

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains oxycodone hydrochloride 10 mg (equivalent to 9 mg of oxycodone base).

Each 1 ml ampoule contains oxycodone hydrochloride 10 mg (equivalent to 9 mg of oxycodone base).

Each 2 ml contains oxycodone hydrochloride 20 mg (equivalent to 18mg of oxycodone base).

This medicinal product contains less than 1 mmol sodium (23 mg) per dose.

For full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion (injection or infusion).

A Clear, colourless solution practically free of particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the treatment of moderate to severe pain in patients with cancer and post-operative pain. For the treatment of severe pain requiring the use of a strong opioid.

4.2 Posology and method of administration

Route of administration:

Subcutaneous injection or infusion.

Intravenous injection or infusion.

Posology:

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

Adults over 18 years:

The following starting doses are recommended. A gradual increase in dose may be required if analgesia is inadequate or if pain severity increases.

i.v. (Bolus): Dilute to 1 mg/ml in 0.9% saline, 5% dextrose or water for injections. Administer a bolus dose of 1 to 10 mg slowly over one to two minutes.

Doses should not be administered more frequently than every four hours.

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

i.v. (PCA): Dilute to 1 mg/ml in 0.9% saline, 5% dextrose or water for injections. Bolus doses of 0.03 mg/kg should be administered with a minimum lock-out time of five minutes.

s.c. (Bolus): Use as 10 mg/ml concentration. A starting dose of 5 mg is recommended, repeated at four-hourly intervals as required.

s.c. (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 much higher doses (see below).

Transferring patients between oral and parenteral oxycodone:

The dose should be based on the following ratio: 2 mg of oral oxycodone is equivalent to 1 mg of parenteral oxycodone. It must be emphasised that this is a guide to the dose required. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

Elderly:

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

Patients with renal and hepatic impairment:

Patients with mild to moderate renal impairment and/or mild hepatic impairment should be treated with caution. The lowest dose should be given with careful titration to pain control.

Children under 18 years:

There are no data on the use of Oxycodone injection in patients 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. Types of chronic pain which have been shown to be alleviated by strong opioids include chronic osteoarthritic pain and intervertebral disc disease. The need for continued treatment in non-malignant pain should be assessed at regular intervals.

Cessation of therapy:

When a patient no longer requires therapy with oxycodone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

4.3 Contraindications

Hypersensitivity to oxycodone or to any of the excipients listed in section 6.1, Oxycodone must not be used in any situation where opioids are contraindicated: severe respiratory depression with hypoxia; paralytic ileus; acute abdomen; severe chronic obstructive lung disease; cor pulmonale; severe bronchial asthma; elevated carbon dioxide levels in the blood; moderate to severe hepatic impairment; chronic constipation.

4.4 Special warnings and precautions for use

The major risk of opioid excess is respiratory depression. Caution must be exercised when administering oxycodone to the debilitated elderly; patients with severely impaired pulmonary function, patients with impaired hepatic or renal function; patients with myxedema, hypothyroidism, Addison's disease, toxic psychosis, prostate hypertrophy, adrenocortical insufficiency, alcoholism, delirium tremens, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, hypotension, hypovolaemia, raised intracranial pressure, head injury (due to risk of increased

intracranial pressure) or patients taking MAO inhibitors.

Oxycodone injection should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, Oxycodone injection should be discontinued immediately.

Oxycodone injection should be used with caution pre- or intra-operatively and within the first 12-24 hours post-operatively.

As with all opioid preparations, oxycodone products 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.

For appropriate patients who suffer with chronic non-malignant pain, opioids should be used as part of a comprehensive treatment programme involving other medications and treatment modalities. A crucial part of the assessment of a patient with chronic non-malignant pain is the patient's addiction and substance abuse history.

If opioid treatment is considered appropriate for the patient, then the main aim of treatment is not to minimise the dose of opioid but rather to achieve a dose which provides adequate pain relief with a minimum of side effects. There must be frequent contact between physician and patient so that dosage adjustments can be made. It is strongly recommended that the physician defines treatment outcomes in accordance with pain management guidelines. The physician and patient can then agree to discontinue treatment if these objectives are not met.

The patient may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain control. Prolonged use of this product may lead to physical dependence and a withdrawal syndrome may occur upon abrupt cessation of therapy. When a patient no longer requires therapy with oxycodone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

The opioid abstinence or withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, or increased blood pressure, respiratory rate or heart rate.

Hyperalgesia that will not respond to a further dose increase of oxycodone may occur, particularly in high doses. An oxycodone dose reduction or change to an alternative opioid may be required.

Oxycodone has an abuse profile similar to other strong agonist opioids. Oxycodone may be sought and abused by people with latent or manifest addiction disorders.

There is potential for development of psychological dependence (addiction) to opioid analgesics, including oxycodone. Oxycodone should be used with particular care in patients with a history of alcohol and drug abuse.

As with other opioids, infants who are born to dependent mothers may exhibit withdrawal symptoms and may have respiratory depression at birth.

Concomitant use of alcohol and Oxycodone injection may increase the undesirable effects of Oxycodone injection; concomitant use should be avoided.

Oxycodone injection contains approximately 3mg sodium per ml i.e. essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

There can be an enhanced CNS depressant effect during concomitant therapy with drugs which affect the CNS such as tranquillisers, anaesthetics, hypnotics, antidepressants, sedatives, phenothiazines, neuroleptic drugs, alcohol, other opioids, muscle relaxants and antihypertensives.

Concomitant administration of oxycodone with anticholinergics or medicines with anticholinergic activity (e.g. tricyclic anti-depressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects. Oxycodone should be used with caution and the dosage may need to be

reduced in patients using these medications.

MAO inhibitors are known to interact with narcotic analgesics. MAO inhibitors cause CNS excitation or depression associated with hypertensive or hypotensive crisis. (see section 4.4). There should be a minimum 14 day MAO inhibitor washout period before initiating oxycodone therapy.

Alcohol may enhance the pharmacodynamic effects of Oxycodone, concomitant use should be avoided.

Oxycodone is metabolised 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.

CYP3A4 inhibitors, such as macrolide antibiotics (e.g. clarithromycin, erythromycin and telithromycin), azole-antifungals (e.g. ketoconazole, voriconazole, itraconazole, and posaconazole), protease inhibitors (e.g. boceprevir, ritonavir, indinavir, nelfinavir and saquinavir), cimetidine and grapefruit juice may cause a reduced clearance of oxycodone that could cause an increase of the plasma concentrations of oxycodone. Therefore the oxycodone dose may need to be adjusted accordingly.

Some specific examples are provided below:

- Itraconazole, a potent CYP3A4 inhibitor, administered 200 mg orally for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 2.4 times higher (range 1.5 - 3.4).
- Voriconazole, a CYP3A4 inhibitor, administered 200 mg twice-daily for four days (400 mg given as first two doses), increased the AUC of oral oxycodone. On average, the AUC was approximately 3.6 times higher (range 2.7 - 5.6).
- Telithromycin, a CYP3A4 inhibitor, administered 800 mg orally for four days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.8 times higher (range 1.3 – 2.3).
- Grapefruit Juice, a CYP3A4 inhibitor, administered as 200 ml three times a day for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.7 times higher (range 1.1 – 2.1).

CYP3A4 inducers, such as rifampicin, carbamazepine, phenytoin and St John's Wort may induce the metabolism of oxycodone and cause an increased clearance of oxycodone that could cause a reduction of the plasma concentrations of oxycodone. The oxycodone dose may need to be adjusted accordingly.

Some specific examples are provided below:

- St John's Wort, a CYP3A4 inducer, administered as 300 mg three times a day for fifteen days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 50% lower (range 37-57%).
- Rifampicin, a CYP3A4 inducer, administered as 600 mg once-daily for seven days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 86% lower

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of oxycodone in pregnant women. Infants born to mothers who have received opioids during the last 3 to 4 weeks before giving birth pregnancy should be monitored for respiratory depression. Withdrawal symptoms may be observed in the newborn of mothers undergoing treatment with oxycodone.

No studies on fertility or the post-natal effects of intrauterine exposure have been carried out. However, studies in rats and rabbits with oral doses of oxycodone equivalent to 3 and 47 times an adult dose of 160 mg/day, respectively, did not reveal evidence of harm to the foetus due to oxycodone. Oxycodone injection is not recommended for use in pregnancy nor during labour.

Oxycodone may be secreted in breast milk and may cause respiratory depression in the newborn. Oxycodone should therefore not be used in breast-feeding mothers.

4.7 Effects on ability to drive and use machines

Oxycodone may impair the ability to drive and use machines. Oxycodone may modify patients’ reactions to a varying extent depending on the dosage and individual susceptibility. Therefore patients should not drive or operate machinery, if affected.

This medicine can impair cognitive function and can affect a patient’s ability to drive safely. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It may be an offence to drive while under the influence of this medicine.

4.8 Undesirable effects

Adverse drug reactions are typical of full opioid agonists. Tolerance and dependence may occur (see Tolerance and Dependence, below). Constipation may be prevented with an appropriate laxative. If nausea or vomiting are troublesome, oxycodone may be combined with an antiemetic.

The following frequency categories form the basis for classification of the undesirable effects:

Term	Frequency
Very common	≥ 1/10
Common	≥ 1/100 to <1/10
Uncommon	≥ 1/1,000 to <1/100
Rare	≥1/10,000 to <1/1,000
Very rare	<1/10,000
Frequency not known	Cannot be estimated from the available data

Immune system disorders:
Uncommon: hypersensitivity.
Frequency not known: anaphylactic reaction, anaphylactoid reaction.

Metabolism and nutrition disorders:
Common: decreased appetite.
Uncommon: dehydration.

Psychiatric disorders:
Common: anxiety, confusional state, depression, insomnia, nervousness, abnormal thinking, abnormal dreams
Uncommon: agitation, affect lability, euphoric mood, hallucinations, decreased libido, drug dependence (see section 4.4), disorientation, mood altered, restlessness, dysphoria
Frequency not known: aggression.

Nervous system disorders:
Very common: somnolence, dizziness, headache.
Common: tremor, lethargy, sedation.
Uncommon: amnesia, convulsion, hypertonia, hypoaesthesia, involuntary muscle contractions, speech disorder, syncope, paraesthesia, dysgeusia, hypotonia.
Frequency not known: hyperalgesia.

Eye disorders:
Uncommon: visual impairment, miosis.

Ear and labyrinth disorders:
Uncommon: vertigo.

Cardiac disorders:

Uncommon: palpitations (in the context of withdrawal syndrome), supraventricular tachycardia.

Vascular disorders:

Uncommon: vasodilatation, facial flushing.

Rare: hypotension, orthostatic hypotension.

Respiratory, thoracic and mediastinal disorders:

Common: dyspnoea, bronchospasm, cough decreased.

Uncommon: respiratory depression, hiccups.

Gastrointestinal disorders:

Very common: constipation, nausea, vomiting.

Common: abdominal pain, diarrhoea, dry mouth, dyspepsia.

Uncommon: dysphagia, flatulence, eructation, ileus, gastritis.

Frequency not known: dental caries.

Hepato-biliary disorders:

Uncommon: increased hepatic enzymes, biliary colic.

Frequency not known: cholestasis.

Skin and subcutaneous tissue disorders:

Very common: pruritus.

Common: rash, hyperhidrosis.

Uncommon: dry skin, exfoliative dermatitis.

Rare: urticaria.

Renal and urinary disorders:

Uncommon: urinary retention, ureteral spasm.

Reproductive system and breast disorders:

Uncommon: erectile dysfunction, hypogonadism.

Frequency not known: amenorrhoea.

General disorders and administration site conditions:

Common: asthenia, fatigue.

Uncommon: drug withdrawal syndrome, malaise, oedema, peripheral oedema, drug tolerance, thirst, pyrexia, chills.

Frequency not known: drug withdrawal syndrome neonatal.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie

4.9 Overdose**Symptoms of overdosage**

Acute overdose with oxycodone can be manifested by miosis, respiratory depression, hypotension and hallucinations. Nausea and vomiting are common in less severe cases. Non-cardiac pulmonary oedema and rhabdomyolysis are particularly common after intravenous injection of opioid analgesics. Circulatory failure and somnolence progressing to stupor or coma, hypotonia, bradycardia, pulmonary oedema and death may occur in more severe cases.

The effects of overdosage will be potentiated by the simultaneous ingestion of alcohol or other psychotropic drugs

Treatment of overdosage

Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation. The pure opioid antagonists such as naloxone are specific antidotes against symptoms from opioid overdose. Other supportive measures should be employed as needed.

In the case of massive overdosage, administer naloxone intravenously (0.4 to 2mg for an adult and 0.01mg/kg body weight for children) if the patient is in a coma or respiratory depression is present. Repeat the dose at 2 minute intervals if there is no response. If repeated doses are required then an infusion of 60% of the initial dose per hour is a useful starting point. A solution of 10 mg made up in 50 ml dextrose will produce 200 micrograms/ml for infusion using an IV pump (dose adjusted to the clinical response). Infusions are not a substitute for frequent review of the patient's clinical state.

Intramuscular naloxone is an alternative in the event that IV access is not possible. As the duration of action of naloxone is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established. Naloxone is a competitive antagonist and large doses (4 mg) may be required in seriously poisoned patients.

For less severe overdosage, administer naloxone 0.2 mg intravenously followed by increments of 0.1 mg every 2 minutes if required.

The patient should be observed for at least 6 hours after the last dose of naloxone.

Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdosage. Naloxone should be administered cautiously to persons who are known, or suspected, to be physically dependent on oxycodone. In such cases, an abrupt or complete reversal of opioid effects may precipitate pain and an acute withdrawal syndrome.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids

ATC code: N02A A05

Oxycodone is a full opioid agonist with no antagonist properties. It has an affinity for kappa, mu and delta opioid receptors in the brain and spinal cord. Oxycodone is similar to morphine in its action. The therapeutic effect is mainly analgesic, anxiolytic, antitussive and sedative.

Gastrointestinal System

Opioids may induce spasm of the sphincter of Oddi.

Endocrine system

Opioids may influence the hypothalamic-pituitary-adrenal or gonadal axes. Some changes that can be seen include an increase in serum prolactin and decreases in plasma cortisol and testosterone. Clinical symptoms may be manifest from these hormonal changes.

Other pharmacological effects

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 Pharmacokinetic properties

Pharmacokinetic studies in healthy subjects demonstrated an equivalent availability of oxycodone from Oxycodone injection when administered by the intravenous and subcutaneous routes, as a single bolus dose or a continuous infusion over 8 hours.

Following absorption, oxycodone is distributed throughout the entire body. Approximately 45% is bound to plasma protein. It is metabolised in the liver to produce noroxycodone, oxymorphone and various conjugated glucuronides. The analgesic effects of the metabolites are clinically insignificant.

The active drug and its metabolites are excreted in both urine and faeces.

The plasma concentrations of oxycodone are only minimally affected by age, being 15% greater in elderly as compared to young subjects.

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis.

The drug penetrates the placenta and can be found in breast milk.

When compared to normal subjects, patients with mild to severe hepatic dysfunction may have higher plasma concentrations of oxycodone and noroxycodone, and lower plasma concentrations of oxymorphone. There may be an increase in the elimination half-life of oxycodone and this may be accompanied by an increase in drug effects.

When compared to normal subjects, patients with mild to severe renal dysfunction may have higher plasma concentrations of oxycodone and its metabolites. There may be an increase in the elimination half-life of oxycodone and this may be accompanied by an increase in drug effects.

5.3 Preclinical safety data

Oxycodone was not mutagenic in the following assays: Ames Salmonella and E. Coli test with and without metabolic activation at doses of up to 5000 µg, chromosomal aberration test in human lymphocytes (in the absence of metabolic activation and with activation after 48 hours of exposure) at doses of up to 1500 µg/ml, and in the in vivo bone marrow micronucleus assay in mice (at plasma levels of up to 48 µg/ml). Mutagenic results occurred in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 µg/ml) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 µg/ml or greater with metabolic activation and at 400 µg/ml or greater without metabolic activation. The data from these tests indicate that the genotoxic risk to humans may be considered low.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate
Sodium citrate
Sodium chloride
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
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 injection, 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 injection at cyclizine concentrations greater than 3 mg/ml or when diluted with 0.9% saline. 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 injection.

6.3 Shelf life

Unopened: 2 years.

The injection should be given immediately after opening the ampoule. Once opened, any unused portion should be discarded. Chemical and physical in-use stability has been demonstrated for 24 hours at room temperature.

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 reconstitution, dilution, etc as taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Keep the ampoules in the outer carton in order to protect from light.

6.5 Nature and contents of container

Type I clear glass ampoules: 1 ml and 2 ml.

Pack size: 5 ampoules.

6.6 Special precautions for disposal and other handling

Oxycodone injection has been shown to be compatible with the following drugs:

Hyoscine butylbromide
Hyoscine hydrobromide
Dexamethasone sodium phosphate
Haloperidol
Midazolam hydrochloride
Metoclopramide hydrochloride
Levomepromazine hydrochloride

Oxycodone injection, 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 room temperature.

The injection, whether undiluted or diluted to 1 mg/ml in the infusion fluids used in these studies and contained in the various assemblies, does not need to be protected from light.

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 MARKETING AUTHORISATION HOLDER

Wockhardt UK Limited
Ash Road North
Wrexham
LL13 9UF
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA1339/025/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16th July 2010

10 DATE OF REVISION OF THE TEXT

April 2017