SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Oxypro 20 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 20 mg oxycodone hydrochloride corresponding to 17.9 mg oxycodone.

Excipients with known effect:

Each prolonged-release tablet contains 46 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet

Light pink, round, biconvex, prolonged-release tablets with a diameter of 6.9 – 7.3 mm and a height of 3.2 – 3.9 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Severe pain, which can be adequately managed only with opioid analgesics.

Oxypro is indicated in adults and adolescents aged 12 years and older.

4.2 Posology and method of administration

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a

strategy for ending treatment with oxycodone in order to minimise the risk of addiction and drug withdrawal syndrome (see sections 4.2 and 4.4).

Posology

The dosage should be adjusted to the intensity of pain and the patient's individual susceptibility.

Unless otherwise prescribed, the following general dosage recommendations apply for Oxypro:

Adults and adolescents (12 years of age and older)

Dose titration

The usual starting dose for an opioid naïve patient or patients with severe pain that cannot be controlled by weaker opioids is 10 mg oxycodone hydrochloride given at intervals of 12 hours.

Patients already receiving opioids may start treatment with higher dosages taking into account their experience with former opioid therapies.

Switching from morphine to oxycodone

The inter-patient variability requires that each patient be carefully adjusted to the dose that is appropriate for them. At the beginning of the change, a dose that is lower than the dose equivalent may be recommended. Patients who have received oral morphine prior to oxycodone therapy should receive their daily dose based on the following ratio: 10 mg oral oxycodone is equivalent to 20 mg oral morphine.

Because of individual differences in sensitivity for different opioids, it is recommended that patients should start conservatively with oxycodone hydrochloride prolonged-release tablets after conversion from other opioids, with 50-75% of the calculated oxycodone dose.

Dose adjustment

Some patients who receive Oxypro following a fixed schedule additionally need rapid release analgesics as rescue medication in order to control breakthrough pain. Oxypro prolonged-release tablets are not indicated for the treatment of breakthrough pain. The single dose of the rescue medication should amount to 1/4 of the equianalgesic daily dose of Oxypro and can be administered every 6 hours. Use of the rescue medication more than twice daily indicates that the dose of Oxypro prolonged-release tablets needs to be increased. The dose should not be adjusted more often than once every 1-2 days until a stable 12-hour dose is reached.

Following a dose increase from 10 mg to 20 mg taken every 12 hours, dose adjustments should be made in steps of approximately one third of the daily dose until the desired effect is obtained. The aim is a patient-specific 12 hourly dose maintaining adequate analgesia with tolerable undesirable effects and as little rescue medication as possible for as long as pain control is needed.

Even distribution (the same dose mornings and evenings) following a fixed schedule (every 12 hours) is appropriate for the majority of patients. For some patients it may be advantageous to distribute the doses unevenly.

In general, the lowest effective analgesic dose should be chosen.

For the treatment of non-malignant pain, a daily dose of 40 mg is generally sufficient; but higher dosages may be necessary. Patients with cancer-related pain require in general dosages of 80 to 120 mg, which in individual cases can be increased to up to 400 mg. If even higher

doses are required, the dose should be decided individually, balancing efficacy with the tolerance and risk of undesirable effects.

Duration of treatment

Oxypro should not be taken longer than necessary.

Elderly patients

Elderly patients without clinical manifestation of impaired liver or kidney function usually do not require dose adjustments.

Patients with hepatic or renal impairment

The treatment initiation should follow a conservative approach in these patients. The recommended adult starting dose 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 according to their clinical situation. Therefore, the lowest recommended dosage mentioned in this SmPC i.e., 10 mg, may not be suitable as a starting dose. In this case Oxypro 5 mg prolonged release tablets should be used.

Other risk patients

In patients with low body weight or in slow metabolisers who are also opioid-naive, the recommended starting dose should be reduced to half of the recommended starting dose for adults. Therefore the lowest recommended dosage mentioned in this SmPC i.e. 10 mg, may not be suitable as a starting dose. In this case Oxypro 5 mg prolonged release tablets should be used.

Children (under 12 years of age)

Oxycodone is not recommended for use in children below 12 years of age due to insufficient data on safety and efficacy.

Method of administration

For oral use.

Oxypro should be taken twice daily based on a fixed schedule at the dosage determined.

The prolonged-release tablets may be taken with or independent of meals with a sufficient amount of liquid. Oxypro must not be broken, divided, chewed or crushed.

Treatment goals and discontinuation

Before initiating treatment with Oxypro, 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).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1,
- severe respiratory depression with hypoxia and/or hypercapnia,
- severe chronic obstructive pulmonary disease,
- cor pulmonale.
- severe bronchial asthma.
- paralytic ileus.

4.4 Special warnings and precautions for use

Oxycodone must be administered with caution in patients with:

- Severely impaired respiratory function
- Sleep apnoea
- CNS depressants co-administration (see below and section 4.5)
- Monoamine oxidase inhibitors (MAOIs, see below and section 4.5)
- Tolerance, physical dependence, and withdrawal (see below)
- Psychological dependence [addiction], abuse profile and history of substance and/or alcohol abuse (see below)
- Debilitated elderly
- Head injury, intracranial lesions or increased intracranial pressure, reduced level of consciousness of uncertain origin
- Hypotension
- Hypovolemia
- Epileptic disorder or predisposition to convulsions
- Pancreatitis
- Obstructive and inflammatory intestinal diseases
- Impaired hepatic or renal function
- Myxoedema
- Hypothyroidism
- Addison’s disease
- Prostate hypertrophy
- Alcoholism
- Toxic psychosis
- Delirium tremens
- Constipation
- Disease of the biliary tract.

With the occurrence or suspicion of paralytic ileus, Oxypro should be immediately discontinued.

<u>Respiratory depression</u>

The primary risk of opioid excess is respiratory depression.

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.

Risks of concomitant use of sedative medicines such as benzodiazepines or related drugs:

Concomitant use of opioids including 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 Oxypro concomitantly with sedative 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. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

To avoid damage to the controlled release properties of the tablets the prolonged release tablets must be swallowed as a whole, not be chewed, divided, or crushed. The administration of divided, chewed, or crushed tablets leads to a rapid release and absorption of a potentially fatal dose of oxycodone (see section 4.9).

MAOIs

Oxycodone must be administered with caution in patients taking MAOIs or who have received MAOIs within the previous two weeks.

Tolerance

A comprehensive patient history should be taken to document concomitant medications, including over the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction.

The clinical need for analgesic treatment should be reviewed regularly.

Drug withdrawal syndrome

Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with Oxypro.

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

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

If women take this drug during pregnancy, there is a risk that their new-born infants will experience neonatal withdrawal syndrome.

Opioids are not the first line of treatment for chronic non-cancer pain, nor are they recommended as the only treatment. Opioids should be used as part of a comprehensive treatment program that includes other drugs and treatment modalities. Patients with chronic non-cancer related pain should be monitored for addiction development and abuse. In accordance with the pain guidelines, regular reviews should be made to ensure that treatment goals are being achieved. If appropriate, the dose is to be adjusted. In case the treatment objectives are not met, discontinuation of therapy should be considered.

Psychological dependence [addiction], abuse profile and history of substance and/or alcohol abuse

There is potential for development of psychological dependence [addiction] to opioid analgesics, including oxycodone. Oxycodone has an abuse profile similar to other strong opioid receptor agonists. Oxycodone may be abused by people with latent or manifest dependence disorders. There is potential for development of psychological dependence (addiction) after administration of opioid containing analgesics like Oxypro. Oxycodone should be used with particular care in patients with a history of alcohol and drug abuse.

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 Oxypro 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 Oxypro 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 other mental health disorders (e.g., major depression, anxiety and personality disorders).

Before initiating treatment with Oxypro 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.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

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

Hyperalgesia

Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

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

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.

Oxypro should not be used in children younger than 12 years of age because of safety and efficacy concerns.

Oxypro is not recommended for pre-operative use. Do not use Oxypro for acute post-operative pain owing to the increased risk of persistent post-operative opioid use (PPOU) and opioid-induced ventilatory impairment (OIVI).

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 a decrease in plasma cortisol and testosterone. Clinical symptoms may manifest from these hormonal changes.

Like all opioid containing preparations, Oxypro should be used with caution in patients undergoing bowel-surgery due to the known impairments of intestinal motility. Opioids should only be used after the doctor has verified the normalisation of the bowel function.

Oxypro consists of a polymer matrix and is intended for oral use only. In case of abusive parenteral venous injection, the tablet excipients (especially talc) may lead to serious, potentially fatal events.

The empty tablet matrix may be excreted visibly with the faeces.

The use of Oxypro may lead to positive results for doping controls. Use of Oxypro as a doping agent may become a health hazard.

This medicinal product contains lactose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma, and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4). Drugs affecting the central nervous system (CNS) include other opioids, gabapentinoids such as pregabalin, anxiolytics, sedatives hypnotics (including benzodiazepines), antipsychotics, antidepressants, phenothiazines and alcohol.

Alcohol may enhance the pharmacodynamic effects of Oxypro; concomitant use should be avoided.

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.

Agents with anticholinergic activity (e.g., antipsychotics, tricyclic antidepressants, antihistamines, antiemetics, muscle relaxants, medicinal products against Morbus Parkinson) may result in increased anticholinergic adverse effects (e.g., constipation, dry mouth, or dysfunction of urinary excretion).

Oxypro should be used with caution in patients administered MAO-inhibitors or who have received MAO-inhibitors during the last two weeks.

A clinically relevant decrease or increase of INR (International Normalized Ratio) has been observed in individual cases in simultaneous use of oxycodone and coumarin anticoagulants.

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. The following sections explain these interactions in more detail.

CYP3A4 inhibitors, such as macrolide antibiotics (e.g., clarithromycin, erythromycin and telithromycin), azolantifungals (e.g., ketoconazole, voriconazole, itraconazole, or posaconazole), protease inhibitors (e.g., boceprevir, ritonavir, indinavir, nelfinavir or 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 of CYP3A4 enzyme inhibition 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 or 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 of CYP3A4 enzyme inducer 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.

Children and adolescents

Drug interaction studies have only been conducted in adults.

4.6 Fertility, pregnancy and lactation

Use of this medicinal product should be avoided to the extent possible in patients who are pregnant or lactating.

Pregnancy

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal

symptoms in the neonate.

If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Breast-feeding

Administration to nursing women is not recommended as oxycodone may be secreted in breast milk and may cause respiratory depression in the infant.

Fertility

No human data on the effect of oxycodone on fertility are available. Studies in rats have not shown any effects upon fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Oxycodone may impair the ability to drive and use machines. This is particularly likely at the beginning of the treatment with Oxypro, after dose increase or change of product and if Oxycodone is combined with other CNS depressant agents.

With stable therapy, a general ban on driving a vehicle is not necessary.

The treating physician should decide on a case-by-case basis whether the patient is allowed to drive or operate machines.

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 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 under the influence of this medicine

However, you would not be committing an offence (called 'statutory defence') if:

- The medicine has been prescribed to treat a medical or dental problem and
- You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and;
- It was not affecting your ability to drive safely

Oxycodone may impair the ability to drive and use machines. This is particularly likely at the beginning of the treatment with Oxypro, after dose increase or change of product and if Oxycodone is combined with other CNS depressant agents. With stable therapy, a general ban on driving a vehicle is not necessary.

The treating physician should decide on a case-by-case basis whether the patient is allowed to drive or operate machines.

4.8 Undesirable effects

Due to its pharmacological properties, oxycodone can cause respiratory depression, miosis, bronchial spasms and spasms of the smooth muscles and can suppress the cough reflex.

The most frequently reported undesirable effects are nausea (especially at the beginning of the treatment) and obstipation.

The most serious adverse reaction, as with other opioids, is respiratory depression. This is most likely to occur in elderly, debilitated or opioid-intolerant patients.

In susceptible patients, opioids may cause a severe drop in blood pressure.

The frequency of adverse reactions is based on the following categories:

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

	Very common	**Common**	**Uncommon**	**Rare**	**Not known**
Infections and infestations				Herpes simplex.	
Immune system disorders:			Hypersen-sitivity reactions.		Anaphylactic reactions. anaphylactoid reaction.
Metabolism and nutrition disorders:		decreased appetite up to loss of appetite.	Dehydration.	Increased appetite.	
Psychiatric disorders:		Anxiety, confusional state, depression, decreased activity, restlessness, psychomotor hyperactivity,	Agitation, affect lability, euphoric mood, perception disorder (e.g. hallucinations, derealisation), decreased		Aggression. Drug dependence (see section 4.4)

		nervousness, insomnia, abnormal thinking.	libido		
Nervous system disorders:	Somnolence; sedation, dizziness; headache.	Tremor, lethargy.	Amnesia, convulsion (especially in patients with epilepsy or predisposition to convulsions), concentration impaired, migraine, hypertonia; involuntary muscle contractions, hypoaesthesia; abnormal coordination, speech disorder, syncope, paraesthesia, dysgeusia.		Hyperalgesia.
Eye disorders:			visual impairment; miosis.		
Ear and labyrinth disorders:			Hearing disorders, Vertigo.		
Cardiac disorders:			tachycardia, palpitations (in context of withdrawal syndrome).		
Vascular disorders:			Vasodilatation	Hypotension; orthostatic hypotension.	
Respiratory, thoracic and mediastinal disorders:		Dyspnoea.	Respiratory depression; Dysphonia, coughing.		Central sleep apnoea syndrome
Gastrointestinal disorders:	Constipation; nausea; vomiting.	abdominal pain; diarrhoea; dry mouth, hiccups, dyspepsia.	Oral ulcers; stomatitis; flatulence; eructation; dysphagia; ileus.	Malaena, dental disease, tooth disorders, gingival bleeding	Dental caries.
Hepatobiliary disorders:			Increased hepatic enzymes.		Cholestasis; biliary colic; Sphincter of Oddi dysfunction.
Skin and subcutaneous tissue disorders:	Pruritus.	Skin reaction/rash; hyperhidrosis.	Dry skin.	urticaria.	

Renal and urinary disorders:		Dysuria, Micturition urgency	Urinary retention.		
Reproductive system and breast disorders:			Erectile dysfunction, Hypogonadism.		Amenorrhoea.
General disorders and administration site conditions:		Asthenic conditions, fatigue.	Chills; withdrawal syndrome, pain (e.g., chest pain); malaise; oedema; peripheral oedema; drug tolerance; thirst. Drug withdrawal syndrome	Weight increase or decrease.	Drug withdrawal syndrome in new-borns.
Injury, poisoning and complications			Injuries from accidents.		

Children and adolescents

The frequency, nature and severity of adverse reactions in patients under 12 years of age are not expected to be different from those in adults and adolescents 12 years and above. For newborns born to mothers receiving oxycodone, see section 4.6.

Drug dependence

Repeated use of Oxypro 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, website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Patients should be informed of the signs and symptoms of overdose and to ensure that family and

friends are also aware of these signs and to seek immediate medical help if they occur.

Symptoms of intoxication:

Acute overdose with oxycodone may result in respiratory depression, somnolence, progressing up to stupor or coma, decreased skeletal muscle tone miosis, bradycardia and drop in blood pressure, pulmonary edema. circulatory failure and death. Toxic leukoencephalopathy has been observed with oxycodone overdose.

Therapy of intoxications:

The airways must be kept clear. Pure opioid antagonists such as naloxone are specific antidotes against symptoms of opioid overdose. Other supportive measures should be employed as needed.

Naloxone: e.g., 0.4-2 mg intravenous. Administration of single doses must be repeated depending on the clinical situation at intervals of 2 to 3 minutes. Intravenous infusion of 2 mg of naloxone in 500 ml isotonic saline or 5% dextrose solution (corresponding to 0.004 mg naloxone/ml) is possible. The rate of infusion should be adjusted to the previous bolus injections and the response of the patient.

Other supportive measures including artificial respiration, oxygen supply, administration of vasopressors and infusion therapy should be applied in the treatment of accompanying circulatory shock. Upon cardiac arrest or cardiac arrhythmias, cardiac massage or defibrillation may be indicated. Water and electrolyte balance should be maintained.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids

ATC-Code: N02A A05

Oxycodone shows an affinity to kappa, mu and delta opioid receptors in the brain, spinal cord and peripheral organs. Oxycodone acts at these receptors as an opioid agonist without an antagonistic effect. The therapeutic effect is mainly analgesic and sedative. Compared to non-retarded oxycodone, given alone or in combination with other substances, the Oxypro prolonged-release tablets provide pain relief for a markedly longer period without increased occurrence of undesirable effects.

Endocrine System

See section 4.4

Gastrointestinal System

Opioids may induce spasm of the sphincter of Oddi.

Paediatric population

Overall, safety data obtained with oral oxycodone in 9 clinical, pharmacodynamic and pharmacokinetic studies including a total of 629 infants and children (aged 2 months to 17 years), demonstrates that oral oxycodone is well tolerated in paediatric patients, with only minor adverse events affecting mainly the gastrointestinal and nervous system. The positive safety data obtained with oral oxycodone is confirmed by 9 studies performed with buccally, intramuscularly and intravenously administered oxycodone in a total of 1860 infants and children who also experienced only mild adverse events comparable to those observed with the use of oral oxycodone.

The dose of oxycodone administered parenterally to infants and children in clinical trials was in the range of 0.025 mg/kg to 0.1 mg/kg, with 0.1 mg/kg being the most frequently used dosage followed by 0.05 mg/kg. The dose of i.v. oxycodone was in the range of 0.025 mg/kg to 0.1 mg/kg, with 0.1 mg/kg being the most frequently used dosage followed by 0.05 mg/kg. The dose of i.m. oxycodone was in the range of 0.02 mg/kg to 0.1 mg/kg. The dose of orally administered oxycodone was in the range of 0.1 mg/kg (starting dose) to 1.24 mg/kg/day. Buccally administered dose of oxycodone was 0.1 mg/kg.

Overall, the adverse reactions in these studies of oxycodone in infants and children appear consistent with the known safety profile of oxycodone elaborated in the numerous clinical trials performed in adults. No new or unexpected safety signals were identified in these studies. All of these adverse events reported were consistent with the known safety profile of oxycodone as well as other comparable strong opioids. However, Oxypro is not recommended in children below 12 years of age due to insufficient data on safety and efficacy.

5.2 Pharmacokinetic properties

Absorption:

To avoid damage to the controlled release properties of the tablets, the prolonged-release tablets must be swallowed as a whole, not be chewed, divided or crushed. The administration of divided, chewed or crushed tablets leads to a rapid release and absorption of a potentially fatal dose of oxycodone.

The relative bioavailability of prolonged-release oxycodone is comparable to the conventional oral oxycodone, but the former achieves maximal plasma concentrations at about 3 hours rather than 1 to 1.5 hours. Peak and trough concentrations of the prolonged-release and the immediate-release oxycodone are similar when dosed 12 hourly and 6 hourly, respectively with the same total daily dose.

The absolute bioavailability of oxycodone amounts to about two thirds relative to parenteral drug. Across the 5-80 mg dose range of prolonged release oxycodone tablets, linearity of plasma concentrations was demonstrated in terms of rate and extent of absorption. Following ingestion of a high-fat meal, peak plasma concentrations may be increased relative to dosing in the fasting state.

Distribution

In *steady state*, the volume of distribution of oxycodone amounts to 2.6 l/kg and plasma protein binding to 38-45%; the elimination half-life to 4 to 6 hours and plasma clearance to 0.8 l/min. The elimination half-life of oxycodone from prolonged-release tablets is 4.5 hours with a steady state that is reached on average after one day.

Metabolism:

Oxycodone is metabolized in the intestine and liver via CYP3A4 and CYP2D6 to noroxycodone, oxymorphone and noroxymorphone, which are then glucuronidated. It is assumed that none of these metabolites contribute significantly to the pain relieving effects of oxycodone. In vitro studies indicate that therapeutic doses of cimetidine are unlikely to significantly affect the formation of noroxycodone. Quinidine reduces the production of oxymorphone in humans, but the pharmacodynamic of oxycodone remains essentially unaffected. The contribution of the metabolites to the overall pharmacodynamic effect is insignificant.

Elimination:

Oxycodone and its metabolic products are excreted via urine and faeces. Oxycodone crosses the placenta and is found in breast milk. Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis.

5.3 Preclinical safety data

Reproductive and Developmental Toxicology

Oxycodone had no effect on fertility or early embryonic development in male and female rats at doses as high as 8 mg/kg/day. Also, oxycodone did not induce any malformation in rats at doses as high as 8 mg/kg/day or in rabbits at doses as high as 125 mg/kg/day. Dose-related increases in developmental variations (increased incidence of extra (27) presacral vertebrae and extra pairs of ribs) were observed in rabbits when the data for individual foetuses were analysed. However, when the same data were analysed using litters as opposed to individual foetuses, there was no dose-related increase in developmental variations, although the incidence of extra presacral vertebrae remained significantly higher in the 125 mg/kg/day group compared to the control group. Since this dose level was associated with severe pharmacotoxic effects in the pregnant animals, the foetal findings may have been a secondary consequence of severe maternal toxicity. In a prenatal and postnatal development study in rats, maternal body weight and food intake parameters were reduced for doses ≥2 mg/kg/day compared to the control group. Body weights were lower in the F1 generation from maternal rats in the 6 mg/kg/day dosing group. There were no effects on physical, reflexological, or sensory developmental parameters or on behavioural and reproductive indices in the F1 pups (the NOEL of the F1 pups was 2 mg/kg/day based on body weight effects seen at 6 mg/kg/day).

There were no effects on the F2 generation at any dose in the study.

Genotoxicity

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

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. The doses were limited by opioid related pharmacological effects of oxycodone.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Ammonio Methacrylate Copolymer Type B
Povidone (K29/32)
Talc
Triacetin
Stearyl alcohol
Magnesium stearate
Tablet coating:
Hypromellose
Talc
Macrogol 400
Titanium dioxide (E171)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Child resistant PVC/PVdC-Aluminium blisters with 10, 14, 20, 25, 28, 30, 40, 50, 56, 60, 98 and 100 prolonged-release tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Ridge Pharma Limited
Merlin House
Brunel Road, Theale,
Reading, RG7 4AB,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 48804/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/09/2018

10 DATE OF REVISION OF THE TEXT

17/02/2025