokinetics of oxycodone 160 mg (not registered in New Zealand) in 30 healthy males and found that the

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$C_{max}$  was increased by a mean of 25% (range 8 to 52%), and the overall bioavailability ( $AUC_{inf}$ ) by an average of 14%. As the Mean Residence Time (MRT) was unchanged in the presence of food (9.4 hours fasting, 9.3 hours fed), the change in  $C_{max}$  may have been partly due to an increase in the extent of absorption, rather than solely due to an increased rate of absorption. There was no evidence of dose dumping, and the 90% CIs around the AUC ratios were within the range 80 to 125%.

A second recent study compared the effects of a high-fat meal on two 5 mg oxycodone tablets taken by 24 healthy males. The  $C_{max}$  was increased by a mean of 29% and the  $AUC_{inf}$  by an average of 14.5%. Again, there was no evidence of dose dumping.

### 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 Sandoz tablets could be calculated biphasic with an initially relatively rapid half-life of 0.6 hours accounting for a minority of the active substance, and a slower half-life of 6.9 hours accounting for the majority of the active substance.

Oxycodone Sandoz tablets are expected to provide onset of analgesia within one hour in most patients with a 12 hour duration of action. Steady state is achieved in about one day.

Following single dose oral administration of Oxycodone Sandoz tablets to healthy subjects under fasting conditions, mean peak plasma concentrations of oxycodone were achieved within 2-4 hours.

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

Oxycodone Sandoz tablets 5 mg, 10 mg, 20 mg, 40 mg and 80 mg are dose-proportional in terms of both rate and extent of absorption.

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 however, two later studies on the lowest (5 mg) and highest (160 mg not registered in New Zealand) oxycodone strengths suggested that a high-fat meal increased the AUC by up to 20% and the  $C_{max}$  by up to 29%.

#### Metabolism and 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 hydrochloride is metabolised in the liver to form noroxycodone, oxymorphone, noroxymorphone, 6  $\alpha$  and  $\beta$  oxycodol and conjugated glucuronides. CYP3A4 and CYP2D6 are involved in the formation of noroxycodone and oxymorphone, respectively (see section 4.5). The contribution of these metabolites to the analgesic effect is insignificant.

## New Zealand Data sheet

### 5.3 Preclinical safety data

#### Carcinogenicity, Mutagenicity and Impairment of Fertility

##### 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.

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## 6 PHARMACEUTICAL PARTICULARS

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### 6.1 List of excipients

Excipients core:

- behenoyl polyoxylglycerides,
- colloidal anhydrous silica,
- copovidone,
- hydrogenated castor oil,
- lactose monohydrate
- magnesium stearate.
- maize starch,
- medium chain triglycerides,

Excipients coating:

- hypromellose,
- microcrystalline cellulose,
- stearic acid,
- titanium dioxide,
- indigo carmine aluminium lake (5mg tablets only),
- iron oxide red (20mg tablets only),
- iron oxide yellow (40mg tablets only),
- iron oxide black (80mg tablets only) and
- 815063 Spectracol Green Lake (80mg tablets only).

### 6.2 Incompatibilities

None applicable.

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

Store below 25°C

## New Zealand Data sheet

### 6.5 Nature and contents of container

Blister packs or bottles of 20, 28 or 60 tablets.

Not all pack type/sizes of all strengths are available in NZ.

### 6.6 Special precautions for handling, reconstitution and disposal

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

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## 7 MEDICINE SCHEDULE

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Controlled Drug B3.

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## 8 SPONSOR

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Auckland 1149  
Telephone: 0800 354 335

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## 9 DATE OF FIRST APPROVAL

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30 Jun 2016

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## 10 DATE OF REVISION OF THE TEXT

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06/06/2019

### SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
Section 5.2	Expansion of pharmacokinetic data - Absorption
Section 2 and 6.1	Name of excipients updated