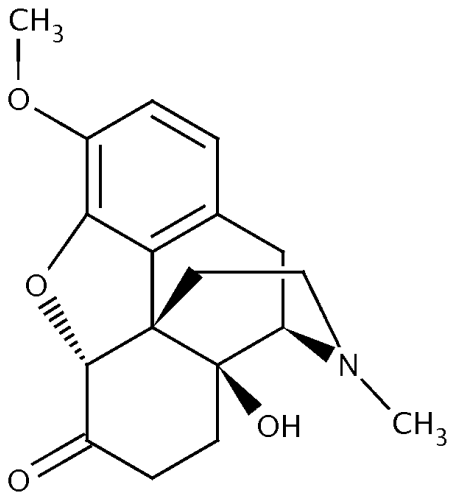
PRODUCT INFORMATION
OXYCODONE SANDOZ® 5mg/ 10mg/ 20mg/ 40mg/ 80mg MODIFIED RELEASE TABLETS

NAME OF THE MEDICINE

Oxycodone hydrochloride

4,5α-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride



, HCl

CAS Number : 124-90-3

Empirical formula: $C_{18}H_{21}NO_4.HCl$ MW: 351.87

DESCRIPTION

Oxycodone hydrochloride is a white or almost white, hygroscopic powder that is freely soluble in water, sparingly soluble in anhydrous ethanol and practically insoluble in toluene.

Oxycodone Sandoz tablets contain 5mg, 10mg, 20mg, 40mg or 80mg oxycodone hydrochloride.

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

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).

PHARMACOLOGY

Pharmacodynamics

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 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 vasodilation, 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 manifest from these hormonal changes.

Pharmacokinetics

Elimination and metabolism. 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, 6alpha and beta 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.

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.

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, 10, 20, 40 and 80mg 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 marketed in Australia) oxycodone strengths suggested that a high fat meal increased the AUC by up to 20% and the C_{max} by up to 29%.

CLINICAL TRIALS

A recent study assessed the effects of a standard high fat meal on the pharmacokinetics of oxycodone 160 mg (not marketed in Australia) in 30 healthy males and found that the 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.

INDICATIONS

Oxycodone Sandoz is indicated for the management of moderate to severe chronic pain unresponsive to non-narcotic analgesia.

CONTRAINDICATIONS

Hypersensitivity to opioids or to any of the constituents of Oxycodone Sandoz tablets, acute respiratory depression, cor pulmonale, cardiac arrhythmias, acute asthma or other obstructive airways disease, paralytic ileus, suspected surgical abdomen, severe renal impairment (creatinine clearance < 10 mL/minute) or severe hepatic impairment (see PRECAUTIONS - 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 preoperative use or for the first 24 hours postoperatively. Pregnancy.

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 raised intracranial pressure, hypotension, hypovolaemia, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, prostatic hypertrophy, adrenocortical insufficiency (Addison's disease), toxic psychosis, chronic respiratory, renal and 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 Sandoz tablets for 24 hours before surgery. Pain in the immediate preoperative period, and any symptoms of opioid withdrawal, should be managed with short acting analgesic agents. If further treatment with Oxycodone Sandoz tablets is then indicated the dosage should be adjusted to the new postoperative 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 Sandoz tablets should be used with caution following abdominal surgery as opioids are known to impair intestinal motility and should not be used until the doctor is assured of normal bowel function. Should paralytic ileus be suspected or occur during use, Oxycodone Sandoz tablets should be discontinued immediately.

Use caution when prescribing Oxycodone Sandoz 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.

Oxycodone Sandoz 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 Oxycodone Sandoz tablets, they should be advised to seek immediate medical attention.

<u>Use in chronic, non-malignant pain</u>

The use of Oxycodone Sandoz 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 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 long-term prescription, a trial of Oxycodone Sandoz or a shorter acting opioid should be undertaken. Long-term administration of Oxycodone Sandoz should only occur if this trial demonstrates that the pain is opioid sensitive. Opioid naive 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 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: 30-34).

<u>Drug dependence</u>

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. Oxycodone Sandoz 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. 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 Sandoz is 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

Gender. Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a bodyweight 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.

Impaired renal function

In renal impairment, the administration of oxycodone 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 function. Therefore, initiation of dosing in patients with renal impairment (creatinine clearance < 60 mL/minute) should be reduced to one-third to one-half of the usual dose with cautious titration.

Impaired hepatic function

In hepatic impairment, the administration of oxycodone 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 hepatic function. Therefore, initiation of dosing in patients with hepatic impairment should be reduced to one-third to one-half of the usual dose with cautious titration.

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 (Category C)

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 prenatal 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.

Australian categorisation definition of 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. Accompanying texts should be consulted for further details.

Use in lactation

Oxycodone accumulates in human milk, with a median maternal plasma: milk ratio of 3:1 recorded in one study. Oxycodone (7.5 ng/mL) was detected in the plasma of one of 41 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 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.

Use in the elderly
The plasma concentrations of oxycodone are only nominally affected by age, being approximately 15% greater in elderly as compared to 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 one-third to one-half of the usual doses.

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.

Effect on ability to drive or operate 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 anticholinergics activity (e.g.tricyclic antidepressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson medications) may result in increased anticholinergic 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.

Central nervous system depressants (including hypnotics, general anaesthetics, phenothiazines, other tranquillizers, alcohol, other opioids and neuroleptic drugs). 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 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.

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

Monoamine oxidase inhibitors (MAOIs). Nonselective 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 nonselective 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.

CYP3A4 and CYP2D6 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 Oxycodone Sandoz.

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.

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.

Ear and labyrinth disorders
Uncommon: tinnitis, vertigo

Eye disorders
Uncommon: miosis, visual impairment

Gastrointestinal disorders
Very Common: nausea, vomiting, constipation
Common: dry mouth, gastritis, hiccup, dyspepsia, abdominal pain, diarrhoea.
Uncommon: colic, dental caries, stomatitis, dysphagia, eructation, flatulence, gastrointestinal disorders, ileus, regurgitation, retching

Nervous system disorders
Very Common: dizziness, headache, somnolence
Common: faintness, sedation, twitching, tremor, lethargy
Uncommon: drowsiness, raised intracranial pressure, hypothermia, abnormal gait, amnesia, hyperkinesia, hypoaesthesia, hypertonia, muscle contractions involuntary, paraesthesia, speech disorder, stupor, seizures, syncope, convulsion, dysgeusia (taste perversion)
Not known: hyperalgesia

Psychiatric disorders
Common: abnormal dreams, anxiety, confusional state, insomnia, nervousness, thinking abnormal, depression
Uncommon: affect lability, agitation, decreased libido, disorientation, drug dependence, dysphoria, euphoric mood, hallucinations, altered mood, restlessness
Unknown: aggression

Renal and urinary disorders
Uncommon: ureteric spasm, urinary retention, urinary abnormalities, urinary tract infections

Reproductive system and breast disorders
Uncommon: amenorrhoea, erectile dysfunction, hypogonadism

Hepatobiliary disorders
Uncommon: biliary spasm, cholestasis, increased hepatic enzymes

Immune system disorders
Uncommon: allergic reaction, anaphylactic reaction, anaphylactoid reaction, hypersensitivity

Cardiac disorders
Uncommon: palpitations (as part of withdrawal syndrome), bradycardia, supraventricular tachycardia, blood pressure and heart rate reductions, ST depression, chest pain

Metabolic and nutritional disorders
Common: decreased appetite
Uncommon: anorexia, increased appetite, dehydration, hyponatraemia

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, vasodilation

General disorders and administration site conditions
Common: asthenic conditions, sweating, fever, chills, fatigue
Uncommon: accidental injury, pain, neck pain, drug tolerance, drug withdrawal syndrome (with or without seizures), facial flushing, malaise, muscular rigidity, lymphadenopathy, oedema, peripheral oedema, thirst.
Not known*:* drug withdrawal syndrome neonatal

Injury, poisoning and procedural complications
Uncommon: medication struck in throat

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 Oxycodone 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

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

Oxycodone Sandoz tablets are to be swallowed whole, and are not to be cut, broken, chewed, crushed or dissolved. Taking cut, broken, chewed, crushed or dissolved Oxycodone Sandoz tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone.

To avoid difficulty swallowing, Oxycodone Sandoz 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 Oxycodone Sandoz tablets, therefore rectal administration of Oxycodone Sandoz tablets is not recommended.

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

Alcoholic beverages should be avoided while the patient is being treated with Oxycodone Sandoz tablets.

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. Oxycodone Sandoz 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. Increasing severity of pain will require an increased dosage of Oxycodone Sandoz tablets using the 10, 20, 40 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 so 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 to 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 a guide to the dose of Oxycodone Sandoz tablets required. Interpatient 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 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 ⅓ to ½, and each patient should be titrated to adequate pain control according to their clinical situation (see **PRECAUTIONS**, Special Risk Groups).

Transfer from other products
(For transfer from oral morphine, also see Adults, elderly and children over 12 years.)
Patients receiving other oral oxycodone formulations may be transferred to Oxycodone Sandoz at the same total daily dosage, equally divided into two 12 hourly Oxycodone Sandoz 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 (see Table 1) 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 doses. Please refer to table 2.

Table 1: Multiplication factors for converting the daily dose of prior opioids to the daily dose of oral oxycodone*

Prior opioid	mg/day prior opioid x factor = mg/day oral oxycodone	
	Prior oral opioid	Prior parenteral opioid
Oxycodone	1	-
Codeine	0.15	-
Fentanyl TTS	**	**
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: 18 hours following the removal of the transdermal fentanyl patch, Oxycodone Sandoz treatment can be initiated. Although there has been no systematic assessment of such conversion, a conservative oxycodone dose, approximately 10mg every 12 hours of Oxycodone Sandoz, should initially be substituted for each 25 microgram/hour fentanyl transdermal patch. The patient should be followed closely.

OVERDOSAGE

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

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, skeletal muscle flaccidity, 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 modified release product such as Oxycodone Sandoz tablets.

Treatment

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 0.4mg 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.

PRESENTATION AND STORAGE CONDITIONS

Oxycodone Sandoz 5mg – round, blue, biconvex, modified release tablets containing 5mg oxycodone hydrochloride.

Oxycodone Sandoz 10mg – round, white, biconvex, modified release tablets containing 10mg oxycodone hydrochloride.

Oxycodone Sandoz 20mg – round, pink, biconvex, modified release tablets containing 20mg oxycodone hydrochloride.

Oxycodone Sandoz 40mg – round, yellow, biconvex, modified release tablets containing 40mg oxycodone hydrochloride.

Oxycodone Sandoz 80mg – round, green, biconvex, modified release tablets containing 80mg oxycodone hydrochloride.

Packaged in blister packs or bottles of 20, 28 or 60 tablets.

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Sandoz Pty Ltd
ABN 60 075 449 553
54 Waterloo Road
Macquarie Park, NSW 2113
Australia
Tel: 1800 634 500

POISON SCHEDULE OF THE MEDICINE

Schedule 8 – Controlled drug

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG): 20/01/2010

Date of most recent amendment: 24/04/2017