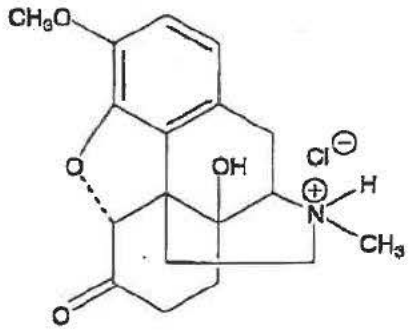
PRODUCT INFORMATION

OxyContin® tablets

COMPOSITION 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 4,5α-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 351.87. The structural formula for oxycodone hydrochloride is:



The inactive ingredients in OxyContin tablets are : lactose, povidone, ammonio methacrylate copolymer type B, 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 mg tablets); iron oxide red CI77491 (20 mg tablets); iron oxide yellow CI77492 (40 & 80 mg tablets) and indigo carmine CI73015 (80 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 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).

Pharmacokinetics

Elimination and Metabolism
Oxycodone has an elimination half-life of approximately 3 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.

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 ($T\frac{1}{2}$ = 0.6 hrs) providing onset of analgesia within 1 hour in most patients, followed by a more controlled absorption, which determines the 12 hour duration of action ($T\frac{1}{2}$ = 6.2 hrs). The mean apparent half-life of OxyContin 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 3 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 10 mg, 20 mg, 40 mg and 80 mg are dose-proportional in terms of both rate and extent of absorption. Ingestion of a standard high-fat meal does not alter the peak oxycodone concentration or the extent of oxycodone absorption from OxyContin tablets.

INDICATIONS

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

CONTRAINDICATIONS

Hypersensitivity to opioids, acute respiratory depression, cor pulmonale, cardiac arrhythmias, acute asthma or other obstructive airways disease, paralytic ileus, suspected surgical abdomen, delayed gastric emptying, acute alcoholism, brain tumour, increased cerebrospinal or intracranial pressure, head injury, severe CNS depression, convulsive disorders, delirium tremens, hypercarbia, concurrent administration of monoamine oxidase inhibitors or within 2 weeks of discontinuation of their use. Not recommended for pre-operative use or for the first 24 hours post-operatively.

PRECAUTIONS

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, chronic renal and hepatic disease, and debilitated 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.

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.

Use in chronic, non-malignant pain

The use of OxyContin 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.

Prior to long term prescription, a trial of OxyContin or shorter acting opioid should be undertaken. Long term administration of OxyContin 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;167:30-4).

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 should therefore be prescribed and handled with a high degree of caution appropriate to the use of a drug with strong abuse potential.

Drug abuse is not, however, a problem in patients with severe pain in which oxycodone is appropriately indicated. On the other hand, 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. 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.

OxyContin consists of a dual-polymer matrix, intended for oral use only. Parenteral venous injection of the tablet constituents, especially talc, can be expected to result in local tissue necrosis and pulmonary granulomas.

Special risk groups

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 <60ml/min) or hepatic impairment should be reduced to $^1/_3$ to ½ of the usual dose with cautious titration.

Elderly

The plasma concentrations of oxycodone are only nominally affected by age, being approximately 15% greater in elderly as compared 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 $^1/_3$ 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.

Driving and operating dangerous machinery

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

Carcinogenicity/Mutagenicity

Oxycodone was not mutagenic in the Ames *Salmonella* and *E.coli* 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.

Use in pregnancy

Category C: Oxycodone, when used during labour, may cause respiratory depression in the new born. Reproduction studies have been performed in rats and rabbits by oral administration at doses up to 8.0 mg/kg (48 mg/m^2) and 125.0 mg/kg (1375 mg/m^2), respectively, which are 0.4 and 11 times the human dose of 160 mg, based on Body Surface Area (BSA), respectively. The studies did not show evidence of harm to foetus. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, this drug should be used during pregnancy only if clearly needed.

Use in lactation

Low concentrations of oxycodone have been detected in breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of an opioid analgesic is stopped.

Interactions

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 and alcohol)
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.

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)
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.

Oxycodone hydrochloride is metabolised in the intestines and liver to form noroxycodone, oxymorphone and other conjugated glucuronides. CYP3A4 and CYP2D6 are probably involved in the formation of noroxycodone and oxymorphone, respectively. The contribution of these metabolites to the analgesic effect is insignificant.

Metabolic interactions with drugs that involve the cytochrome P450 enzyme system (CYP3A4, CYP2D6) can cause the plasma concentration of oxycodone to increase. Quinidine, which is a potent CYP2D6 inhibitor, has blocked the formation of oxymorphone, while the oxycodone concentration increased marginally. Concurrent administration of quinidine does not alter the pharmacodynamic effects of oxycodone. The metabolic pathway 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.

The potential effects of oxycodone on CYP enzyme have not been studied either *in vitro* or *in vivo.*

ADVERSE REACTIONS

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.

Gastrointestinal
Common Constipation, nausea, vomiting, dry mouth, anorexia, gastritis, hiccup, dyspepsia, abdominal pain & diarrhoea
Uncommon Colic, stomatitis, dysphagia, eructation, flatulence, gastrointestinal disorders, increased appetite, ileus & taste perversion

Central Nervous System
Common Headache, confusion, asthenia, faintness, dizziness, sedation, anxiety, abnormal dreams, nervousness, insomnia, thought abnormalities, somnolence & twitching.
Uncommon Vertigo, hallucinations, drowsiness, disorientation, mood changes, restlessness, raised intracranial pressure, hypothermia, abnormal gait, agitation, depression, tinnitus, tremor, withdrawal syndrome (with or without seizures), amnesia, hyperkinesia, hypesthesia, hypotonia, malaise, paresthesia, speech disorder, stupor, euphoria, dysphoria, seizures & vision abnormalities.

Genitourinary
Uncommon Biliary or ureteric spasm, water retention, impotence & urinary abnormalities.

Cardiovascular
Common Orthostatic hypotension
Uncommon Palpitation, bradycardia, supraventricular tachycardia, blood pressure and heart rate reductions, syncope, migraine, vasodilation, ST depression & chest pain

Metabolic and Nutritional
Uncommon Dehydration, oedema, hyponatraemia, peripheral oedema & thirst.

Respiratory
Common Bronchospasm, dyspnoea, cough increased, pharyngitis, voice alteration

Dermatological

Common Rash

Uncommon Dry skin, exfoliative dermatitis, urticaria and other skin rashes

General

Common Sweating, pruritus, fever & chills

Uncommon Accidental injury, pain, neck pain, facial flushing, miosis, muscular rigidity & lymphadenopathy.

Key: ≥ 1 % *Common* , ≤ 1% *Uncommon*

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 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.

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. OxyContin tablets 80 mg should only be used in opioid-tolerant patients.

Increasing severity of pain will require an increased dosage of OxyContin tablets using the 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 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% - 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 naive patients or patients presenting with severe pain uncontrolled by weaker opioids is 10 mg 12 hourly. 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. 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 receiving other oral oxycodone formulation may be transferred to OxyContin at the same total daily dosage, equally divided into two 12-hourly OxyContin 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 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**
Hydrocodone	0.9	--
Hydromorphone	4	20
Levorphano	4.5	15
Meperidine	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: 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 q12h of OxyContin, should be initially substituted for each 25µg/hr fentanyl transdermal patch. The patient should be followed closely.

OVERDOSAGE

Symptoms: Acute overdosage with oxycodone can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, and death.

Treatment of oxycodone overdosage: Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation.

Gastric lavage with a wide-bore tube followed by a suspension of activated charcoal will aid the removal of oxycodone. A saline cathartic or sorbitol added to the first dose of activated charcoal may speed gastrointestinal passage of the product.

Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated.

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 against respiratory depression due to overdosage. 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 to maintain adequate respiration.

In an individual physically dependent on opioids, the administration of the usual dose of opioid antagonist will precipitate an acute withdrawal syndrome. 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.

STORAGE

Store below 25°C.

PRESENTATION

OxyContin Tablets 10 mg (white), 20 mg (pink), 40 mg (yellow), 80 mg (green) : blister packs of 20 or 3 x 20 tablets and polypropylene bottles of 20 or 60 tablets.

POISON SCHEDULE : S8

SPONSOR

Mundipharma Pty Limited
ACN 081 322 509
Level 26, 6 O'Connell Street
SYDNEY NSW 2000

TGA APPROVAL DATE

15 July 1999

DATE OF THIS AMENDMENT

20 December 1999

OxyContin® tablets are a registered trademark.