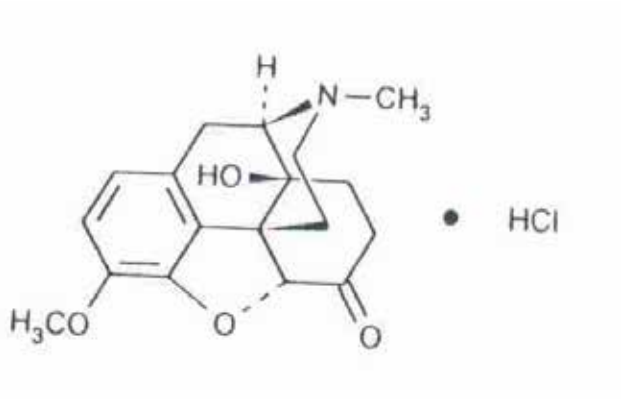
PRODUCT INFORMATION

OxyContin® tablets
(5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 120 mg, 160 mg)

NAME OF THE MEDICINE Oxycodone hydrochloride USP

DESCRIPTION

Oxycodone hydrochloride is a white, crystalline, odourless powder readily soluble in water, sparingly soluble in ethanol and nearly insoluble in ether. The chemical name is 4,5a-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride (CAS No.: 124-90-3). The molecular formula is $C_{18}H_{21}NO_4$. HCl and molecular weight is 351.83. The structural formula for oxycodone hydrochloride is:



The inactive ingredients in OxyContin® tablets are: lactose, povidone, Eudragit RS 30D (solids), glycerol triacetate, stearyl alcohol, talc and magnesium stearate. All of the tablets are coated with hypromellose, titanium dioxide and macrogol 400. The tablet coatings also contain: hydroxypropylcellulose (10 & 80 mg tablets), polysorbate 80 (20 & 40, 60, 120 & 160 mg tablets), iron oxide red CI 77491 (15, 20, 30, 60 & 120 mg tablets), iron oxide yellow CI 77492 (15, 30, 40 & 80 mg tablets), indigo carmine CI 73015 aluminium lake (80 & 160 mg tablets), brilliant blue CI 42090 (5 mg tablets) and iron oxide black E172 (15, 30, 60 & 120 mg tablets).

PHARMACOLOGY

Actions

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

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.

Pharmacokinetics

Absorption

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

The absorption of oxycodone from OxyContin® tablets is biphasic, with an initial absorption of approximately 40% of the active drug (T½ = 0.6 hrs) providing onset of analgesia within one hour in most patients, followed by a more controlled absorption, which determines the 12- hour duration of action (T½ = 6.2 hrs). The mean apparent half-life of OxyContin® 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 OxyContin® tablets is independent of pH under physiological conditions.

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

OxyContin® tablets 5 mg, 10 mg, 20 mg, 40 mg and 80 mg are dose-proportional in terms of both rate and extent of absorption. OxyContin® tablets 15 mg and 30 mg are bioequivalent to OxyContin® tablets 40 mg in terms of AUC_t, AUC_{inf} and C_{max} of oxycodone, and mean half-life values and median T_{max} were all similar.

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 OxyContin® tablets, however, two later studies on the lowest (5 mg) and highest (160 mg not marketed in Australia) OxyContin® tablet 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 α and β oxycodol and conjugated glucuronides. CYP3A4 and CYP2D6 are involved in the formation of noroxycodone and oxymorphone, respectively (see

INTERACTIONS WITH OTHER MEDICINES). The contribution of these metabolites to the analgesic effect is insignificant.

CLINICAL TRIALS

A recent study assessed the effects of a standard high-fat meal on the pharmacokinetics of OxyContin® tablet 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 – 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 – 125%.

A second recent study compared the effects of a high-fat meal on two 5 mg OxyContin® 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

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

CONTRAINDICATIONS

Hypersensitivity to opioids or to any of the constituents of OxyContin® 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/min), severe hepatic impairment (refer to Special Risk Groups), delayed gastric emptying, acute alcoholism, brain tumour, increased cerebrospinal or intracranial pressure, head injury (due to risk of raised intracranial pressure), severe CNS depression, convulsive disorders, *delirium tremens,* hypercarbia, concurrent administration of monoamine oxidase inhibitors or within two weeks of discontinuation of their use. Not recommended for pre-operative use or for the first 24 hours post-operatively. Pregnancy.

PRECAUTIONS

The major risk of opioid excess is respiratory depression, including subclinical respiratory depression. As with all opioids, a reduction in dosage may be advisable in hypothyroidism. Use with caution in opioid-dependent patients and in patients with hypotension, hypovolaemia, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, prostatic hypertrophy, adrenocortical insufficiency (Addison's disease), toxic psychosis, chronic pulmonary, renal or hepatic disease, myxoedema and debilitated elderly or infirm patients. 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.

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, 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.

Use in chronic, non-malignant pain

The use of OxyContin® 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 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 OxyContin® tablets or shorter-acting opioid should be undertaken. Long-term administration of OxyContin® 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 prescription and monitoring of the patient's opioid use. Prescribers should consult appropriate clinical guidelines on the use of opioid analgesics in such patients (e.g. those published by the Australian Pain Society in the Medical Journal of Australia 1997; 167: 30-4).

Drug dependence

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

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

Oxycodone should be used with caution and under close supervision in patients with pain not due to malignancy who have a prior history of substance abuse. 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

OxyContin® tablets consist of a dual-polymer matrix, intended for oral use only. The controlled-release tablets must be swallowed whole, and not 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.

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.

Use in pregnancy

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

Oxycodone used during pregnancy or labour may cause withdrawal symptoms and/or respiratory depression in the newborn infant. Oral administration of oxycodone during the period of organogenesis did not elicit teratogenicity or 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. 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 plasma:milk 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. OxyContin® tablets should not be used in breastfeeding mothers unless the benefits outweigh the risks. Breastfed infants should be monitored for respiratory depression, sedation, poor attachment and gastrointestinal signs.

Special Risk Groups

Use in renal and hepatic impairment

In renal and hepatic impairment, the administration of OxyContin® 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 $^{1}/_{3}$ to ½ of the usual dose with cautious titration.

Use in the elderly

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

Use in elderly, debilitated patients

As with other opioid initiation and titration, doses in elderly patients who are debilitated should be reduced to $^{1}/_{3}$ 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.

Genotoxicity

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

Carcinogenicity

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

Driving and operating dangerous machinery

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

INTERACTIONS WITH OTHER MEDICINES

Anticholinergic agents

Concurrent use with oxycodone may result in 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 drugs, 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 OxyContin® tablets should be avoided because this may lead to more frequent undesirable effects such as somnolence and respiratory depression. Oxycodone hydrochloride containing products should be avoided in patients with a history of or present alcohol, drug or medicines abuse.

Coumarin derivatives

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

CYP2D6 and CYP3A4 inhibitors and inducers

Oxycodone is metabolised in part via the CYP2D6 and CYP3A4 pathways. The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs or dietary elements, which may alter plasma oxycodone concentrations. Oxycodone doses may need to be adjusted accordingly. Drugs that inhibit CYP2D6 activity, such as paroxetine and quinidine, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. Concurrent administration of quinidine does not alter the pharmacodynamic effects of oxycodone. CYP3A4 inhibitors such as macrolide antibiotics (e.g. clarithromycin), azole antifungal agents (e.g. ketoconazole), protease inhibitors (e.g. ritonavir) and grapefruit juice may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. Oxycodone metabolism may be blocked by a variety of drugs (e.g. cimetidine, certain cardiovascular drugs and antidepressants), although such blockade has not yet been shown to be of clinical significance with OxyContin® tablets.

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

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

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

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

Neuromuscular blocking agents
Oxycodone may enhance the effects of neuromuscular blocking agents resulting in increased respiratory depression.
Opioid agonist analgesics (including morphine, pethidine)
Additive CNS depressant, respiratory depressant and hypotensive effects may occur if two or more opioid agonist analgesics are used concurrently.

Opioid agonist-antagonist analgesics (including pentazocine, butorphanol, buprenorphine)
Mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms.

ADVERSE EFFECTS

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

Cardiac disorders

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

Ear and labyrinth disorders

Uncommon	tinnitus, vertigo

Eye disorders

Uncommon	miosis, visual impairment

Gastrointestinal disorders

Very common	nausea, vomiting, constipation
Common	abdominal pain, diarrhoea, dry mouth, dyspepsia, gastritis, hiccup
Uncommon	colic, dental caries, dysphagia, eructation, flatulence, gastrointestinal disorder, ileus, stomatitis

General disorders and administration site conditions

Common asthenic conditions, 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

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 decreased appetite

Uncommon increased appetite, dehydration, hyponatraemia

Nervous system disorders

Very common dizziness, headache, somnolence

Common faintness, sedation, twitching, tremor

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

Not Known hyperalgesia

Psychiatric disorders

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

Uncommon affect lability, agitation, disorientation, drug dependence, dysphoria, euphoric mood, hallucination, libido decreased, mood altered, restlessness

Renal and urinary disorders

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

Reproductive system and breast disorders

Uncommon amenorrhoea, erectile dysfunction

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

Vascular disorders

Common	orthostatic hypotension
Uncommon	hypotension, migraine, vasodilatation

Key: *Very common* (≥ 1/10)

Common	(≥ 1/100 to < 1/10)
Uncommon	(≥ 1/1000 to < 1/100)
Rare	(≥ 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.

DOSAGE AND ADMINISTRATION

OxyContin® tablets 80 mg, 120 mg and 160 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.

OxyContin® tablets are to be swallowed whole, and are not to be broken, chewed or crushed. Taking broken, chewed or crushed OxyContin® 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 OxyContin® 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. OxyContin® 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 OxyContin® tablets using the 5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 120 mg & 160 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 OxyContin® 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.

Patients receiving oral morphine before OxyContin® 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 OxyContin® tablets required only. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

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

Children under 12 years: Not recommended.

Patients transferring from other opioid formulations: Patients receiving other oral oxycodone formulations may be transferred to OxyContin® tablets at the same total daily dosage, equally divided into two 12-hourly OxyContin® 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 OxyContin® tablet doses.

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

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

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

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

** Conversion from transdermal fentanyl to OxyContin® tablets: 18 hours following the removal of the transdermal fentanyl patch, OxyContin® treatment can be initiated. Although there has been no systematic assessment of such conversion, a conservative oxycodone dose, approximately 10 mg 12-hourly of OxyContin® tablets, should be initially substituted for each 25 µg/hr fentanyl transdermal patch. The patient should be followed closely.

OVERDOSAGE

Symptoms: Acute overdosage with oxycodone can be manifested by respiratory depression (reduced respiratory rate and/or tidal volume, 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 OxyContin® tablets.

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

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

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

If there are signs of clinically significant respiratory or cardiovascular depression, the use of an opioid antagonist should be considered. The opioid antagonist naloxone hydrochloride is a specific antidote for respiratory depression due to overdosage or as a result of unusual sensitivity to opioid. The usual intravenous adult dose of naloxone is 0.4 mg or higher (please refer to naloxone product information for further information). The onset of naloxone effect may be delayed by 30 minutes or more. Concomitant efforts at respiratory resuscitation should be carried out. Since the duration of action of oxycodone, particularly sustained release formulations, may exceed that of the antagonist, the patient should be under continued surveillance and doses of the antagonist should be repeated as needed, or an antagonist infusion established, to maintain adequate respiration.

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

antagonist administered. The use of opioid antagonists in such individuals should be avoided if possible. If an opioid antagonist must be used to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care by using dosage titration, commencing with 10 to 20% of the usual recommended initial dose.

Toxicity: Oxycodone toxicity may result from overdosage but because of the great interindividual variation in sensitivity to opioids it is difficult to determine an exact dose of any opioid that is toxic or lethal. Crushing and taking the contents of a modified release dosage form leads to the release of oxycodone in an immediate fashion; this might result in a fatal overdose. The toxic effects and signs of overdosage may be less pronounced than expected, when pain and/or tolerance are manifest.
Please phone the Poisons Information Centre on 131126 for advice on managing overdose.

STORAGE CONDITIONS
Store below 25ºC.

PRESENTATION
OxyContin® tablets 5 mg (pale blue), 10 mg (white), 15 mg (grey), 20 mg (pink), 30 mg (brown), 40 mg (yellow), 60 mg (red)*, 80 mg (green), 120 mg (purple)* and 160 mg (blue)*:

Pack sizes:
5 mg – 20, 28 and 60 tablets in blister packs
10 mg – 20, 28 and 60 tablets in blister packs or bottles*
15 mg – 20, 28 and 60* tablets in blister packs
20 mg – 20, 28 and 60 tablets in blister packs or bottles*
30 mg – 20, 28 and 60* tablets in blister packs
40 mg – 20, 28 and 60 tablets in blister packs or bottles*
60 mg* – 20 and 60 tablets in blister packs
80 mg – 20, 28 and 60 tablets in blister packs or bottles*
120 mg* – 20 and 60 tablets in blister packs
160 mg* – 20 and 60 tablets in blister packs or bottles

* Not available in Australia.

NAME AND ADDRESS OF THE SPONSOR
Mundipharma Pty Limited
ABN 87 081 322 509
50 Bridge Street
SYDNEY, NSW 2000

Further information may be obtained from Mundipharma's Medical Information Department 1800 188 009.

POISON SCHEDULE OF THE MEDICINE: S8

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

OxyContin® tablets 10 mg, 20 mg, 40 mg and 80 mg: 23 July 1999
OxyContin® tablets 160 mg*: 29 May 2002
OxyContin® tablets 5 mg: 20 April 2003
OxyContin® tablets 15 mg and 30 mg: 12 August 2008
OxyContin® tablets 60 mg* and 120 mg*: 20 May 2009

DATE OF MOST RECENT AMENDMENT

30 April 2003 (Safety-related changes)
18 February 2004 (Safety-related changes)
14 July 2004 (Safety-related changes)
29 October 2004 (Safety-related changes)
15 September 2008 (Safety-related changes)
9 March 2009 (Safety-related changes, addition of 15 and 30 mg strengths)
30 November 2009 (Minor editorial changes)
15 February 2010 (Safety-related changes)
25 November 2010 (Minor editorial changes)
17 February 2011 (Minor editorial changes)
03 November 2011 (Safety-related and Minor editorial changes)

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