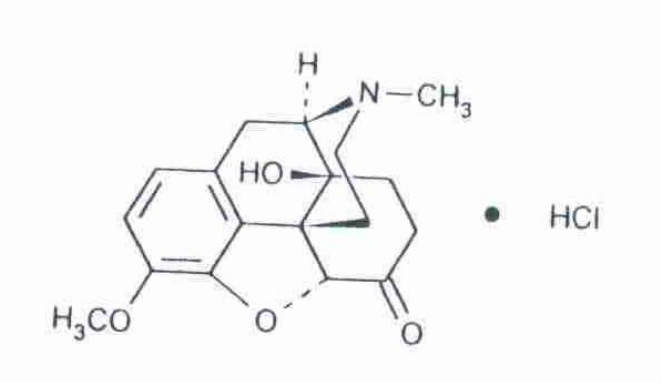
PRODUCT INFORMATION

OXYNORM® solution for injection or infusion
10 mg in 1 mL and 20 mg in 2 mL
OXYNORM® solution for infusion 50 mg in 1 mL
OXYNORM® solution for infusion 200 mg in 20 mL

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:



The inactive ingredients in OXYNORM® solution for injection or infusion 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).

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

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

Pharmacokinetic studies with OXYNORM® solution for injection or infusion 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.

Metabolism and Elimination

Oxycodone has an elimination half-life of approximately 3 hours and is metabolized principally in the liver 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 metabolized 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.

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 with other Medicines.

Patients with mild to severe hepatic or renal dysfunction may have an increase in the elimination half-life compared with normal subjects, and therefore, may have higher plasma concentrations of oxycodone and noroxycodone, and lower concentrations of oxymorphone compared with normal subjects. This may be accompanied by an increase in drug effects. Considerable inter-individual variability may be seen in these patients.

CLINICAL TRIALS

OXYNORM® solution for injection or infusion 10 mg in 1 mL

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. 10 mg/mL oxycodone or morphine solution for injection was diluted to 1 mg/mL with 0.9% saline, and 2 mg i.v. bolus doses were used during stabilisation. The PCA machine delivered bolus doses of 1 mg 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 69.0 mg (12-336 mg) for oxycodone and 54.0 mg (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 EFFECTS**.

INDICATIONS
The management of opioid responsive, moderate to severe pain.

CONTRAINDICATIONS
Hypersensitivity to opioids or any of the constituents of OXYNORM® solution for injection or infusion, 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), moderate to severe hepatic impairment (refer to Special Risk Groups), acute abdominal pain, chronic constipation, delayed gastric emptying, acute alcoholism, coma, 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 2 weeks of discontinuation of their use, 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 hypotension, hypovolaemia, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, prostatic hypertrophy, adrenocortical insufficiency (Addison's disease), toxic psychosis, chronic pulmonary, renal and hepatic disease, myxoedema and debilitated elderly or infirm patients. As with all opioid preparations, patients who are to undergo cordotomy or other pain relieving neural blockade procedures should not receive OXYNORM® solution for injection or infusion for 6 hours before surgery. As with all opioid preparations, OXYNORM® solution for injection or infusion 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® solution for injection or infusion should be discontinued immediately. OXYNORM® solution for injection or infusion should be used with caution pre- or intra-operatively and within the first 12-24 hours post-operatively. OXYNORM® solution for infusion 50mg/mL should not be used for more than 4 weeks consecutively.

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® solution for injection or infusion should therefore be prescribed and handled with a high degree of caution appropriate to the use of a drug with strong abuse potential.

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.

Special risk groups

Renal and hepatic impairment

In renal and hepatic impairment, the administration of OXYNORM® solution for injection or infusion 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.

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 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.

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

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

Effects on Fertility
In reproductive toxicology studies, no evidence of impaired fertility was seen in male or female rats at 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
Category C: Oxycodone used during pregnancy or labour may cause withdrawal symptoms and/or respiratory depression in the newborn infant. Oral administration of oxycodone during the period of organogenesis did not elicit teratogenicity or embryofoetal toxicity in rats or rabbits at doses up to 8 mg/kg/day in rats (equivalent to 17 mg/day in women, based on estimated plasma AUC values) or 125 mg/kg/day in rabbits.

Oral administration of oxycodone to rats from early gestation to weaning did not affect postnatal development parameters at doses up to 6 mg/kg/day (equivalent to 9 mg/day in women, based on estimated AUC values). In a study designed specifically to investigate the effect of 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 breast-feeding infants when maternal administration of an opioid analgesic is stopped. OXYNORM® solution for injection or infusion should not be used in breastfeeding mothers unless the benefits outweigh the risks. Breast-fed infants should be monitored for respiratory depression, sedation, poor attachment and gastrointestinal signs.

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 an 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 OXYNORM® solution for injection or infusion 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.

CYP3A4 and CYP2D6 inhibitors
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, which may alter plasma concentrations. Oxycodone doses may need to be adjusted accordingly. Quinidine, a 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. Ketoconazole, a CYP3A4 inhibitor, inhibited the formation of noroxycodone from oxycodone in human liver enzymes *in vitro.* No clinical oxycodone/ketoconazole drug interaction data are available. Oxycodone metabolism may be blocked by a variety of drugs (e.g. cimetidine, certain cardiovascular drugs, fluoxetine and other antidepressants and erythromycin), although such blockade has not yet been shown to be of clinical significance with OXYNORM® solution for injection or infusion.

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

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*

Cardiac disorders
Common tachycardia
Uncommon palpitations (as part of withdrawal syndrome)

Ear and labyrinth disorders
Common vertigo

Endocrine disorders
Common increased ADH release

Eye disorders
Common miosis, visual impairment

Gastrointestinal disorders

Very common nausea, vomiting

Common abdominal pain, constipation, diarrhoea, dry mouth, dyspepsia, flatulence, hiccup

Uncommon dental caries, dysphagia, eructation, gastrointestinal disorder, ileus

General disorders and administration site conditions

Common asthenic conditions, chills, fatigue, hot/warm, injection site hypersensitivity/pain, generalized oedema, pain, pallor

Uncommon drug tolerance, drug withdrawal syndrome, malaise, peripheral oedema, thirst

Hepatobiliary disorders

Uncommon biliary spasm, cholestasis, increased hepatic enzymes

Immune system disorders

Uncommon anaphylactic reaction, anaphylactoid reaction

Metabolic and nutritional disorders

Common anorexia

Uncommon dehydration

Nervous system disorders

Very common dizziness, drowsiness, headache, somnolence

Common hypokinesia, stupor

Uncommon amnesia, convulsion, grogginess, hypertonia, hypoaesthesia, muscle contractions involuntary, paraesthesia, speech disorder, syncope, taste perversion, tremor

Psychiatric disorders

Very common euphoria

Common anxiety, confusional state, disorientation, insomnia, nervousness, thinking abnormal

Uncommon affect lability, agitation, depression, drug dependence, dysphoria, hallucinations, libido decreased

Renal and urinary disorders

Common urinary retention

Uncommon urinary spasm

Reproductive system and breast disorders

Uncommon amenorrhoea, erectile dysfunction

Respiratory, thoracic and mediastinal disorders

Common dyspnoea, hyperventilation

Uncommon bronchoconstriction, respiratory depression

Skin and subcutaneous tissue disorders

Very common pruritus

Common hyperhidrosis, rash

Uncommon dry skin, urticaria

Vascular disorders
Common hypotension, vasodilation
Uncommon orthostatic hypotension

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® solution for injection or infusion should not be used in patients under 18 years as there are no data on use in children under 18 years of age.

Routes of administration
OXYNORM® solution for injection or infusion 10 mg in 1 mL and 20 mg in 2 mL:
Intravenous injection or infusion, and subcutaneous injection or infusion.

OXYNORM® solution for infusion 50 mg in 1 mL and 200 mg in 20 mL:
Intravenous infusion and subcutaneous infusion, suitable for use in a palliative care setting.

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
OXYNORM® solution for injection or infusion 10 mg in 1 mL and 20 mg in 2 mL:
The following starting doses are recommended for the 10 mg in 1 mL and 20 mg in 2 mL solution for injections, although 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. A gradual increase in dose may be required if analgesia is inadequate or if pain severity increases.

i.v. (Injection): Dilute to 1 mg/mL in 0.9% saline, 5% dextrose or water for injections.
To establish analgesia, administer an intravenous bolus dose of 1 to 5 mg 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 (5-15 mg) oxycodone have been associated with significant sedation and respiratory depression.
For maintenance analgesia, doses should not be administered more frequently than every 4 hours.

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

i.v. (PCA): Dilute to 1 mg/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. (Injection): Use as 10 mg/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 non-surgical pain in palliative care in opioid-tolerant patients, titrate gradually according to pain control.

OXYNORM® solution for infusion 50 mg in 1 mL:
The use of OXYNORM solution for infusion 50 mg in 1 mL is indicated for opioid-tolerant patients in a palliative care setting. The following starting doses are recommended, although 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. A gradual increase in dose may be required if analgesia is inadequate or if pain severity increases. OXYNORM® 50 mg in 1 mL solution for infusion should not be used for more than 4 consecutive weeks.

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

i.v. (PCA): Dilute to 1 mg/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. (Infusion): Dilute in 0.9% saline, 5% dextrose or water for injections. Continuous subcutaneous infusion of a strong opioid is typically commenced via a syringe driver apparatus.

OXYNORM® solution for infusion 200 mg in 20 mL:
The use of OXYNORM solution for infusion 200 mg in 20 mL is indicated for opioid-tolerant patients in a palliative care setting.

The dosage should be individualised for each patient, based on the patient's current opioid dosage and analgesic requirements. Recommended diluents are 0.9% saline, 5% dextrose or water for injections, with dilution to 1 mg/mL as a general starting dose for adults over 18 years. Gradual increases in dose may be required if analgesia is inadequate or if pain severity increases.

Transferring patients from oral to parenteral oxycodone
The dose should be based on the following ratio: 2 mg of oral oxycodone is approximately equivalent to 1 mg 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. For cancer patients transferring from oral oxycodone, or rotating from other opioid infusions, dosage requirements may be higher.

Transferring patients from i.v. morphine to i.v. oxycodone
The dose should be based on the following ratio: 1 mg of i.v. oxycodone is approximately equivalent to 1 mg 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. For cancer patients transferring from oral oxycodone, or rotating from other opioid injections or infusions, the dosage requirements may be higher.

Elderly
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 to 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<60 mL/min) or hepatic impairment should be reduced to 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® solution for injection or infusion.

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, skeletal muscle flaccidity, constricted pupils (dilated if hypoxia is severe), cold and/or clammy skin, and sometimes bradycardia, hypotension, and death. Severe overdose may result in apnoea, pulmonary oedema, circulatory collapse and death.

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.

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, 0.8 mg naloxone may be administered intravenously, repeating at 2-3 minute intervals as necessary, or by a titrated infusion of 2 mg in 500 mL of normal saline or 5% dextrose (0.004 mg/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 hydrochloride injection 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 inter-individual 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 solution for injection or infusion should be given immediately after opening the ampoule. The diluted solution should be used immediately after dilution. 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® solution for injection or infusion is for single use in one patient only.

STORAGE CONDITIONS

OXYNORM® solution for injection or infusion should be stored below 25°C and protected from light.

PRESENTATION
Clear glass ampoules containing the following strengths of oxycodone hydrochloride:

- 10 mg in 1 mL and 20 mg in 2 mL in packs of 5 ampoules
- 50 mg in 1 mL in packs of 5 ampoules
- 200 mg in 20 mL in packs of 4 ampoules.

POISON SCHEDULE S8

SPONSOR
Mundipharma Pty Limited
ABN 87 081 322 509
50 Bridge Street
SYDNEY, NSW 2000

TGA APPROVAL DATE
8 November 2005 (10 mg in 1 mL; 20 mg in 2 mL solutions for injection or infusion)
7 April 2010 (50 mg in 1 mL solution for infusion)
7 April 2010 (200 mg in 20 mL solution for infusion)

DATE OF MOST RECENT AMENDMENT
7 August 2006 (Safety-related changes)
15 September 2008 (Safety-related changes)
30 November 2009 (Safety-related changes)
15 February 2010 (Safety-related and minor changes)
6 May 2010 (Safety-related and minor changes)
9 July 2010 (Minor editorial changes)

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