SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Oxycodone Hydrochloride 10 mg/ml oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Oxycodone Hydrochloride 10 mg/ml oral solution
Each ml contains 1 mg oxycodone hydrochloride equivalent to 9 mg oxycodone.
Excipients with known effect:
Oxycodone Hydrochloride 10 mg/ml oral solution contains 0.11 mg sunset yellow FCF (E 110) and 1 mg sodium benzoate (E 211) in each ml.

3 PHARMACEUTICAL FORM

Oral solution.

Oxycodone Hydrochloride 10 mg/ml oral solution is a clear, orange coloured solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Severe opioid-sensitive pain, such as pain from cancer.

4.2 Posology and method of administration

Posology

Adults (over 18 years of age)
Opioids should be individually dose titrated due to large differences between different patients in terms of pharmacokinetics, pain intensity, pain origin, possible tolerance, and age.

The usual starting dose for opioid naïve patients:
The dose should be adjusted individually according to the patient's condition and any previous pain treatment. The starting dose for opioid naïve patients is 5 mg every 6 hours, but a higher initial dose may be required for pain control, depending on the patient’s need. If the pain responds to opioid, the dose may be increased daily until the required effect is achieved or unacceptable side effects occur.

Conversion from oral morphine
For patients who have received oral morphine before Oxycodone Hydrochloride treatment, the daily dose should be based on the following ratio: 5 mg oral oxycodone is equivalent to 10 mg of oral morphine. It must be emphasised that this is a guide to the required dose of Oxycodone Hydrochloride. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose. At treatment initiation it might be advisable to use a lower dose than the equivalent dose.

Patients already receiving opioids may start with a higher dose of Oxycodone Hydrochloride, depending on previous experience.

When Oxycodone Hydrochloride is used to treat breakthrough pain in patients treated with a prolonged-release formulation of oxycodone, Oxycodone Hydrochloride 1/8 to 1/6 of the daily dose of the prolonged-release formulation should be administered.

Particular attention should be paid to the treatment of opioid related adverse effects.

After initiating treatment, patients should be regularly checked for pain relief and other opioid adverse effects. The dose should be adjusted to achieve the most effective pain control with minimal adverse effects.

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

Duration of treatment
Oxycodone should not be used longer than necessary.

Children under 18 years of age
Oxycodone Hydrochloride is not recommended for children under 18 years of age as the safety and efficacy has not been established.

Elderly
Caution should be exercised when elderly patients are treated with oxycodone. Oxycodone plasma concentration appears to be higher in the elderly patients, compared with younger adults.
A dose adjustment is not usually necessary in elderly patients.

Renal impairment
Oxycodone plasma concentrations are higher in patients with renal impairment, compared to patients with normal renal function. Dose initiation should follow a conservative approach in these patients. The recommended starting dose for adults should be reduced by 50% (for example, a total daily dose of 10 mg orally in opioid naïve patients), and each patient should be titrated to adequate pain control based on their clinical situation (see sections 4.4 and 5.2).

Hepatic impairment

Oxycodone plasma concentrations are higher in patients with hepatic impairment, compared to patients with normal liver function. Dose initiation should follow a conservative approach in these patients. The recommended starting dose for adults should be reduced by 50% (for example, a total daily dose of 10 mg orally in opioid naïve patients), and each patient should be titrated to adequate pain control based on their clinical situation (see sections 4.4 and 5.2)

Method of administration

Oral use.

Treatment goals and discontinuation
Before initiating treatment with Oxycodone Hydrochloride, 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 dosage 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)

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Oxycodone must not be used in any situation where opioids are contraindicated:

- severe chronic obstructive pulmonary disease
- cor pulmonale
- severe bronchial asthma
- severe respiratory depression with hypoxia and/or hypercapnia (see section 4.4)
- paralytic ileus

4.4 Special warnings and precautions for use

Respiratory depression
The major risk of opioid excess is respiratory depression. The respiratory depression effect of oxycodone is due to inhibition of the carbon dioxide stimulating effect on the respiratory centres in the medulla oblongata. This effect may lead to respiratory failure, particularly in patients with impaired lung capacity due to lung disease or exposure to other medicinal products (see also section 4.5)

Sleep-related breathing disorders
Opioids may cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use may increase the risk of CSA in a dose-dependent manner in some patients. Opioids may also cause worsening of pre-existing sleep apnoea (see section 4.8). In patients who present with CSA, consider decreasing the total opioid dosage.

Gastrointestinal motility and surgery
Oxycodone increases smooth muscle tone in the gastrointestinal tract, causing constipation with delayed intestinal passage of food (see section 4.8). Should paralytic ileus be suspected or occur during use, this medicinal product should be discontinued immediately. 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.

Oxycodone Hydrochloride is not recommended for pre-operative use or within the first 12-24 hours post-operatively. The post-operative treatment initiation with Oxycodone Hydrochloride must be evaluated for each individual patient based on the type and extent of surgery, the method of anaesthesia, concomitant use of other drugs and the patient's condition. Increased smooth muscle tone also causes pressure increase in the biliary and urinary tracts, hence oxycodone is less suitable for biliary or urinary tract spasms.

Special populations
Caution should be exercised in the treatment of debilitated elderly, patients with severe pulmonary, renal or hepatic impairment, hyperthyroidism, hypothyroidism, myxoedema, Addison's disease, toxic psychosis, hypotonia, prostate hypertrophy, adrenocortical insufficiency, alcoholism, delirium tremens, biliary tract diseases, pancreatitis, inflammatory bowel disease, hypotension, hypovolemia, head injuries (due to the risk of increased intracranial pressure) or patients treated with MAO inhibitors, benzodiazepines, other CNS depressants (including alcohol) or who have been treated with MAO inhibitors the last two weeks (see section 4.5). There may be a need to reduce the dose (see also section 4.2).

Hepatobiliary disorders
Oxycodone may cause dysfunction and spasm of the sphincter of Oddi, thus 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.

Oxycodone and sedatives
Concomitant use of oxycodone and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe oxycodone concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2). The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Other warnings and precautions
The effect of oxycodone may be enhanced after encephalitis.
Oxycodone should not be used in idiopathic or psychopathological pain conditions.

The drug may inhibit the cough reflex.

Opioids, such as Oxycodone Hydrochloride, can affect the hypothalamic-pituitary-adrenal or gonadal axes. Some changes that can be seen include increase in serum prolactin, and a decrease in plasma cortisol and testosterone. Clinical symptoms may manifest from these hormonal changes.

Addictive drug
As with all opioids, long-term use of Oxycodone Hydrochloride can cause addiction. Abrupt treatment discontinuation can cause withdrawal syndrome. When a patient no longer needs oxycodone treatment, it is recommended that the dose is gradually reduced to avoid withdrawal symptoms. Withdrawal symptoms may include yawning, mydriasis, lacrimation, rhinorrhoea, tremor, hyperhidrosis, anxiety, restlessness, convulsions and insomnia.
Sudden treatment discontinuation within 24 hours may precipitate the following withdrawal symptoms: restlessness, watery eyes, runny nose, sweating and restless sleep. These symptoms may increase over the next three days.

Opioid Use Disorder (abuse and dependence)
Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as oxycodone.

Repeated use of Oxycodone may 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 a 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 others mental health disorders (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with Oxycodone Hydrochloride and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). 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 drug-seeking behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

Tolerance
As with all opioids, the patient may develop tolerance to the medicinal product with chronic use and may need gradually higher doses to maintain pain control.

Hyperalgesia that will not respond to a further dose increase of oxycodone may occur, particularly at high doses. It may be necessary to reduce the oxycodone dose or switch to another opioid.

Alcohol

Concomitant use of alcohol and Oxycodone Hydrochloride may increase the risk of oxycodone side effects.
Concomitant use should be avoided (see section 4.5).

Abuse
Abuse of oral drug formulations by parenteral administration can be expected to result in serious adverse reactions, which may be fatal (see section 4.9).

Important information about excipients
Oxycodone Hydrochloride 10 mg/ml oral solution contains sunset yellow FCF (E 110) which may cause allergic reactions.

Oxycodone Hydrochloride contains 1 mg sodium benzoate in each ml which may increase jaundice in newborn babies (up to 4 weeks old).

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

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products that inhibit central nervous system (e.g. other opioids, sedatives, non-benzodiazepine sedatives, hypnotics, phenothiazines, antipsychotics, anaesthetics, antidepressants, antiemetics, benzodiazepines) may aggravate side effects of oxycodone, in particular, sedation, respiratory depression, coma and death.

Alcohol may enhance the pharmacodynamic effects of Oxycodone Hydrochloride oral solution. Concomitant use should be avoided.

Concomitant administration of oxycodone with anticholinergics or medicines with anticholinergic activity (e.g. tricyclic antidepressants, antipsychotics, antihistamines, anti-Parkinson’s drugs and muscle relaxants) may result in increased anticholinergic adverse effects, such as constipation, dry mouth and urinary disorders.

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, diarrhoea). 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). Oxycodone Hydrochloride should be used with caution in patients administered MAO-inhibitors or who have received MAO-inhibitors during the last two weeks (see section 4.4).

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, which may result in altered plasma concentrations of oxycodone. As a result, it may be necessary to adjust the oxycodone dose.

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 Johns 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, fluoxetine and quinidine, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. However, concomitant use of CYP2D6 inhibitors has only had a negligible effect on the elimination of oxycodone and no effect on the pharmacodynamic effects of oxycodone.

4.6 Fertility, pregnancy and lactation

This medicinal product should be avoided in pregnant or lactating patients.

Pregnancy

There are limited data from the use of oxycodone during pregnancy. Animal studies have not shown relevant reproductive toxicity (see section 5.3). Prolonged use of

oxycodone during pregnancy may cause withdrawal symptoms in the neonates. Administration of oxycodone during labour may cause respiratory depression in the neonate. A careful risk/benefit assessment should be made before administration to pregnant women because of possible adverse effects on the foetus and neonate. Neonates born to mothers treated with oxycodone during the last 3 to 4 weeks of pregnancy should be closely monitored due to increased risk of respiratory depression and/or withdrawal symptoms.

Breast-feeding
Oxycodone is excreted in human milk and may cause respiratory depression in the breastfed infant. The concentration ratio between milk and plasma was 3.4:1.
Oxycodone should not be used in breast-feeding mothers.

Fertility
There are no data available from humans. Oxycodone has not shown an effect on fertility in rats (see section 5.3).

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. This class of medicine is in the list of drugs included in regulations under 5a of the Road of Traffic Act 1988. 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 is an offence to drive while you have this medicine in your body over a specified limit unless you have a defence (called the 'statutory defence').

• This defence applies when:

o The medicine has been prescribed to treat a medical or dental problem and

o You have taken it according to the instructions given by the prescriber and in the information provided with the medicine.

• Please note that it is still an offence to drive if you are unfit because of the medicine (i.e. your ability to drive is being affected).

Details regarding a new driving offence concerning driving after drugs have been taken in the UK may be found here: https://www.gov.uk/drug-driving-law

4.8 Undesirable effects

The most commonly reported adverse reactions are nausea and constipation, both occurring in approximately 25 to 30% of patients. Nausea and vomiting are usually temporary, but may be treated with an antiemetic. As with any strong opioid, constipation may occur and should be treated with appropriate laxatives. If the opioid related adverse effects continue, they should be investigated for an alternative cause.

The adverse drug reactions typical for full opioid agonists tend to reduce with time, except for constipation.

As with other opioids the most serious adverse reaction is respiratory depression (see section 4.4 and 4.9). Respiratory depression is most likely to occur in elderly, debilitated or opioid-naïve patients.

The following frequency categories form the basis for classification of adverse reactions:
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), not known (cannot be estimated from the available data).

System Organ Class	**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)**	**Frequency not known**
Immune system disorders			hypersensitivity		anaphylactic reaction, anaphylactoid reaction.
Metabolism and nutrition disorders		decreased appetite	dehydration		
Psychiatric disorders		anxiety, depression, insomnia, nervousness, changes in cognitive performance (including abnormal thinking and confusion)	agitation, affect lability, euphoric mood, hallucinations, decreased libido, drug dependence (see section 4.4)		aggression, drug

System Organ Class	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)	Frequency not known
Nervous system disorders	somnolence, dizziness, headache	tremor, lethargy,	amnesia, convulsion, hypertonia, involuntary muscle contractions; hypaesthesia; speech disorder, syncope, paraesthesia, dysgeusia		Hyperalgesia, Central sleep apnea syndrome
Eye disorders			visual impairment, miosis		
Ear and labyrinth disorders			vertigo		
Cardiac disorders			palpitations (in the context of withdrawal syndrome)		
Vascular disorders			vasodilatation,	hypotension, orthostatic hypotension	
Respiratory, thoracic and mediastinal disorders		dyspnoea,	respiratory depression		Central sleep apnoea syndrome
Gastrointestinal disorders	constipation, nausea, vomiting	abdominal pain, diarrhoea, dry mouth, dyspepsia	dysphagia, flatulence, eructation, ileus		dental caries
Hepato-biliary disorders			increased hepatic enzymes		Cholestasis, biliary colic, sphincter of Oddi dysfunction
Skin and subcutaneous tissue disorders	pruritus	rash, hyperhidrosis	dry skin	urticaria	
Renal and urinary disorders			urinary retention		

System Organ Class	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)	Frequency not known
Reproductive system and breast disorders			erectile disfunction, hypogonadism		amenorrhoea
General disorders and administration site conditions		asthenia, fatigue	drug withdrawal syndrome, malaise, oedema, peripheral oedema, drug tolerance, thirst, chills		drug withdrawal syndrome neonatal

Drug Dependence
Repeated use of Oxycodone Hydrochloride can 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).

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 the Yellow Card Scheme at: Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms of overdose
Signs of overdose are pin-sized pupils (miosis), respiratory depression, drowsiness, muscle weakness, bradycardia, hypotension and pulmonary oedema. Stupor or coma and death may occur in more severe cases.

Treatment of oxycodone overdose
Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation. Respiration and circulation should be maintained and supported.

If necessary gastric lavage or activated charcoal can be administered

Naloxone is a specific antidote against opioid overdose, which can be given intravenously. The dose is adjusted according to severity and response (0.4 mg i.v. for adults and 0.01 mg/kg i.v. for children).

The infusion should be continued at a rate corresponding to the previous bolus dose and in accordance with the patient's response. As naloxone has a relatively short duration of action, the patient must be closely monitored until spontaneous respiration

is reliably re-established. Patients should be monitored for a further 24-48 hours due to risk of symptoms reoccurrence.

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.

Toxicity
Lethal dose for adults (without tolerance development) is stated to be approximately 60-100 mg orally. Concomitant use of drugs/medicines (e.g. alcohol or benzodiazepines) enhances the toxic effect.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgetics, natural opium alkaloids, ATC code: N02A A05

Oxycodone is an opioid analgesic with potent analgesic effect. Oxycodone is a full opioid agonist with no antagonistic properties and with morphine-like effect. Its main effect appears to be via mu-opioid receptors, but affinity for delta or kappa opiate receptors has also been demonstrated. Oral oxycodone is equipotent to oral morphine in a ratio of 1:2. The analgesic effect is due in part to altered pain experience and in part to an increase in the pain threshold. Oxycodone exerts its analgesic effect at various levels in the CNS.

Oxycodone inhibits the carbon dioxide stimulating effect on the respiratory centre in medulla oblongata and may cause respiratory depression.

Oxycodone stimulates dopamine receptors. Dopamine receptors stimulation in the "chemoreceptor trigger zone" of the medulla oblongata may trigger nausea and vomiting (see section 4.8).

Endocrine system
See section 4.4.

Gastrointestinal system
Opioids may induce spasm of the sphincter of Oddi.

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

Correlation between dose and oxycodone plasma concentration as well as between plasma concentration and expected opioid effects, has been demonstrated.

Absorption
The average absolute bioavailability is estimated to be approximately 50%.

Distribution
After absorption, the active substance is distributed throughout the body. Maximum plasma concentration is reached after approximately 1 hour and the effect lasts approximately 6 hours. About 45% is bound to plasma protein, and the volume of distribution at steady state is 2.6 L/kg.

The bioavalability (AUC) after a single 10 mg oxycodone oral solution dose is similar to oxycodone prolonged-release tablets. However, maximum plasma concentration is approximately 150 % higher and is achieved faster (in about 1 hour and 2-3 hours after administration, respectively).

Biotransformation
Oxycodone is metabolized in the gut and liver via CYP3A4 and CYP2D6 to noroxycodone, oxymorphone and noroxymorphone, which are subsequently glucuronidated. Noroxycodone and noroxymorphone are the major circulating metabolites. Noroxycodone is a weak mu-opioid agonist. Noroxymorphone is a potent mu-opioid agonist, but does not cross the blood-brain barrier to a significant extent. Oxymorphone is a potent mu-opioid agonist, but is present at very low concentrations after oxycodone administration. None of these metabolites are thought to contribute significantly to the analgesic effect of oxycodone.

Clearance is 0.8 L/min, and the half-life of Oxycodone Hydrochloride solution is approximately 3 hours.

Elimination
The active substance and its metabolites are excreted in both urine and faeces.
In urine, 45+ 21% are excreted as N-demethylated metabolites (including noroxycodone and noroxymorphone) and 11 + 6% of the dose as O-demethylated metabolites (including oxymorphone).

Special populations
The plasma concentration of oxycodone is only negligibly affected by age and is 15% higher in the elderly than in younger patients.

Female patients have on average up to 25% higher oxycodone plasma concentrations than men, based on body weight.

Patients with mild, moderate and severe hepatic impairment showed 1.2, 2.0 and 1.9 times increased plasma concentrations, respectively, compared with patients with normal hepatic function. The AUC values was increased on average 1.4, 3.2 and 3.2 times, respectively, compared with patients with normal liver function. The elimination half-lives of oxycodone were increased 1.1, 1.8 and 1.8 times, respectively, compared with patients with normal liver function.

Patients with mild, moderate and severe renal impairment showed 1.1, 1.4 and 1.7 times increased plasma concentrations, respectively, compared with patients with normal renal function. The AUC values were increased on average 1.5, 1.7 and 2.3 times, respectively, compared with patients with normal renal function. The elimination half-lives of oxycodone were increased 1.5, 1.2 and 1.4-fold, respectively, compared with patients with normal renal function.

5.3 Preclinical safety data

Reproductive toxicity

Oxycodone had no effect on fertility and early embryonic development in male and female rats at doses up to 8 mg/kg body weight, and did not cause malformations in rats at doses up to 8 mg/kg or in rabbits at doses up to 125 mg/kg body weight. However, when individual foetuses were used in statistical evaluation of rabbits, a dose-related increase in developmental abnormalities was observed (increased incidence of 27 presacral vertebrae, and extra pair of ribs). When these parameters were statistically evaluated using litters, only the incidence of 27 presacral vertebrae was increased and only in the 125 mg/kg group, a dose level that produced severe pharmacotoxic effects in the pregnant animals.

In a study of pre- and postnatal development in rats, reduced body weight was observed in the rat pups at 6 mg/kg/day, at doses that reduced maternal weight and nutrient intake (NOAEL 2 mg/kg body weight). There were no effects on physical, reflective, or sensory development parameters, or on behavioural or reproductive indicators.

Genotoxicity/carcinogenesis

As for other opioids, oxycodone was genotoxic in some in vitro assays (e.g. mouse lymphoma assay). No genotoxic effects were seen in the bacterial mutation test (Ames assay) or in the micronucleus test in mice.

No long-term carcinogenicity studies have been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Oxycodone Hydrochloride 10 mg/ml oral solution

Saccharin sodium

Sodium benzoate (E 211)
Citric acid monohydrate
Sodium citrate
Hydrochloric acid (for pH-adjustment)
Sodium hydroxide (for pH-adjustment)
Purified water
Sunset yellow FCF (E 110)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened: 24 months.
After first opening: 30 days.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Oxycodone Hydrochloride 10 mg/ml oral solution is packed in 125 mL type III amber glass bottles, sealed with a white polyethylene tamper evident childproof cap. The cap has an EPE liner wad. Each bottle contains 120 mL solution. A 2 ml oral syringe is also supplied.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Macarthys Laboratories Limited t/a Martindale Pharma

Bampton Road, Harold Hill

Romford, Essex,

RM3 8UG, UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 01883/0368

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/10/2021

10 DATE OF REVISION OF THE TEXT

14/05/2025