OXYNORM® (solution for injection or infusion)

Oxycodone hydrochloride

1 PRODUCT NAME

OXYNORM® 10mg/mL solution for injection or infusion
OXYNORM® 50mg/mL solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Oxycodone hydrochloride 10 mg/ml (equivalent to 9 mg/ml oxycodone)
Oxycodone hydrochloride 50 mg/ml (equivalent to 45 mg/ml oxycodone)

For the full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM

Solution for injection or infusion
10 mg/ml: Clear, colourless solution, practically free from particulates
50 mg/ml: Clear, colourless to pale yellow solution, practically free from particulates

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The management of opioid-responsive moderate to severe pain.

OXYNORM is indicated in adults over 18 years.

4.2 Dose and method of administration

Adults, elderly and children over 18 years

Prior to initiation and titration of doses, refer to Section 4.4 for information on special risk groups such as females and the elderly. The lowest dose should be administered with careful titration to pain control.

Dose

The dose should be adjusted to the intensity of the pain and the sensitivity of the individual patient. The patient's previous history of analgesic requirements, their body weight, and sex (higher plasma concentrations are produced in females), should also be taken into account when determining the dose.

Generally, the lowest effective dose for analgesia should be selected. If higher doses are necessary, increases should be made in 25% - 50% increments where possible.

The correct dosage per individual patient is that which controls the pain with no or tolerable side effects.

Adults over 18 years:

The following 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.

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

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

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

SC (Bolus): Where necessary, dilute to 10mg/mL concentration using 0.9% saline, 5% dextrose or water for injections. A starting dose of 5mg is recommended, depending on age and medical status, repeated at 4-hourly intervals as required.

SC (Infusion): Dilute in 0.9% saline, 5% dextrose or water for injections if required. A starting dose of 7.5 mg/day is recommended in opioid naïve patients, titrating gradually according to symptom control. Cancer patients transferring from oral oxycodone may require higher doses.

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: 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). 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 IV morphine to IV oxycodone

The dose should be based on the following ratio: 1 mg of IV oxycodone is approximately equivalent to 1 mg of IV morphine. The approximate conversion ratio between IV 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.

Conversion from morphine:

It must be emphasised that this is a guide to the dose of oxycodone required. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose. Initially, a lower-than-equivalent dose may be advisable. Patients switching from parenteral morphine to parenteral oxycodone therapy should do so on the basis of a 1:1 dose ratio.

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 to Section 4.4 – Use in renal and hepatic impairment).

The recommended adult starting dose should be reduced by 50% and each patient should be titrated to adequate pain control according to their clinical situation.

Paediatric population

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

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 to Section 4.4 – Non-malignant pain).

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.

Route of Administration

Intravenous injection or infusion.
Subcutaneous injection or infusion.

4.3 Contraindications

Hypersensitivity to opioids or any of the constituents of OXYNORM solution for injection or infusion listed in section 6.1, 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, chronic constipation, acute abdominal pain, 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 two weeks of discontinuation of their use, anxiety states under the influence of alcohol or hypnotics, and pregnancy.

4.4 Special warnings and precautions for use

Oxycodone has to be administered with caution in the debilitated elderly or patients with:

- Severely impaired respiratory function
- Sleep apnoea
- CNS depressants co-administration (see below and section 4.5)
- Tolerance, physical dependence and withdrawal (see below)
- Psychological dependence (addiction), abuse profile and history of substance and/or alcohol abuse (see below)
- Intracranial lesions, reduced level of consciousness of uncertain origin
- Hypotension
- Pancreatitis
- Myxedema
- Hypothyroidism
- Addison's disease
- Prostate hypertrophy
- Alcoholism
- Toxic psychosis
- Constipation
- Hypovolaemia
- Inflammatory bowel disorders
- Chronic pulmonary

Hazardous and harmful use

OXYNORM contains the opioid oxycodone hydrochloride and is a potential drug of abuse, misuse and addiction. Addiction can occur in patients appropriately prescribed OXYNORM at recommended doses.

The risk of addiction is increased in patients with a personal or family history of substance abuse (including alcohol and prescription and illicit drugs) or mental illness. The risk also increases the longer the drug is used and with higher doses. Patients should be assessed for their risks for opioid abuse or addiction prior to being prescribed OXYNORM.

All patients receiving opioids should be routinely monitored for signs of misuse and abuse. Opioids are sought by people with addiction and may be subject to diversion. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the safe storage and proper disposal of any unused drug (see section 6.4 and section 6.6). Caution patients that abuse of oral or transdermal forms of opioids by parenteral administration can result in serious adverse events, which may be fatal.

Patients should be advised not to share OXYNORM with anyone else.

Respiratory depression and sedation

Serious, life-threatening or fatal respiratory depression can occur with the use of opioids even when used as recommended. It can occur at any time during the use of OXYNORM but the risk is greatest during initiation of therapy or following an increase in dose. Patients should be monitored closely for respiratory depression at these times.

The risk of life-threatening respiratory depression is also higher in elderly, frail, or debilitated patients and in patients with existing impairment of respiratory function (e.g. chronic obstructive pulmonary disease; asthma). Opioids should be used with caution and with close monitoring in these patients (see section 4.2). The use of opioids is contraindicated in patients with severe respiratory disease, acute respiratory disease and respiratory depression (see section 4.3).

The risk of respiratory depression is greater with the use of high doses of opioids, especially high potency and modified release formulations, and in opioid naïve patients. Initiation of opioid treatment should be at the lower end of the dosage recommendations with careful titration of doses to achieve effective pain relief. Careful calculation of equi-analgesic doses is required when changing opioids or switching from immediate release to modified release formulations, (see section 4.2).

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. Opioids may also cause worsening of pre-existing sleep apnoea (see section 4.8). In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper.

Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol

Concomitant use of OXYNORM and benzodiazepines or other CNS depressants, including alcohol may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of OXYNORM with CNS depressant medicines, such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics and other CNS depressants should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe OXYNORM concomitantly with any of the medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. Patients and their caregivers should be made aware of these symptoms. Patients and their caregivers should also be informed of the potential harms of consuming alcohol while taking OXYNORM.

Advise both patients and caregivers about the risks of respiratory depression and sedation when OXYNORM is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see Section 4.5).

Use of opioids in chronic (long-term) non-cancer pain (CNCP)

Opioid analgesics have an established role in the treatment of acute pain, cancer pain and palliative and end-of-life care. Current evidence does not generally support opioid analgesics in improving pain and function for most patients with chronic non-cancer pain. The development of tolerance and physical dependence and risks of adverse effects, including hazardous and harmful use, increase with the length of time a patient takes an opioid. The use of opioids for long-term treatment of CNCP is not recommended.

The use of an opioid to treat CNCP should only be considered after maximised non-pharmacological and non-opioid treatments have been tried and found ineffective, not tolerated or otherwise inadequate to provide sufficient management of pain. Opioids should only be prescribed as a component of comprehensive multidisciplinary and multimodal pain management.

Opioid therapy for CNCP should be initiated as a trial in accordance with clinical guidelines and after a comprehensive biopsychosocial assessment has established a cause for the pain and the appropriateness of opioid therapy for the patient (see Hazardous and harmful use, above). The expected outcome of therapy (pain reduction rather than complete abolition of pain, improved function and quality of life) should be discussed with the patient before commencing opioid treatment, with agreement to discontinue treatment if these objectives are not met.

Owing to the varied response to opioids between individuals, it is recommended that all patients be started at the lowest appropriate dose and titrated to achieve an adequate level of analgesia and functional improvement with minimum adverse reactions. Immediate-release products should not be used to treat chronic pain, but may be used for a short period in opioid-naïve patients to develop a level of tolerance before switching to a modified-release formulation. Careful and regular assessment and monitoring is required to establish the clinical need for ongoing treatment. Discontinue opioid therapy if there is no improvement of pain and/or function during the trial period or if there is any evidence of misuse or abuse. Treatment should only continue if the trial has demonstrated that the pain is opioid responsive and there has been functional improvement. The patient's condition should be reviewed regularly and the dose tapered off slowly if opioid treatment is no longer appropriate (see Ceasing Opioids).

Tolerance, physical dependence and withdrawal

Neuroadaptation of the opioid receptors to repeated administration of opioids can produce tolerance and physical dependence. Tolerance is the need for increasing doses to maintain analgesia. Tolerance may occur to both the desired and undesired effects of the opioid.

Physical dependence, which can occur after several days to weeks of continued opioid usage, results in withdrawal symptoms if the opioid is ceased abruptly or the dose is significantly reduced.

Withdrawal symptoms can also occur following the administration of an opioid antagonist (e.g. naloxone) or partial agonist (e.g. buprenorphine). Withdrawal can result in some or all of the following symptoms: dysphoria, restlessness/agitation, lacrimation, rhinorrhoea, yawning, sweating, chills, myalgia, mydriasis, irritability, anxiety, increasing pain, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, increased blood pressure, increased respiratory rate and increased heart rate.

When discontinuing OXYNORM in a person who may be physically-dependent, the drug should not be ceased abruptly but withdrawn by tapering the dose gradually (see Ceasing opioids and section 4.2).

Accidental ingestion/exposure

Accidental ingestion or exposure of OXYNORM especially by children, can result in a fatal overdose of oxycodone. Patients and their caregivers should be given information on safe storage and disposal of unused OXYNORM (see section 6.4 and section 6.6).

Hyperalgesia

Hyperalgesia may occur with the use of opioids, particularly at high doses. Hyperalgesia may manifest as an unexplained increase in pain, increased levels of pain with increasing opioid dosages or diffuse sensitivity not associated with the original pain. Hyperalgesia should not be confused with tolerance (see Tolerance, dependence and withdrawal). If opioid induced hyperalgesia is suspected, the dose should be reduced and tapered off if possible. A change to a different opioid may be required.

Ceasing opioids

Abrupt discontinuation or rapid decreasing of the dose in a person physically dependent on an opioid may result in serious withdrawal symptoms and uncontrolled pain (see Tolerance, dependence and withdrawal). Such symptoms may lead the patient to seek other sources of licit or illicit opioids. Opioids should not be ceased abruptly in a patient who is physically dependent but withdrawn by tapering the dose slowly. Factors to take into account when deciding how to discontinue or decrease therapy include the dose and duration of the opioid the patient has been taking, the type of pain being treated and the physical and psychological attributes of the patient. A multimodal approach to pain management should be in place before initiating an opioid analgesic taper. During tapering, patients require regular review and support to manage any increase in pain, psychological distress and withdrawal symptoms.

There are no standard tapering schedules suitable for all patients and an individualised plan is necessary. In general, tapering should involve a dose reduction of no more than 10 percent to 25 percent every 2 to 4 weeks (see section 4.2). If the patient is experiencing increased pain or serious withdrawal symptoms, it may be necessary to go back to the previous dose until stable before proceeding with a more gradual taper.

When ceasing opioids in a patient who has a suspected opioid use disorder, the need for medication assisted treatment and/or referral to a specialist should be considered.

Pre- and post-operative use

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.

Effects on hypothalamic-pituitary-adrenal or gonadal axes

Opioids, such as oxycodone hydrochloride, 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 manifest from these hormonal changes. As with all opioids, a reduction in dosage may be advisable in hypothyroidism.

Special Risk Groups

Use in 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. The recommended adult starting dose should be reduced by 50%.

Use in the elderly

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

Use in elderly, debilitated patients

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

4.5 Interaction with other medicines and other forms of interaction

Anticholinergic agents

Concomitant administration of oxycodone with anticholinergics or medications with anticholinergic activity (e.g. tricyclic antidepressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects.

Antihypertensive agents

Hypotensive effects of these medications may be potentiated when used concurrently with oxycodone, leading to increased risk of orthostatic hypotension.

The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect.

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. The dose and duration of concomitant use should be limited. Follow patients closely for signs of respiratory depression and sedation (see Section 4.4 Warnings and Precautions).

Drugs which depress the CNS include, but are not limited to: other opioids, gabapentinoids such as pregabalin, anxiolytics, hypnotics and sedatives (incl. benzodiazepines), tranquilizers, muscle relaxants, general anaesthetics, drugs with antihistamine-sedating actions such as antipsychotics, antidepressants, phenothiazines and alcohol.

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.

CYP2D6 and CYP3A4 Inhibitors and Inducers

Oxycodone is metabolized mainly by CYP3A4 with a contribution from CYP2D6. The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs or dietary elements. Oxycodone doses may need to be adjusted accordingly.

CYP3A4 inhibitors, such as macrolide antibiotics (e.g., clarithromycin), azole-antifungal agents (e.g., ketoconazole), protease inhibitors (e.g., ritonavir), and grapefruit juice may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. Oxycodone metabolism may be blocked by a variety of drugs (e.g. cimetidine, certain cardiovascular drugs, 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.

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

Drugs that inhibit CYP2D6 activity, such as paroxetine and quinidine, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. Concurrent administration of quinidine does not alter the pharmacodynamic effects of oxycodone.

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

Serotonin Agents

Concomitant administration of oxycodone with serotonin agents, such as a Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) may cause serotonin toxicity. The symptoms of serotonin toxicity may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Oxycodone should be used with caution and the dosage may need to be reduced in patients using these medications.

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 medicines 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 medicine 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.

4.6 Fertility, pregnancy and lactation

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

Oxycodone used during pregnancy and 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. Prolonged use of oxycodone during pregnancy can result in neonatal opioid withdrawal syndrome. 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.

The drug penetrates the placenta. Therefore, use of this medicinal product should be avoided to the extent possible in patients who are pregnant.

Breast-feeding

Use of this medicinal product should be avoided to the extent possible in patients who are lactating. Oxycodone accumulates in human milk, with a median maternal milk: plasma ratio of 3:1 recorded in one study. Oxycodone (7.5 ng/mL) was detected in the plasma of one of forty-one infants 72 hours after caesarean section. Opioids may cause respiratory depression in the newborn and withdrawal symptoms can occur in breastfeeding infants when maternal administration of an opioid analgesic is stopped. OXYNORM solution for injection or infusion should not be used in breastfeeding mothers unless the benefits outweigh the risks. Breastfed infants should be monitored for respiratory depression, sedation, poor attachment and gastrointestinal signs.

Fertility

No human data on the effect of oxycodone on fertility are available. In rats, there was no effect on mating or fertility with oxycodone treatment (see section 5.3).

Despite these fertility studies in animals, prolonged use of opioids may result in impairment of reproductive function, including fertility and sexual dysfunction in both sexes, and irregular menses in women.

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

Summary of the safety profile

Anticipation of adverse drug reactions and appropriate patient management can improve acceptability.

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.

Tabulated list of adverse reactions:

	Very common (1/10)	***Common*** (1/100 to <1/10)	***Uncommon*** uncommon (1/1000 to <1/100)	***Rare***	***Not known***
Immune system disorders			Hypersensitivity		Anaphylactic reaction, Anaphylactoid reaction
Metabolism and nutrition disorders		Decreased appetite	Dehydration		
Psychiatric disorders		Anxiety, Confusional state, Disorientation, Insomnia, Nervousness, Thinking abnormal, Depression	Affect lability, Agitation, Drug dependence, Dysphoria, Euphoric mood, Hallucinations, Libido decreased		Aggression
Nervous system disorders	Dizziness, Headache, Somnolence	Tremor, Lethargy	Amnesia, Convulsion, Hypertonia, Hypoaesthesia, Muscle contractions involuntary, Paraesthesia, Speech disorder, Syncope, Dysgeusia (taste perversion)		Hyperalgesia, Sleep apnoea syndrome
Eye disorders			Miosis, Visual impairment		
Ear and labyrinth disorders			Vertigo		
Cardiac disorders			Palpitations (as part of withdrawal syndrome)		
Vascular disorders			Vasodilatation	Orthostatic hypotension, Hypotension	
Respiratory, thoracic and mediastinal disorders		Dyspnoea,	Respiratory depression		
Gastrointestinal disorders	Nausea, Vomiting, Constipation	Abdominal pain, Diarrhoea, Dry mouth, Dyspepsia	Dysphagia, Eructation, Ileus, Flatulence		Dental caries

	Very common (1/10)	***Common*** (1/100 to <1/10)	***Uncommon*** uncommon (1/1000 to <1/100)	***Rare***	***Not known***
Hepatobiliary disorders			Hepatic enzymes increased		Cholestasis
Skin and subcutaneous tissue disorders	Pruritus	Hyperhidrosis, Rash	Dry skin,	Urticaria	
Renal and urinary disorders			Urinary retention		
Reproductive system and breast disorders			Erectile dysfunction, Hypogonadism		Amenorrhoea
General disorders and administration site conditions		Asthenia, Fatigue,	Drug tolerance, Drug withdrawal syndrome, Malaise, Peripheral oedema, Thirst, Chills, Oedema.		Drug withdrawal syndrome neonatal

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Acute overdosage with oxycodone can be manifested by respiratory depression (reduced respiratory rate and/or tidal volume, cyanosis), extreme somnolence progressing to stupor or coma, hypotonia, miosis (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.

Primary attention should be given to immediate supportive therapy with the establishment of adequate respiratory exchange through the provision of a patent airway and institution of assisted or controlled ventilation. Adequate body temperature and fluid balance should be maintained. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated, to manage the circulatory shock accompanying an overdose. The opioid antagonist naloxone hydrochloride is a specific antidote against respiratory depression due to overdosage.

Please phone the National Poisons Centre on 0800 POISON or 0800 764 766 for advice on managing overdose.

5 PHARMACOLOGICAL PROPERTIES

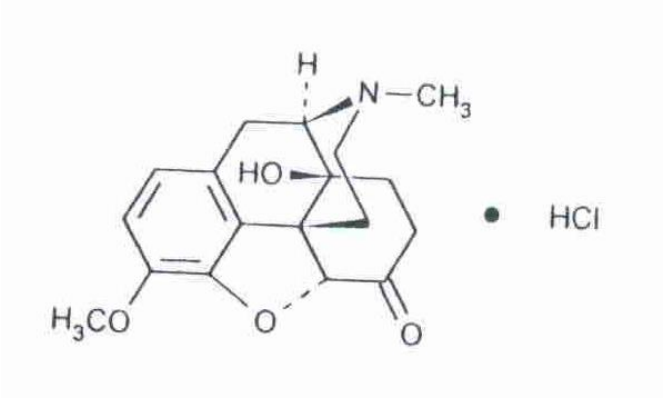
5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids

ATC code: N02A A05

Non-proprietary name: Oxycodone hydrochloride
Chemical name:4,5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride
CAS No.: 124-90-3
Molecular formula: $C_{18}H_{21}NO_4$
Molecular weight: 351.83

The structural formula for oxycodone hydrochloride is:



Oxycodone hydrochloride is a white, crystalline, odourless powder freely soluble in water, sparingly soluble in ethanol and nearly insoluble in ether.

Mechanism of Action

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.

Pharmacodynamic effects

Other pharmacological actions of oxycodone are in the central nervous system (CNS), (respiratory depression, antitussive, anxiolytic, sedative and miosis), smooth muscle (constipation, reduction in gastric, biliary and pancreatic secretions, spasm of sphincter of Oddi and transient elevations in serum amylase) and cardiovascular system (release of histamine and/or peripheral vasodilatation, possibly causing pruritus, flushing, red eyes, sweating and/or orthostatic hypotension). Endocrine System (See section 4.4 – special warnings and precautions.)

In vitro and animal studies indicate various effects of natural opioids, such as morphine, on components of the immune system; the clinical significance of these findings is unknown. Whether oxycodone, a semisynthetic opioid, has immunological effects similar to morphine is unknown.

Clinical efficacy and safety

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 IV oxycodone with IV morphine in patients using patient-controlled analgesia (PCA) for acute postoperative pain. The intention to treat and safety populations included 133 patients (64 oxycodone, 69 morphine); 117 patients completed, 56 on oxycodone and 61 on morphine. Oxycodone 10 mg/mL or morphine solution for injection was diluted to 1 mg/mL with 0.9% saline, and 2 mg IV 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 score was 4.6 $\pm$ 2.6 for oxycodone and 4.1 $\pm$ 2.0 for morphine with a pain intensity difference of 0.55 (95% CI: -0.37 to 1.48). The 95% CI for the treatment difference was within the established equivalence limits (-1.5 to 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 to 0.92)	-0.23 (-0.98 to 0.51)
	24 hours	0.55 (-0.37 to 1.48)	0.65 (0.02 to 1.27)
	Completion or discontinuation	-0.31 (-1.27 to 0.64)	0.26 (-0.42 to 0.94)
ITT population	24 hours	0.24 (-0.61 to 1.09)	0.18 (-0.44 to 0.80)

PP: Per Protocol
ITT: Intention to treat

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**.

5.2 Pharmacokinetic properties

Absorption

The Tmax 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 (IV) and subcutaneous (SC) 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 Cmax 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.

Biotransformation

Oxycodone hydrochloride is metabolised in the liver to form noroxycodone, oxymorphone, noroxymorphone, 6 α and β oxycodol and conjugated glucuronides. Oxymorphone has some analgesic activity but is present in plasma in low concentrations and is not considered to contribute to oxycodone's pharmacological effect. CYP3A4 and CYP2D6 are involved in the formation of noroxycodone and oxymorphone, respectively (see Section 4.5). 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 Section 4.5 – Interactions with other medicines and other forms of interaction.

Elimination

The plasma elimination half-life is approximately 4.5 hours. The active drug and its metabolites are excreted in both urine and faeces.

Patients with mild to severe hepatic or renal dysfunction may have an increase in 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.

5.3 Preclinical safety data

Reproductive and Developmental Toxicology

Oxycodone had no effect on fertility or early embryonic development in male and female rats at doses as high as 8 mg/kg/day. Also, oxycodone did not induce any malformations in rats at doses as high as 8 mg/kg/day or in rabbits at doses as high as 125 mg/kg/day. Dose-related increases in developmental variations (increased incidences of extra (27) presacral vertebrae and extra pairs of ribs) were observed in rabbits when the data for individual fetuses were analyzed. However, when the same data were analyzed using litters as opposed to individual fetuses, there was no dose-related increase in developmental variations although the incidence of extra presacral vertebrae remained significantly higher in the 125 mg/kg/day group compared to the control group. Since this dose level was associated with severe pharmacotoxic effects in the pregnant animals, the fetal findings may have been a secondary consequence of severe maternal toxicity.

In a prenatal and postnatal development study in rats, maternal body weight and food intake parameters were reduced for doses ≥2 mg/kg/day compared to the control group. Body weights were lower in the F1 generation from maternal rats in the 6 mg/kg/day dosing group. There were no effects on physical, reflexological, or sensory developmental parameters or on behavioral and reproductive indices in the F1 pups (the NOEL for F1 pups was 2 mg/kg/day based on body weight effects seen at 6 mg/kg/day). There were no effects on the F2 generation at any dose in the study.

Carcinogenicity

Carcinogenicity was evaluated in a 2-year oral gavage study conducted in Sprague-Dawley rats. Oxycodone did not increase the incidence of tumors in male and female rats at doses up to 6 mg/kg/day. The doses were limited by opioid-related pharmacological effects of oxycodone

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.

The results of *in vitro* and *in vivo* studies indicate that the genotoxic risk of oxycodone to humans is minimal or absent at the systemic oxycodone concentrations that are achieved therapeutically. Oxycodone was not genotoxic in a bacterial mutagenicity assay or in an *in vivo* micronucleus assay in the mouse. Oxycodone produced a positive response in the *in vitro* mouse lymphoma assay in the presence of rat liver S9 metabolic activation at dose levels greater than 25 μg/mL. Two *in vitro* chromosomal aberrations assays with human lymphocytes were conducted. In the first assay, oxycodone was negative without metabolic activation but was positive with S9 metabolic activation at the 24 hour time point but not at 48 hours after exposure. In the second assay, oxycodone did not show any clastogenicity either with or without metabolic activation at any concentration or time point.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate
Citric acid monohydrate
Sodium chloride
Hydrochloric acid
Sodium hydroxide
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Cyclizine at concentrations of 3 mg/ml or less, when mixed with oxycodone solution for injection or infusion, either undiluted or diluted with water for injections, shows no sign of precipitation over a period of 24 hours storage at room temperature. Precipitation has been shown to occur in mixtures with oxycodone solution for injection or infusion at cyclizine concentrations greater than 3 mg/ml or when diluted with 0.9% saline. However, if the dose of oxycodone solution for injection or infusion is reduced and the solution is sufficiently diluted with Water for Injections, concentrations greater than 3 mg/ml are possible. It is recommended that Water for Injections be used as a diluent when cyclizine and oxycodone hydrochloride are co-administered either intravenously or subcutaneously as an infusion.

Prochlorperazine is chemically incompatible with oxycodone solution for injection or infusion.

It is recommended that OXYNORM solution for injection or infusion should not be administered in combination with other parenteral formulations unless there is compatibility data to support the combination.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store below 25°C and protected from light

For further information on use after opening see Section 6.6

6.5 Nature and contents of container

OXYNORM solution for injection or infusion 10 mg/mL in clear glass ampoules available as either:

10 mg/ml:

Clear neutral glass ampoules: 1 ml and 2 ml.
Pack size: 5 ampoules.
Clear neutral glass ampoules: 20 ml (not currently available in NZ)
Pack size: 4 ampoules.

50 mg/ml:

Clear neutral glass ampoules: 1 ml
Pack size: 5 ampoules.

6.6 Special precautions for disposal and other handling

OXYNORM solution for injection or infusion is for single use in one patient only.

The results from studies indicate that:

- oxycodone hydrochloride injection 10 mg/ml, undiluted or diluted to 1 mg/ml with 0.9% w/v saline, 5% w/v dextrose and WFI, and
- oxycodone hydrochloride injection 50 mg/ml, undiluted or diluted to 3 mg/ml with 0.9% w/v saline, 5% w/v dextrose and water for injections (WFI)

are physically and chemically stable when in contact with representative brands of polypropylene or polycarbonate syringes, polyethylene or polyvinylchloride tubing and polyvinylchloride or

ethylvinylacetate infusion bags over a 24 hour period at ambient temperature. Both injections, whether undiluted or diluted in the infusion fluids used in these studies and contained in the various assemblies, do not need to be protected from light

If not used immediately, in-use storage times and conditions prior to use would not be longer than 24 hours at 2 to 8 °C, unless reconstitution, dilution, etc has taken place in controlled and validated aseptic conditions.

Inappropriate handling of the undiluted solution after opening of the original ampoule, or of the diluted solutions may compromise the sterility of the product.

Solution for injection or infusion 10 mg/ml

The compatibility with representative brands of a range of drugs (hyoscine butylbromide, hyoscine hydrobromide, dexamethasone sodium phosphate, haloperidol, midazolam hydrochloride, metoclopramide hydrochloride, levomepromazine hydrochloride) likely to be co-administered with oxycodone hydrochloride injection was also assessed when stored in high and low dose combinations in polypropylene syringes over a 24 hour period at ambient temperature. No evidence of incompatibility between oxycodone hydrochloride injection 10 mg/ml and any of the solutions of the seven drugs tested was observed.

Solution for injection or infusion 50 mg/ml

The compatibility with representative brands of a range of drugs (hyoscine butylbromide, hyoscine hydrobromide, dexamethasone sodium phosphate, haloperidol, midazolam hydrochloride, metoclopramide hydrochloride, levomepromazine hydrochloride, glycopyrronium bromide and ketamine hydrochloride) likely to be co-administered with oxycodone hydrochloride injection was also assessed when stored in high and low dose combinations in polypropylene syringes over a 24 hour period at ambient temperature. No evidence of incompatibility between oxycodone hydrochloride injection 50 mg/ml and any of the solutions of the nine drugs tested was observed.

7 MEDICINE SCHEDULE

Controlled Drug B3

8 SPONSOR

Mundipharma New Zealand Limited:
Distributed by:
Pharmaco (N.Z.) Ltd
4 Fisher Crescent
Mt Wellington
Auckland 1060
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Toll Free [Medical Enquiries]: 0800 773 310

9 DATE OF FIRST APPROVAL

OXYNORM 10mg/mL solution for injection or infusion 17 August 2008

OXYNORM 50mg/mL solution for injection or infusion 11 February 2010

10 DATE OF REVISION OF THE TEXT

19 Nov 2021

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(Based on CCDS v 17, 09 Aug 2021), Medsafe request 28 June 2021

SUMMARY TABLE OF CHANGES

Section changed	**Summary of new information**
Section 4.2	Addition of wording "where necessary" to description of administration for parenteral formulations (for i.v. and s.c.) and addition of information about solution for dilution (s.c. bolus) for clarification of instructions.
Section 4.4	Additional warning in the following sections as requested by Medsafe: • Hazardous and harmful use • Respiratory depression • Risk form concomitant use of benzodiazepines or other CMS depressants, including alcohol • Use of opioids in chronic (long-term) non-cancer pain • Tolerance, dependence and withdrawal • Accidental ingestion/exposure • Hyperalgesia Ceasing opioids
Section 4.8	Removal of sentence re reduction of adverse drug reactions with time.