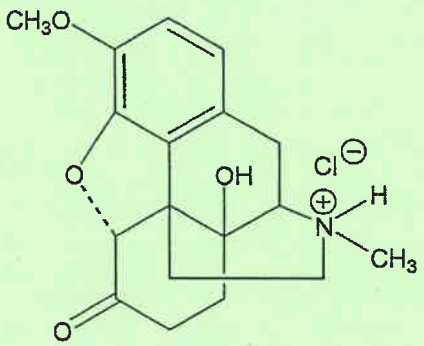
PRODUCT INFORMATION

OxyNorm®
Capsules and liquid

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 351.83. The structural formula for oxycodone hydrochloride is:



OxyNorm is available as capsules and oral solution (see **PRESENTATION**).

The inactive ingredients in OxyNorm capsules are: microcrystalline cellulose and magnesium stearate.

The capsule shells contain sodium lauryl sulfate and gelatin and are printed in black ink which contains industrial methylated spirit, shellac, iron oxide black (E172), soya lecithin, dimethicone and butyl alcohol.

The inactive ingredients in OxyNorm liquid are: saccharin sodium, sodium benzoate, citric acid monohydrate, sodium citrate and hypromellose (OxyNorm liquid only).

The capsule shells contain the following colouring materials:

Colouring Material	5 mg capsule	10 mg capsule	20 mg capsule
Indigo carmine CI73015 (E132)	•	•	•
Iron oxide red CI77491 (E172)	•	•	•
Iron oxide yellow CI77492 (E172)	•	•	•
Sunset yellow FCF CI15985 (E110)	•		
Titanium dioxide (E171)	•	•	•

PHARMACOLOGY

Actions

Oxycodone is a full opioid agonist with no antagonist properties whose principal therapeutic action is analgesia. It has 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

Absorption
Compared with morphine, which has an absolute bioavailability of approximately 30%, oxycodone undergoes relatively low "first pass" metabolism and has a high absolute bioavailability of up to 87% following oral administration. Peak plasma concentrations of oxycodone are reached approximately 1 hour after administration of OxyNorm capsules, and less than 1 hour (approximately 45 minutes) after administration of OxyNorm liquid.

No data are available on the effect of food on the absorption of OxyNorm capsules or liquid. Limited data indicate that the absorption of oxycodone from an oral solution may be significantly affected by food. An increase in mean AUC of approximately 20% and decrease in Cmax of approximately 20% have been reported.

Metabolism and Elimination
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.

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.

INDICATIONS

The management of opioid responsive, moderate to severe pain.

CONTRAINDICATIONS

Hypersensitivity to opioids, 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) 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.

PRECAUTIONS

The major risk of opioid excess is 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, toxic psychosis, chronic pulmonary, renal and hepatic disease, myxedema and debilitated patients. As with all opioid preparations, patients who are to undergo cordotomy or other pain relieving surgical procedures should not receive OxyNorm for 6 hours before surgery. As with all opioid preparations, OxyNorm 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.

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. OxyNorm 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 moderate to 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.

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 that the benefit of treatment outweighs the risk of abuse. OxyNorm capsules and oral liquids are intended for oral use only. Parenteral injection can be expected to result in severe adverse reactions which may be fatal.

Special risk groups

Renal and hepatic impairment
In renal and hepatic impairment, the administration of OxyNorm 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. The data from these assays indicate that the genotoxic risk to humans may be considered low.

Studies of oxycodone in animals to evaluate its carcinogenic potential have not been conducted owing to the length of clinical experience with the drug substance.

Use in pregnancy

Category C: Oxycodone pentrates the placenta, and 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 0.5 and 15 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. OxyNorm should not be used in breastfeeding mothers.

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, 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.

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.

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 OxyNorm.

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

ADVERSE REACTIONS

Immediate release formulations such as OxyNorm may have a higher incidence of some adverse reactions than controlled-release formulations such as OxyContin. 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, hypaesthesia, hypertonia, malaise, paraesthesia, speech disorder, stupor, euphoria, dysphoria, seizures & vision abnormalities.

Genitourinary

Uncommon Biliary or ureteric spasm, urinary retention, impotence, urinary abnormalities, urinary infection, amenorrhea and decreased libido.

Cardiovascular

Common Orthostatic hypotension.

Uncommon Palpitation (as part of withdrawal syndrome), 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, pharyngitis, voice alteration.

Uncommon Respiratory depression

Dermatological

Common	Rash.
Uncommon	Dry skin, exfoliative dermatitis, urticaria, angioedema and other skin rashes.

General

Common	Sweating, pruritus, fever & chills.
Uncommon	Accidental injury, pain, neck pain, facial flushing, miosis, muscular rigidity, lymphadenopathy, allergic reaction, anaphylactic reaction and anaphylactoid reaction.

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

OxyNorm oral dose forms may not be interchangeable with Endone tablets. OxyNorm capsules should be swallowed whole and not opened, chewed or crushed.

Limited data suggest that food may significantly increase the amount of oxycodone absorbed from an oral solution – see Pharmacokinetics, ***Absorption.***

Non-malignant pain:
In common with other strong opioids, the need for continued treatment should be assessed at regular intervals.

Adults, elderly and children over 18 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.

OxyNorm should be taken at 4-6 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 OxyNorm. The correct dosage for any individual patient is that which controls the pain and is well tolerated throughout the dosing period. Patients should be titrated to pain relief unless unmanageable adverse drug reactions prevent this.

OxyNorm will generally be used in a short term trial (4-6 weeks) to determine if the pain is opioid responsive, before transferring to a longer acting oxycodone preparation such as OxyContin tablets, in accordance with the 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). However, OxyNorm liquid may be used longer term in patients unable to take solid oral dosage forms, or when more precise dose titration is necessary.

The usual starting dose for opioid naive patients or patients presenting with severe pain uncontrolled by weaker opioids is 5 mg, 4-6 hourly. The dose should then be carefully titrated, as frequently as once a day if necessary, to achieve pain relief. The majority of patients will not require a daily dose greater than 400 mg. However, a few patients may require higher doses.

Patients receiving oral morphine before oxycodone 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 OxyNorm required. Inter-patient variability requires that each patient be 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.

Adults with mild to moderate renal impairment and mild hepatic impairment. The plasma concentration in this patient population may be increased. Therefore, dose initiation should follow a conservative approach (refer PRECAUTION Section).

Children under 18 years: OxyNorm should not be used in patients under 18 years.

*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	--
Hydromorphone	4	20
Pethidine (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.

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.

A saline cathartic or sorbitol added to the first dose of activated charcoal may speed gastrointestinal passage of the product. Administration of activated charcoal should be restricted to patients with an intact gag reflex or protected airway.

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. 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 30°C.

PRESENTATION

OxyNorm is available in the following presentations for oral use:

Capsules:
OxyNorm capsules 5 mg (orange/beige), 10 mg (white/beige), 20 mg (pink/beige), in blister packs of 20 capsules.

Liquid (solution):
OxyNorm liquid 5 mg/5 mL, is a clear, colourless to straw coloured solution in bottles of 250 mL.

POISON SCHEDULE : S8

SPONSOR

Mundipharma Pty Limited
Level 26, 6 O'Connell Street
SYDNEY, NSW 2000

TGA APPROVAL DATE

13 November 2001

DATE OF MOST RECENT AMENDMENT

17 April 2002
19 February 2004 (Safety-related changes)
14 July 2004 (Safety-related changes)
29 October 2004 (Safety-related changes)
9 May 2005 (Minor pharmaceutical changes)