NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Oxycodone hydrochloride 10mg/mL solution for injection or infusion
Oxycodone hydrochloride 50mg/mL solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Oxycodone hydrochloride 10 mg/ml
Each 1 ml ampoule contains 10 mg oxycodone hydrochloride (equivalent to 9 mg oxycodone).
Each 2 ml ampoule contains 20 mg oxycodone hydrochloride (equivalent to 18 mg oxycodone).

Oxycodone hydrochloride 50 mg/ml
Each 1 ml ampoule contains 50 mg oxycodone hydrochloride (equivalent to 45 mg/ml oxycodone)

Excipients with known effect:
This medicinal product contains less than 1 mmol sodium (23 mg) per 1 ml, that is to say essentially 'sodium-free'.

For the full list of excipients, see section *6.1 List of excipients*.

3 PHARMACEUTICAL FORM

Solution for injection or infusion,
Clear colourless solution, practically free from visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The management of opioid-responsive moderate to severe pain. Oxycodone hydrochloride solution for injection or infusion 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 Special warnings and precautions for use*, 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.

Treatment goals and discontinuation.

Before initiating treatment with oxycodone, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in

accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with oxycodone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section *4.4 Special warnings and precautions for use*).

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 efficacy and safety** (refer to section *5.1 Pharmacodynamic properties*). 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 Special warnings and precautions for use* – Use in renal impairment and Use in 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

Oxycodone hydrochloride solution for injection or infusion should not be used in patients under 18 years as there are no data on the use of oxycodone hydrochloride 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 Special warnings and precautions for use* – Use in 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 oxycodone hydrochloride solution for injection or infusion listed in section *6.1 List of excipients*, acute respiratory disease, severe respiratory disease, 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 (see section *4.4 Special warnings and*

precautions for use), 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 patients with intracranial lesions or reduced level of consciousness of uncertain origin.

Hazardous and harmful use

This product contains the opioid oxycodone hydrochloride and is a potential medicine of abuse, misuse and addiction. Addiction can occur in patients appropriately prescribed oxycodone hydrochloride 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 medicine is used and with higher doses. Patients should be assessed for their risks for opioid abuse or addiction prior to being prescribed oxycodone.

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 medicine in the smallest appropriate quantity and advising the patient on the safe storage and proper disposal of any unused medicine (see section *6.4 Special precautions for storage* and section *6.6 Special precautions for disposal and other handling*). Caution patients that abuse of oral or transdermal forms of opioids by parenteral administration can result in serious adverse events, which may be fatal.

Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as oxycodone. Repeated use of oxycodone can lead to Opioid Use Disorder (OUD). A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of oxycodone may result in overdose and/or death.

The risk of developing OUD is increased in patients with a personal or family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with oxycodone and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section *4.2 Dose and method of administration*). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician.

Patients will require monitoring for signs of medicine-seeking behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active medicines (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

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

Respiratory depression

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 oxycodone 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, in patients with renal and hepatic impairment 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 Dose and method of administration*). The use of opioids is contraindicated in patients with severe respiratory disease, acute respiratory disease and respiratory depression (see section *4.3 Contraindications*).

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 equianalgesic doses is required when changing opioids or switching from immediate release to modified release formulations, (see section *4.2 Dose and method of administration*), together with consideration of pharmacological differences between opioids. Consider starting the new opioid at a reduced dose to account for individual variation in response.

Sleep related breathing disorders

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. In patients who present with CSA, consider decreasing the total opioid dosage. Opioids may also cause worsening of pre-existing sleep apnoea (see section *4.8 Undesirable effects*).

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

Concomitant use of opioids and benzodiazepines or other CNS depressants, including alcohol, may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of oxycodone 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 other treatment options are not possible. If a decision is made to prescribe oxycodone concomitantly with any of the medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible. 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 oxycodone.

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* below).

Tolerance, 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 oxycodone in a person who may be physically-dependent, the medicine should not be ceased abruptly but withdrawn by tapering the dose gradually (see *Ceasing opioids* and section *4.2 Dose and Method of Administration*).

Accidental ingestion/exposure

Accidental ingestion or exposure of oxycodone, 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 oxycodone (see section *6.4 Special precautions for storage* and section *6.6 Special precautions for disposal and other handling*).

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 Dose and method of administration*). 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.

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.

Use in renal impairment

In renal impairment, the administration of oxycodone hydrochloride 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 function. Therefore, initiation of dosing in patients with renal impairment (CLcr < 60 mL/min) should be reduced to ⅓ to ½ of the usual dose with cautious titration.

Use in hepatic impairment

In hepatic impairment, the administration of oxycodone hydrochloride 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 hepatic function. Therefore, initiation of dosing in patients with hepatic impairment should be reduced to ⅓ to ½ of the usual dose with cautious titration.

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.

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.

Paediatric use

Oxycodone hydrochloride solution for injection or infusion should not be used in patients under 18 years (see section *4.2 Dose and method of administration*).

Effects on laboratory tests

No data available.

Special risk patients

As with all opioids, a reduction in dosage may be advisable in hypothyroidism. Use with caution in patients with hypotension, hypovolaemia, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, prostatic hypertrophy, adrenocortical insufficiency (Addison's disease), toxic psychosis, sleep apnoea, constipation and myxoedema. As with all opioid preparations, patients who are to undergo cordotomy or other pain-relieving neural blockade procedures should not receive oxycodone hydrochloride solution for injection or infusion for 6 hours before surgery. As with all opioid preparations, oxycodone hydrochloride 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, oxycodone hydrochloride solution for injection or infusion should be discontinued immediately. Oxycodone hydrochloride solution for injection or infusion should be used with caution pre- or intra-operatively and within the first 12-24 hours post-operatively.

Hepatobiliary disorders

Oxycodone may cause dysfunction and spasm of the Sphincter of Oddi, thus raising intrabiliary pressure and increasing the risk of biliary tract symptoms and pancreatitis. Therefore, oxycodone has to be administered with caution in patients with pancreatitis and diseases of the biliary tract.

Endocrine effects

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.

4.5 Interaction with other medicines and other forms of interaction

Anticholinergic agents

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

Concurrent use of oxycodone with CNS depressants (include, but are not limited to: other opioids, gabapentinoids such as pregabalin, anxiolytics, hypnotics and sedatives (incl. benzodiazepines), other tranquilizers, general anaesthetics, antipsychotics, antidepressants, phenothiazines, centrally-active anti-emetics, cannabis, neuroleptic medications and alcohol, etc), or related medications increases the risk of profound sedation, respiratory depression, hypotension, coma or death because of additive CNS depressant effect.(see section *4.4 Special warnings and precautions for use*).

Intake of alcoholic beverages while being treated with oxycodone hydrochloride 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 metabolised in part via the CYP3A4 and CYP2D6 pathways. The activities of these metabolic pathways may be inhibited or induced by various co-administered medicines or dietary elements, which may alter plasma concentrations. Oxycodone doses may need to be adjusted accordingly. Medicines 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. 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 medicines (e.g. cimetidine, certain cardiovascular medications, fluoxetine and other antidepressants and erythromycin), although such blockade has not yet been shown to be of clinical significance with oxycodone hydrochloride 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 medicine, resulting in a decrease in oxycodone plasma concentrations.

Oxycodone did not inhibit the activity of P450 isozymes 2D6, 3A4, 1A2, 2A6, 2C19 or 2E1 in human liver microsomes *in vitro*. Non-clinical 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 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.

Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re- uptake Inhibitor (SNRI)

Concurrent 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, diarrhoea). Oxycodone should be used with caution and the dosage may need to be reduced in patients using these medications.

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 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. 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.

Breast-feeding

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. Oxycodone hydrochloride 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

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.

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 cause drowsiness and 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

Adverse reactions are typical of full opioid agonists, and tend to reduce with time, with the exception of constipation. Anticipation of adverse 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 reaction rated treatment-related or not determined. The very common adverse 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 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*** (≥ 1/1000 to < 1/100)	***Rare*** (≥ 1/10,000 to < 1/1,000)	***Not known*** (cannot be estimated from the available data)
Immune system disorders			Anaphylactic reaction, Anaphylactoid reaction Hypersensitivity		
Endocrine disorders		Increased ADH release			
Metabolism and nutrition disorders		Decreased appetite	Dehydration		
Psychiatric disorders	Euphoric mood	Anxiety, Confusional state, Disorientation, Insomnia, Nervousness, Thinking abnormal, Depression	Affect lability, Agitation, Dysphoria, Hallucinations, Libido decreased		Aggression, Drug dependence*
Nervous system disorders	Dizziness, Drowsiness, Headache, Somnolence	Hypokinesia, Stupor, Tremor, Lethargy	Amnesia, Convulsion, Grogginess, Hypertonia, Hypoaesthesia, Muscle contractions involuntary, Paraesthesia, Speech disorder, Syncope, Dysgeusia (taste perversion)		Hyperalgesia
Eye disorders		Miosis, Visual impairment			
Ear and labyrinth disorders		Vertigo			

Cardiac disorders		Tachycardia	Palpitations (as part of withdrawal syndrome)		
Vascular disorders		Hypotension, Vasodilatation	Orthostatic hypotension		
Respiratory, thoracic and mediastinal disorders		Dyspnoea, Hyperventilation	Bronchoconstriction, Respiratory depression		Central sleep apnoea syndrome
Gastrointestinal disorders	Nausea, Vomiting, Constipation	Abdominal pain, Diarrhoea, Dry mouth, Dyspepsia, Flatulence, Hiccups	Dental caries, Dysphagia, Eructation, Gastrointestinal disorder, Ileus		
Hepatobiliary disorders			Biliary spasm, Cholestasis, Hepatic enzymes increased, Sphincter of Oddi dysfunction		
Skin and subcutaneous tissue disorders	Pruritus	Hyperhidrosis, Rash	Dry skin, Urticaria		
Renal and urinary disorders		Urinary retention	Urinary spasm		
Reproductive system and breast disorders			Amenorrhoea, Erectile dysfunction, Hypogonadism		
General disorders and administration site conditions		Asthenia, Fatigue, Chills, Hot/warm, Injection site hypersensitivity/pain, Oedema, Pain, Pallor	Malaise, Peripheral oedema, Thirst		Drug withdrawal syndrome neonatal, Opioid tolerance*, Opioid withdrawal syndrome*

*The frequency of drug dependence, opioid tolerance and opioid withdrawal syndrome cannot be estimated from available evidence (e.g. clinical trials, spontaneous reporting, and the medical literature) and therefore is classified as "not known". 'Not known' should not be interpreted as an indication of the rarity of the occurrence of drug dependence, opioid tolerance and opioid withdrawal syndrome, but a reflection of the limitations in the available evidence that do not support a precise estimate of frequency.

Drug Dependence

The frequency in the above table regarding drug dependence reflects the current evidence, including cumulative data from clinical trials and additional post marketing sources, and indicates that the risk of drug dependence with opioids is highly variable depending upon: definition of drug dependence; duration of treatment; dose; individual patient risk factors; and clinical settings. 'Not known' should not be interpreted as an indication of the rarity of the occurrence of drug dependence, but a reflection of the limitations in the available evidence that do not support a precise estimate of frequency.

Repeated use of oxycodone may lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid

treatment (see section *4.4 Special warnings and precautions for use*).

As an opioid, oxycodone exposes users to the risks of dependence (both physical and psychological), addiction, abuse, and misuse, as well as opioid use disorder and problematic opioid use. Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed oxycodone. Addiction can occur at recommended doses, and if the medicine is misused or abused. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The frequency of drug dependence also increases with longer term use or higher doses of oxycodone (see section *4.4 Special warnings and precautions for use*).

Opioid Tolerance and Opioid Withdrawal Syndrome

The frequency of in the above table regarding opioid tolerance and opioid withdrawal syndrome reflects the high variability of risk depending upon: definition of tolerance and withdrawal syndrome; dose and duration of treatment; and assessment and monitoring methods (specific to withdrawal syndrome). 'Not known' should not be interpreted as an indication of the rarity of the occurrence of opioid tolerance and opioid withdrawal syndrome, but a reflection of the limitations in the available evidence that do not support a precise estimate of frequency. As an opioid, oxycodone exposes users to the risks of dependence (both physical and psychological), tolerance and withdrawal syndrome (see section *4.4 Special warnings and precautions for use*).

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://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

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, hypotonia, miosis (dilated if hypoxia is severe), cold and/or clammy skin and sometimes bradycardia, hypoglycemia, hypotension, pulmonary oedema, and death. Severe overdose may result in apnoea, pulmonary oedema, circulatory collapse and death. Toxic leukoencephalopathy has been observed with oxycodone overdose.

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, to manage the circulatory shock accompanying an overdose. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

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, naloxone may be administered intravenously, repeating as necessary, or by a titrated infusion. 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 Data Sheet 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.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

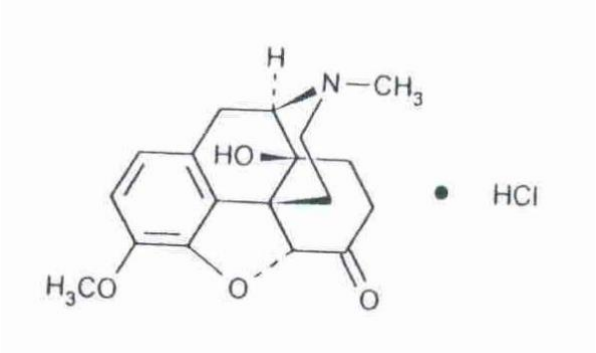
5 PHARMACOLOGICAL PROPERTIES

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 vasodilation, possibly causing pruritus, flushing, red eyes, sweating and/or orthostatic hypotension).

Clinical efficacy and safety

Oxycodone hydrochloride 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 medicine 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 reactions were all known opioid side-effects, but respiratory

depression was uncommon. Further details are provided under section *4.8 Undesirable 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 oxycodone hydrochloride 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 Interaction with other medicines and other forms of interaction*). 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 Interaction with other medicines and other forms of interaction*).

Elimination

Oxycodone has an elimination half-life of between 3 – 5 hours, or approximately 4.5 hours.

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 medicine effects. Considerable inter-individual variability may be seen in these patients.

5.3 Preclinical safety data

Carcinogenicity

Carcinogenicity was evaluated in a 2-year oral gavage study conducted in Sprague-Dawley rats. Oxycodone did not increase the incidence of tumours in male and female rats at doses up to 6 mg/kg/day (equivalent to 6.8 mg/day in men and 24.6 mg/day in women, based on estimated AUC

values). 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate dihydrate
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 Special precautions for disposal and other handling*.

It is recommended that oxycodone hydrochloride 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

Unopened ampoules:

Oxycodone hydrochloride 10mg/mL: 30 months
Oxycodone hydrochloride 50mg/mL: 36 months

Opened ampoules: The product should be used immediately after opening the ampoule.

Prepared infusion solutions:

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C.

For instructions on dilution of the medicinal product before administration, see section *6.6 Special precautions for disposal and other handling*.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store below 30°C and protected from light

For storage conditions after first opening or dilution of the medicinal product, see section *6.3 Shelf life*.

6.5 Nature and contents of container

Colourless glass ampoules with a nominal volume of 1 ml or 2 ml.

Oxycodone hydrochloride 10mg/mL solution for injection or infusion:
Pack sizes:
5 x 1 ml ampoules
10 x 1 ml ampoules
5 x 2 ml ampoules
10 x 2 ml ampoules.

Oxycodone hydrochloride 50mg/mL solution for injection or infusion:
Pack sizes:
5 x 1 ml ampoules
10 x 1 ml ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other 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. Oxycodone hydrochloride solution for injection or infusion is for single use in one patient only.

The medicinal product should be examined visually and should not be used if particulate matter or discolouration are present.

Oxycodone hydrochloride solution for injection or infusion has been shown to be compatible with the following medicines:

Hyoscine butylbromide
Hyoscine hydrobromide
Dexamethasone sodium phosphate
Haloperidol
Midazolam hydrochloride
Metoclopramide hydrochloride
Levomepromazine hydrochloride
Glycopyrronium bromide (Oxycodone hydrochloride 50 mg/ml strength only)
Ketamine hydrochloride (Oxycodone hydrochloride 50 mg/ml strength only).

Oxycodone hydrochloride solution for injection or infusion, undiluted or diluted to 1 mg/ml with 0.9% w/v saline, 5% w/v dextrose or water for injections, is physically and chemically stable when in contact with representative brands of polypropylene or polycarbonate syringes, polyethylene or PVC tubing, and PVC or EVA infusion bags, over a 24 hour period at 25°C.

The 10 mg/ml and 50 mg/ml injection, whether undiluted or diluted to 1 mg/ml in the infusion fluids and containers detailed above, does not need to be protected from light over a 24 hour period.

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

7 MEDICINE SCHEDULE

Controlled Drug B3

8 SPONSOR

Max Health Ltd
PO Box 44452
Pt Chevalier, Auckland 1246

Telephone: (09) 815 2664.

9 DATE OF FIRST APPROVAL

09 April 2020

10 DATE OF REVISION OF THE TEXT

9 October 2025

SUMMARY TABLE OF CHANGES

Section changed	**Summary of new information**
All	Changed 'drug' to 'medicine' where appropriate. Editorial updates.
4.3	Addition of respiratory disease and severe respiratory disease as contraindications.
4.4	Removed bullet pointed list at beginning of this section. Under heading 'Hazardous and harmful use' added '*Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as oxycodone*'. Moved information on Opioid Use Disorder to be under heading 'Hazardous and harmful use'. And amended heading 'Tolerance, dependence and Opioid Use Disorder' to 'Tolerance, dependence and withdrawal'. Text revised under heading 'Tolerance, dependence and withdrawal'. Under heading 'Respiratory depression' added '*patients with renal and hepatic impairment*' as having a higher risk of life-threatening respiratory depression. Under heading 'Respiratory depression' added that pharmacological differences between opioids need to be considered when changing opioids or switching formulations and that it should be considered starting the new opioid at a reduced dose to account for individual variation in responses. Under heading 'Sleep related breathing disorders' added '*Opioids may also cause worsening of pre-existing sleep apnoea*'. Information on renal and hepatic impairment separated to be under headings 'Use in renal impairment' and 'Use in hepatic impairment'. Under heading 'Use in renal impairment' the indicator 'CLcr < 60 mL/min)' has been added and the recommended starting dose has changed from reducing

	by 50% to reducing by ⅓ to ½ of a usual dose. Added section on 'Use in the elderly' and 'Paediatric use' (not to be used in patients under 18 years), and 'Effects on laboratory tests' (no data available). Added under heading 'Special risk patients' to '*Use with caution in patients with hypotension, hypovolaemia, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, prostatic hypertrophy, adrenocortical insufficiency (Addison's disease), toxic psychosis, sleep apnoea, constipation and myxoedem.*'. Addition of 'Hepatobiliary disorders'. Amended heading 'Effects on hypothalamic pituitary adrenal or gonadal axes' to 'Endocrine effects'.
4.5	Under heading 'Anticholinergic agents' added an increased risk of severe constipation and/or urinary retention. Under heading 'CNS depressants' added other examples of CNS depressants and hypotension as a risk with concurrent use. Added 'Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re- uptake Inhibitor (SNRI)' as medications that can interact with oxycodone.
4.6	Under heading 'Pregnancy' removed the statement '*The drug penetrates the placenta. Therefore, use of this medicinal product should be avoided to the extent possible in patients who are pregnant*'. This section already states that oxycodone should not be used during pregnancy unless clearly needed. Under heading 'Breast-feeding' removed the sentence '*Use of this medicinal product should be avoided to the extent possible in patients who are lactating*'. This section already states that oxycodone hydrochloride solution for injection or infusion should not be used in breastfeeding mothers unless the benefits outweigh the risks. Under heading 'Fertility' added information on reproductive toxicology studies that have been done.
4.7	Added that oxycodone may cause drowsiness.
4.8	Added that adverse reactions of full opioid agonists tend to reduce with time, with the exception of constipation. • Immune system disorders Moved anaphylactic reaction and anaphylactoid reaction from 'not known' to 'uncommon'. • Endocrine disorders Addition of increased ADH release (common). • Psychiatric disorders Moved euphoric mood from 'uncommon' to 'very common'. Addition of disorientation (common). • Nervous system disorders Addition of drowsiness (very common), hypokinesia (common), stupor (common) and grogginess (uncommon).

	• Eye disorders Moved miosis and visual impairment from 'uncommon' to 'common'. • Ear an labyrinth disorders Moved vertigo from 'uncommon' to 'common'. • Cardiac disorders Addition of tachycardia (common). • Vascular disorders Moved vasodilation from 'uncommon' to 'common'. Moved hypotension from 'rare' to 'common'. Moved orthostatic hypotension from 'rare' to 'uncommon'. • Respiratory, thoracic and mediastinal disorders Addition of hyperventilation (common) and bronchoconstriction (uncommon). • Gastrointestinal disorders Addition of hiccups (common) and gastrointestinal disorder (uncommon). Moved flatulence from 'uncommon' to 'common'. Moved dental caries from 'not known' to 'uncommon'. • Hepatobiliary disorders Addition of biliary spasm (uncommon) and sphincter of Oddi dysfunction (uncommon). Moved cholestasis from 'not known' to 'uncommon'. • Skin and subcutaneous tissue disorders Moved urticaria from 'rare' to 'uncommon'. • Renal and urinary disorders Addition of urinary spasm (uncommon). Moved urinary retention from 'uncommon' to 'common'. • Reproductive system and breast disorders Moved amenorrhoea from 'not known' to uncommon'. • General disorders and administration site conditions Moved chills from 'uncommon' to 'common'. Moved oedema from 'uncommon' to 'common'. Addition of hot/warm (common), injection site hypersensitivity/pain (common), pain (common) and pallor (common). Under 'Opioid Tolerance and Opioid Withdrawal Syndrome' deleted the statement '*If nausea and vomiting are troublesome, oxycodone may be combined with an antiemetic. Constipation must be treated with appropriate laxatives. Overdose may produce respiratory depression. Compared with other opioids, oxycodone is associated with low histamine release although urticaria and pruritus may occur.*'. Updated adverse reaction reporting URL.

4.9	Addition of hypoglycemia and pulmonary oedema as overdose symptoms. Additional information on the treatment of oxycodone overdosage. Addition of section on toxicity.
5.1	Under 'Pharmacodynamic effects' deleted the statement '*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.*'.
5.2	Under 'Elimination' added the elimination half-life range of between 3 – 5 hours and deleted the statement '*The active drug and its metabolites are excreted in both urine and faeces*.'.
5.3	Removed information on 'Reproductive and Developmental Toxicology'. Under 'Carcinogenicity' added information on men and women equivalence dose to dose given to rats. Under 'Genotoxicity' removed results of *in vitro* and *in vivo* studies.