SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ixyldone 10 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains to 10 mg oxycodone hydrochloride corresponding to 9 mg oxycodone.

Excipients with known effect:

Each prolonged-release tablet contains 56 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet

White, 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 sufficiently managed only with opioid analgesics.
Ixyldone 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 hydrochloride in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4).

The dosage depends on the intensity of pain and the patient's individual susceptibility. to the treatment. The following general dosage recommendations apply:

Adults and adolescents 12 years of age and older
Dose titration and adjustment
In general, the initial dose for opioid naïve patients is 10 mg oxycodone hydrochloride given at intervals of 12 hours.

Some patients may benefit from a starting dose of 5 mg oxycodone hydrochloride to minimize the incidence of adverse reactions.

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

For doses not realisable/practicable with this strength other strengths of this medicinal product are available.

According to well-controlled clinical studies 10-13 mg oxycodone ¬hydrochloride correspond to approximately 20 mg morphine sulphate, both in the prolonged-release formulation.

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

Some patients who take Ixyldone following a fixed schedule need rapid release analgesics as rescue medication in order to control breakthrough pain. Ixyldone is not indicated for the treatment of acute pain and/or breakthrough pain. The single dose of the rescue medication should amount to 1/6 of the equianalgesic daily dose of Ixyldone. Use of the rescue medication more than twice daily indicates that the dose of Ixyldone needs to be increased. The dose should not be adjusted more often than once every 1-2 days until a stable twice daily administration has been achieved.

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. The aim is a patient-specific dosage which, with twice daily administration, allows for adequate analgesia with tolerable undesirable effects and as little rescue medication as possible as long as pain therapy is needed.

Even distribution (the same dose mornings and evenings) following a fixed schedule (every 12 hours) is appropriate for the majority of the 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 may require 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.

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

Risk patients
Risk patients, for example patients with low body weight or slow metabolism of medicinal products, should initially half the recommended adult dose if they are opioid naïve.
Therefore, the lowest recommended dosage, i.e. 10 mg, may not be suitable as a starting dose.
Dose titration should be performed in accordance with the individual clinical situation.

Patients with renal or hepatic impairment
The dose 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.

Children under 12 years of age
Oxycodone has not been studied in children younger than 12 years of age. The safety and efficacy of Ixyldone have not been demonstrated and the use in children younger than 12 years of age is therefore not recommended.

Method of administration
For oral use.
Ixyldone 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. Ixyldone must be swallowed whole, not chewed, divided or crushed. Taking chewed, divided or crushed Ixyldone tablets may lead to a rapid release and absorption of a potentially fatal dose of oxycodone.

Ixyldone should not be taken with alcoholic beverages.

Treatment goals and discontinuation
Before initiating treatment with Ixyldone, 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).

Duration of treatment
Ixyldone should not be taken longer than necessary.

If opioid therapy is no longer indicated, it may be advisable to reduce the daily dose gradually in order to prevent symptoms of a withdrawal syndrome.

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

Respiratory depression is the most significant risk induced by opioids.

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

Caution must be exercised when administering oxycodone to elderly debilitated patients, in patients with severe impairment of pulmonary function, impaired hepatic or renal function, patients with myxoedema, hypothyroidism, Addison's disease, prostatic hypertrophy, toxic psychosis, alcoholism, delirium tremens, known opioid dependence, disease of the biliary tract, pancreatitis, obstructive and inflammatory bowel disorders, head injuries (due to risk of increased intracranial pressure), hypotension, hypovolemia, epileptic disorder or predisposition to convulsions or patients taking benzodiazepines, or other CNS depressant (including alcohol) or MAO inhibitors.

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

Risk from 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 Ixyldone concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. 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).

Long-term use of Ixyldone may cause the development of tolerance which leads to the use of higher doses in order to achieve the desired analgesic effect. Prolonged use of Ixyldone may lead to physical dependence. Withdrawal symptoms may occur following abrupt discontinuation of therapy. If therapy with oxycodone is no longer required, it may be advisable to reduce the daily dose gradually in order to avoid the occurrence of withdrawal syndrome.

Withdrawal symptoms may include yawning, mydriasis, lacrimation, rhinorrhoea, tremor, hyperhidrosis, anxiety, agitation, convulsions, insomnia or myalgia.

Opioids, similar to other strong analgesics, are not the first-line treatment for chronic noncancer 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, adjust dosage as necessary and decide on continuation or discontinuation of therapy. The dosage has to be adjusted if necessary and a decision has to be taken on the continuation or termination of therapy.

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

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.

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

Ixyldone is not recommended for pre-operative use or within the first 12 – 24 hours post operatively. Depending on the type and extent of the surgical procedure, the selected anaesthetic procedure, the other concomitant medication and the patient's individual condition, the timing of the postoperative use of Ixyldone must be determined after careful consideration of the benefit and risk in each individual case.

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, Ixyldone 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.
Ixyldone 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 Ixyldone may lead to positive results for doping controls. Use of Ixyldone 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.
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 Ixyldone 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 Ixyldone 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 Ixyldone 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 behavior (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.

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.

Hepatobiliary disorders
Ixyldone 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.

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 Ixyldone; 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).

Ixyldone 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, 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 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 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 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

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 should be monitored for respiratory depression. Withdrawal symptoms may be observed in the newborn of mothers undergoing treatment with oxycodone.

Breast-feeding

Oxycodone may be excreted in breast milk and may cause sedation and respiratory depression in the breastfed child. Oxycodone should, therefore, not be used in breastfeeding mothers.

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

This medicine can impair the ability to drive and use machines. This is particularly likely at the beginning of the treatment with Oxycodone, 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 Ixyldone, 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 (cannot be estimated from available data)**
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.	Increase appetite	
Psychiatric disorders:		Anxiety, confusional state, depression,de creased activity, restlessness, psychomotor hyperactivity, nervousness, insomnia, abnormal thinking.	Agitation, affect lability, euphoric mood, perception disorder (e.g. hallucinations, derealization), decreased libido, drug dependence (see section 4.4)		Aggression
Nervous system disorders:	Somnolence; sedation, dizziness; headache.	Tremor, lethargy.	Amnesia, convulsion (especially in patients with epilepsy or predisposition to convulsions), concentratio n impaired, migraine, hypertonia; involuntary muscle contractions, hypoaesthesia; abnormal coordination, speech disorder, syncope, paraesthesia, dysgeusia.		Hyperalgesia.
Eye disorders:			visual impairment; miosis		
Ear and labyrinth			Hearing disorders,		

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 dysfuntion
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.	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 over. For new borns, born to mothers receiving oxycodone, see section 4.6.

Drug dependence
Repeated use of Ixyldone 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

Symptoms and 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 oedema, 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 nonretarded oxycodone, given alone or in combination with other substances, the 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 populationOverall, 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 studies 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, oxycodone 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 chewed, divided 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 plasma concentrations of prolonged-release and immediate-release oxycodone are similar when dosed 12 and 6 hours, 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; 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 steady state that is reached on average after one day.

Metabolism:
Oxycodone is metabolized in the intestine and liver via the CYP3A4 and CYP2D6 to noroxycodone and 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 formation of noroxycodone. Quinidine reduces the production of oxymorphone in humans but, the pharmacodynamic of oxycodone remain 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 and 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 $\geq$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 was 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 positive with S9

metabolic activation at the 24-hour time point but not 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 dispersion 30%

Povidone (K29/32)

Talc

Triacetin

Stearyl alcohol

Magnesium stearate

Tablet coating:

Hypromellose

Talc

Macrogol 400

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.

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

Morningside Healthcare Ltd

Unit C, Harcourt Way

Leicester, LE19 1WP

UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 20117/0306

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/02/2025

10 DATE OF REVISION OF THE TEXT

21/02/2025