ATTACHMENT 1

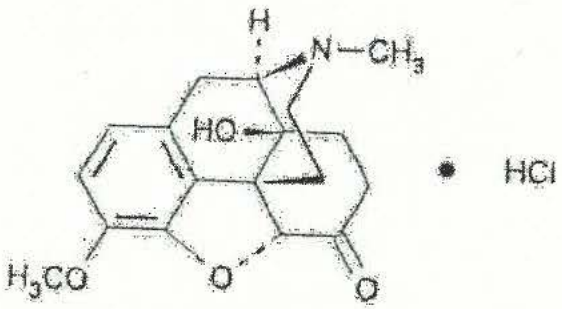
PRODUCT INFORMATION

OxyNorm®
Injection 10mg/1mL and 20mg/2mL

NAME OF THE MEDICINE Oxycodone hydrochloride USP

DESCRIPTION

Oxycodone hydrochloride is a white, crystalline odourless powder freely 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 an injection (see **PRESENTATION**).

The inactive ingredients in OxyNorm injection are: citric acid monohydrate, sodium citrate, sodium chloride, hydrochloric acid, sodium hydroxide and water for injections.

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
The T_{max} for subcutaneous administration was 0.25-0.5 hours. Considerable inter-individual variability was seen in pharmacokinetic studies.

[redacted]

Pharmacokinetic studies with OxyNorm injection in healthy subjects demonstrated an equivalent availability of oxycodone by intravenous and subcutaneous routes, when administered as a single bolus dose or continuous infusion over 8 hours. Following absorption, oxycodone is distributed throughout the entire body. As expected, the C_{max} for subcutaneous bolus was lower than for intravenous administration.

Distribution
Approximately 45% is bound to plasma proteins. The plasma concentrations are only minimally affected by age, being 15% greater in the elderly compared with young subjects. Patients with mild to severe hepatic dysfunction may have higher plasma concentrations of oxycodone and noroxycodone, and lower concentrations of oxymorphone compared with normal subjects.

Metabolism and Elimination
Oxycodone has an elimination half life of approximately 3 hours and 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. Oxymorphone has some analgesic activity but is present in plasma in low concentrations and is not considered to contribute to oxycodone's pharmacological effect.

CYP2D6 is expressed as two phenotypes, extensive and poor metabolisers. Poor metabolisers, constituting about 5-10% of the white population, may have increased plasma concentrations of oxycodone because of the decreased oxidation by CYP2D6 and therefore a lower dosage may be needed. See also **INTERACTIONS**.

Patients with mild to severe hepatic or renal dysfunction may have an increase in the elimination half-life compared with normal subjects, and this may be accompanied by an increase in drug effects. Considerable interindividual variability may be seen in these patients.

Clinical Trials

A randomised, double-blind, parallel group study was performed to compare the tolerability, safety and efficacy of i.v. oxycodone with i.v. morphine in patients using patient controlled analgesia (PCA) for acute postoperative pain. The ITT and safety populations included 133 patients (64 oxycodone, 69 morphine); 117 patients completed, 56 on oxycodone and 61 on morphine. 10mg/mL oxycodone or morphine solution for injection was diluted to 1mg/mL with 0.9% saline, and 2mg i.v. bolus doses were used during stabilisation. The PCA machine delivered bolus doses of 1mg on demand, with a 5 minute lockout. The treatment duration was intended to be 24-72 hours.

The primary efficacy endpoint of the intensity of pain on movement or deep breathing at 24 hours post-operatively, using the BS-11 pain scores, was 4.6±2.6 for oxycodone and 4.1±2.0 for morphine with a pain intensity difference of 0.55 (95% CI: -0.37, 1.48). The 95% CI for treatment difference was within the established equivalence limits (-1.5, 1.5).

	Time point	Treatment difference (95% CI) for pain on movement/deep breathing	Treatment difference (95% CI) for pain at rest
PP population	4 hours	0.05 (-0.82, 0.92)	-0.23 (-0.98, 0.51)
	24 hours	0.55 (-0.37, 1.48)	0.65 (0.02, 1.27)
	Completion or discontinuation	-0.31 (-1.27, 0.64)	0.26 (-0.42, 0.94)
ITT population	24 hours	0.24 (-0.61, 1.09)	0.18 (-0.44, 0.80)

There was no significant difference in the median drug use, which was 69.0mg (12-336 mg) for oxycodone and 54.0mg (7-212 mg) for morphine in the PP population, and similar in the ITT population. The common adverse drug reactions were all known opioid side-effects, but respiratory depression was uncommon. Further details are provided under **ADVERSE REACTIONS**.

INDICATIONS

The management of opioid responsive, moderate to severe pain.

CONTRAINDICATIONS

Hypersensitivity to opioids or any of the constituents of OxyNorm injection, 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. The injection is also contraindicated in moderate to severe hepatic impairment, chronic constipation, acute abdominal pain, coma, anxiety states under the influence of alcohol or hypnotics, and 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, 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 neural blockade 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. Should paralytic ileus be suspected or occur during use, OxyNorm injection should be discontinued immediately.

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 injection 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 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 injection 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 with 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

[redacted]

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 penetrates 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 injection should not be used in breastfeeding mothers.

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.

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, especially in extensive metabolisers (about 90-95% of the white population). 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, fluoxetine and other antidepressants, ketoconazole and erythromycin), although such blockade has not yet been shown to be of clinical significance with OxyNorm.

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.

Injectable formulation:
In a clinical trial where intravenous oxycodone was delivered via patient controlled analgesia, 50 of 64 (78%) patients on oxycodone had at least one adverse drug reaction rated treatment-related or not determined. The very common adverse drug reactions included nausea (50%), vomiting (17%) and pruritus (14%), and the more common reactions included headache (6%), constipation (5%) and insomnia (5%). All of the adverse drug reactions were mild or moderate in intensity, except for one report of vomiting and one of nausea which were rated severe. One treatment-related serious adverse event (abdominal pain caused by postoperative constipation) was noted 17 days after intravenous oxycodone was ceased. In two smaller trials, the very common adverse reactions included headache, dizziness and somnolence.

Drowsiness often abates after a few days, and nausea and vomiting after use for a sustained period. Spasms in the bile duct and urinary tract may arise in predisposed individuals. The respiratory depressive effect is dose-dependent.

Key: ≥ 10% *Very Common*, ≥ 1 % *Common*, < 1% *Uncommon*

Body as a whole

[redacted]

Common Pain, asthenia, injection site hypersensitivity/pain, pallor, hot/warm

Gastrointestinal
Very common Nausea, vomiting
Common Constipation, anorexia, dyspepsia, abdominal pain, dry mouth, flatulence
Uncommon Biliary spasm

Central Nervous System
Very common Headache, dizziness, drowsiness, somnolence, euphoria
Common Insomnia, stupor, hypokinesia, disorientation, vertigo, fatigue
Uncommon Grogginess, dysphoria, respiratory depression

Genitourinary
Common Urinary retention
Uncommon Urinary spasm

Cardiovascular
Common Hypotension, tachycardia, vasodilation
Uncommon Orthostatic hypotension

Endocrine
Common Increased ADH release

Metabolic and Nutritional
Common Generalised oedema

Respiratory
Common Dyspnoea, hiccup, hyperventilation
Uncommon Bronchoconstriction

Dermatological
Very common Pruritus
Common Rash

Special senses
Common Abnormal vision, miosis

DOSAGE AND ADMINISTRATION
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. The lowest dose should be administered with careful titration to pain control. OxyNorm injection should not be used in patients under 18 years. There are no data on the use of OxyNorm injection in children under 18 years of age.

Route of administration:
Intravenous injection or infusion

[redacted]

Subcutaneous injection or infusion

Posology:
The dose should be adjusted according to the severity of pain, the total condition of the patient and previous or concurrent medication.

Adults over 18 years:
The following starting doses are recommended. A gradual increase in dose may be required if analgesia is inadequate or if pain severity increases. The starting dose will vary with age, medical status, surgery, pre-existing opioid tolerance, concomitant medications, individual tolerability, severity of pain and the indication, and may require subsequent dosage adjustment.

i.v. (Bolus): Dilute to 1mg/mL in 0.9% saline, 5% dextrose or water for injections, and administer an intravenous bolus dose of 1 to 5mg slowly over 1-2 minutes. Incremental bolus doses may be required at 5-10 min intervals, with monitoring of the patient. Previous studies have indicated that higher single bolus doses (5-15mg) oxycodone have been associated with significant sedation and respiratory depression. Doses should not be administered more frequently than every 4 hours.

i.v. (Infusion): Dilute to 1mg/mL in 0.9% saline, 5% dextrose or water for injections. A starting dose of 2mg/hour is recommended.

i.v. (PCA): Dilute to 1mg/mL in 0.9% saline, 5% dextrose or water for injections. A starting PCA bolus dose of up to 0.03 mg/kg (e.g. 1-2 mg per 70 Kg) should be administered with a minimum lock-out time of 5 minutes.

s.c. (Bolus): Use as 10mg/mL concentration. A starting dose of 5 to 10 mg is recommended, depending on age and medical status, repeated at 4-hourly intervals as required.

s.c. (Infusion): Dilute in 0.9% saline, 5% dextrose or water for injections if required. For opioid-naïve patients with non-surgical pain, a starting dose in the range 7.5 to 12 mg/day (0.3 – 0.5 mg/hr) is recommended, titrating gradually according to symptom control. For cancer patients transferring from oral oxycodone, or rotating from other opioid infusions, dosage requirements may be much higher (see below).
Note that subcutaneous and intravenous infusions have similar pharmacokinetics.

Transferring patients from oral to parenteral oxycodone:
The dose should be based on the following ratio: 2mg of oral oxycodone is approximately equivalent to 1mg of parenteral oxycodone. The approximate conversion ratio between oral and parenteral oxycodone is 2:1 (oral:parenteral), based on an oral liquid bioavailability of 46% (90% CI 41%-51%). It is emphasised that this is a guide to the required dose only. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

Transferring patients from i.v. morphine to i.v. oxycodone:
The dose should be based on the following ratio: 1mg of i.v. oxycodone is approximately equivalent to 1mg of i.v. morphine. The approximate conversion ratio between i.v. oxycodone and i.v. morphine is 1:1, based on the PCA study described under "Clinical Trials". It is emphasised that this is a guide to the required dose only. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

Elderly:

[redacted]

Elderly patients should be treated with caution. The lowest dose should be administered with careful titration to pain control.

As with other opioid initiation and titration, doses in elderly patients who are debilitated should be reduced ⅓ to ½ of the usual doses.

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 with careful titration to pain control (refer PRECAUTIONS).

As with other opioid initiation and titration, doses in patients with renal impairment (CLcr<60mL/min) or hepatic impairment should be reduced ⅓ to ½ of the usual doses.

Use in non-malignant pain:
Opioids are not first line therapy for chronic non-malignant pain, nor are they recommended as the only treatment. The need for continued treatment in non-malignant pain should be assessed at regular intervals (refer PRECAUTIONS – Drug Dependence).

Cessation of therapy:
When a patient no longer requires therapy with oxycodone, it is advisable to reduce the daily dose gradually to minimise or prevent symptoms of withdrawal.

INCOMPATIBILITIES

Prochlorperazine is chemically incompatible with OxyNorm injection.

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. 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.

For massive overdosage, associated with clinically significant respiratory or cardiovascular depression, 0.8mg naloxone may be administered intravenously, repeating at 2-3 minute intervals as necessary, or by a titrated infusion of 2mg in 500mL of normal saline or 5% dextrose (0.004mg/mL). The infusion should be run at a rate related to previous bolus doses administered and should be in accordance with the patient's response. However, because the duration of action of naloxone is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established. Monitoring for a further 24-48 hours is then recommended in case of possible relapse. Please see naloxone Product Information for further information.

In an individual physically dependent on, or tolerant to, 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.

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. 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.

INSTRUCTIONS FOR STORAGE AND HANDLING

The injection should be given immediately after opening the ampoule. Once opened, any unused portion should be discarded. Inappropriate handling of the undiluted solution after opening of the original ampoule, or of the diluted solutions may compromise the sterility of the product. OxyNorm injection is for one dose in one patient only.

STORAGE

The injection should be stored below 25^0C and protected from light.

PRESENTATION

Clear glass ampoules containing 10mg/1mL and 20mg/2mL oxycodone in packs of 5 ampoules.

POISON SCHEDULE : S8

SPONSOR

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

TGA APPROVAL DATE

8 November 2005

DATE OF MOST RECENT AMENDMENT

1 August 2006 [redacted]

[redacted]