Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dancex SR 40 mg Prolonged-Release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 40 mg oxycodone hydrochloride equivalent to 35.9 mg oxycodone.

Excipient with known effect
Each prolonged-release tablet contains 43.2 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.
Yellow, round, biconvex film coated prolonged-release tablets, diameter: 6.8 mm – 7.4 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Dancex SR prolonged-release tablets are indicated in adults and adolescents aged 12 years and older.

4.2 Posology and method of administration

Posology
The dose should be adjusted to the intensity of the pain and the sensitivity of the individual patient.
For doses not practicable with this medicinal product other strengths are available. The correct dosage per individual patient is the lowest dose which sufficiently controls the pain with no or tolerable side effects.

Adults
Starting dose
The usual starting dose for an opioid-naïve patient or patients presenting with severe pain uncontrolled by weaker opioids is 10 mg oxycodone hydrochloride per dose at intervals of 12 hours.

Patients already receiving opioids may start treatment with higher doses of Dancex SR taking into account their experience with former opioid therapies.

Conversion from morphine
Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.
Initially, a lower-than-equivalent dose may be advisable. Patients receiving oral morphine before oxycodone therapy should have their daily dose based on the following ratio: 10 mg of oral oxycodone is equivalent to 20 mg of oral morphine.
Dose adjustment
Some patients who take Dancex SR prolonged-release tablets following a fixed schedule need rapid-release analgesics as rescue medication in order to control breakthrough pain. Dancex SR is not intended for therapy of breakthrough pain. The single dose of the rescue medication should amount to 1/6 of the equianalgesic daily dose of Dancex SR prolonged-release tablets. Use of the rescue medication more than twice daily indicates that the dose of Dancex SR 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-hourly administration has been achieved.

Following a dose increase from 10 mg to 20 mg oxycodone hydrochloride 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 that will maintain adequate analgesia with acceptable undesirable effects and as little rescue medication as possible as long as pain control is necessary.

Even administration (the same dose in the morning and in the evening) following a fixed schedule (every 12 hours) is appropriate for the majority of the patients. For some patients it may be beneficial to arrange 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 oxycodone hydrochloride is generally sufficient; but higher doses may be necessary.
Patients with cancer-related pain may require doses of 80 to 120 mg oxycodone hydrochloride, which in individual cases can be increased to up to 400 mg.

Duration of administration
Oxycodone should not be used for longer than necessary.

Elderly
A dose adjustment is usually not necessary in elderly patients without clinically manifest impairment of hepatic or renal function.

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 of oxycodone hydrochloride orally in opioid-naïve patients), and each patient should be titrated to adequate pain control according to their clinical situation. In such cases oxycodone hydrochloride 5 mg prolonged-release tablets can be used.

Other patients at risk
Patients with low body weight or slow metabolisers, who are opioid-naïve should initially receive half the dose usually recommended for adults. Therefore, 10 mg of oxycodone hydrochloride per dose at intervals of 12 hours may not be suitable as a starting dose and in such cases oxycodone hydrochloride 5 mg prolonged-release tablets can be used.

Paediatric population
Opioids must only be used for appropriate indications and prescribed by a specialist experienced in managing severe pain in children, with careful assessments of the benefits and risks.

Adolescents (from 12 years and older)
If a prolonged release formulation is required as initial treatment for opioid naive patients, the usual starting dose is 10 mg oxycodone hydrochloride per dose at 12-hour intervals. Considering the guidance for other special populations, some paediatric patients may benefit from a starting dose of 5 mg to minimize the incidence of adverse reactions.

Patients already receiving opioids may be initiated on higher Dancex SR doses depending on their previous opioid experience.

Children under 12 years of age
The safety and efficacy of oxycodone in children below 12 years of age has not yet been established.

Method of administration
Oral use.

Dancex SR prolonged-release tablets should be taken twice daily based on a fixed schedule at the dose determined.

The prolonged-release tablets may be taken with or without food with sufficient liquid.

Dancex SR prolonged-release tablets must not be divided, broken, crushed or chewed.

Treatment goals and discontinuation
Before initiating treatment with Dancex SR, 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
- elevated carbon dioxide levels in the blood (hypercarbia)
- severe chronic obstructive lung disease
- cor pulmonale
- severe bronchial asthma
- paralytic ileus

4.4 Special warnings and precautions for use

Caution should be exercised in

- severely impaired respiratory function
- elderly or debilitated patients,
- sleep apnoea
- in patients taking sedative medicinal products such as benzodiazepines or other centrally depressant active substances including alcohol (see also section 4.5)
- tolerance, physical dependence and withdrawal (see below)
- in patients taking MAO inhibitors or within 2 weeks of discontinuation of their use (see also section 4.5)
- psychological dependence [addiction], abuse profile and history of substance and/or alcohol abuse (see below)
- impaired hepatic or renal function,
- patients with myxedema,
- hypothyroidism,
- Addison's disease,
- prostatic hypertrophy,
- toxic psychosis,
- alcoholism, delirium tremens,
- diseases of the biliary tract,
- constipation
- pancreatitis,
- obstructive and inflammatory bowel disorders,
- head injury (due to risk of increased intracranial pressure),
- hypotension,
- hypovolaemia,
- epilepsy or predisposition to convulsions,

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

Hepatobiliary disorders

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

Respiratory depression

The major 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.

Risk from concomitant use of sedative medicinal products such as benzodiazepines or related medicinal products

Concomitant use of oxycodone and sedative medicinal products such as benzodiazepines or related medicinal products may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicinal products should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe oxycodone concomitantly with sedative medicinal products, 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 prolonged-release tablets, the Dancex SR prolonged-release tablets must be swallowed whole and must not be divided, broken, crushed or chewed. The administration of broken, crushed or chewed tablets leads to 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 MAO inhibitors or who

have received MAO inhibitors within the last two weeks.

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 Dancex SR 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 Dancex SR 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 Dancex SR 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.

Tolerance and dependence

The patient may develop tolerance to the active substance with chronic use and require progressively higher doses to maintain pain control. Prolonged use of this medicinal product may lead to physical dependence and a withdrawal syndrome may occur upon abrupt cessation of therapy. When a patient no longer requires therapy with oxycodone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. Withdrawal symptoms may include yawning, mydriasis, lacrimation, rhinorrhoea, tremor, hyperhidrosis, anxiety, agitation, convulsions, insomnia or myalgia.

Non-malignant pain

Opioids are not first-line therapy for chronic non-malignant pain, nor are they recommended as the

only treatment. Opioids should be used as part of a comprehensive treatment programme involving

other medications and treatment modalities. Patients with chronic non-malignant pain should be

monitored for signs of dependence or substance abuse.

Alcohol

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

Hyperalgesia

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

Surgical procedures

Dancex SR prolonged-release tablets are not recommended for pre-operative use or within the first 12-24 hours post-operatively. Depending on the type and extent of surgery, the anaesthetic procedure selected, other co-medication and the individual condition of the patient, the exact timing for initiating postoperative treatment with Dancex SR depends on a careful risk-benefit assessment for each individual patient.

As with all opioid preparations, oxycodone-containing medicinal 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.

Endocrine system

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

Paediatric population

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

Abuse of oral pharmaceutical forms by parenteral administration can be expected to result in serious adverse events, which may be fatal.

Empty matrix (tablets) may be seen in the stool.

Dancex SR contains lactose

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Anti-Doping Warning: Athletes must be aware that this medicinal product may cause a positive reaction to sports doping control tests. Use of Dancex SR as a doping agent may become a health hazard.

4.5 Interaction with other medicinal products and other forms of interaction

Sedative medicinal products such as benzodiazepines or related medicinal products:
The concomitant use of opioids with sedative medicinal products such as benzodiazepines or related medicinal products 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).

CNS depressant active substances are for example sedatives (including benzodiazepines), gabapentinoids such as pregabalin, anxiolytics, hypnotics, phenothiazines, neuroleptics, antipsychotics, antidepressants or other opioids.

Alcohol may enhance the pharmacodynamic effects of Dancex SR; 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 dose may need to be reduced in patients using these medicinal products.

Medicinal products with anticholinergic effects (e.g. tricyclic antidepressants, antihistamines, antiemetics, psychotropic medicinal products, muscle relaxants, medicinal products against Morbus Parkinson) may intensify the anticholinergic adverse drug reactions of oxycodone, such as constipation, dry mouth or dysfunction of urinary excretion.

Oxycodone 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 Normalised 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 medicinal products or dietary elements. In the following paragraphs these interactions are explained in detail.

CYP3A4 inhibitors, such as macrolide antibiotics (e.g. clarithromycin, erythromycin or telithromycin), azol-antifungals (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 as follows:

- 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 induction are provided as follows:

- 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.

Medicinal products that inhibit CYP2D6 activity, such as paroxetine or quinidine, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations.

Paediatric population

Interaction studies have only been performed 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 breast-feeding.

Pregnancy
There are limited data from the use of oxycodone in pregnant women. Oxycodone passes the placenta. 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 into breast milk and may cause sedation and respiratory depression in the breast-fed infant. Therefore, oxycodone should not be used in breast-feeding mothers.

Fertility
Human data are not 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 initiation of treatment with oxycodone, after dose increase or product rotation and if oxycodone is combined with other CNS depressant agents. Patients stabilised on a specific dose will not necessarily be restricted. Therefore, the physician should decide whether the patient is allowed to drive or use machinery.

4.8 Undesirable effects

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

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

Respiratory depression is the chief hazard of an opioid overdose and occurs most commonly in elderly or debilitated patients. Opioids may cause severe hypotension in susceptible individuals.

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

Infections and infestations
Rare: herpes simplex

Immune system disorders
Uncommon: hypersensitivity
Not known: anaphylactic reactions, anaphylactoid reactions

Metabolism and nutrition disorders
Common: decreased appetite up to loss of appetite
Uncommon: dehydration
Rare: increased appetite

Psychiatric disorders
Common: anxiety, confusional state, depression, decreased activity, restlessness, psychomotor hyperactivity, nervousness, insomnia, abnormal thinking
Uncommon: agitation, affect lability, euphoric mood, perception disturbances such as hallucinations, derealisation; decreased libido, drug dependence (see section 4.4)
Not known: aggression

Nervous system disorders
Very common: somnolence, sedation, dizziness, headache
Common: tremor, lethargy
Uncommon: amnesia, convulsion (especially in persons with epileptic disorder or predisposition to convulsions), concentration impaired, migraine, hypertonia, involuntary muscle contractions, hypoaesthesia, coordination disturbances, speech disorder, syncope, paraesthesia, dysgeusia
Not known: hyperalgesia

Eye disorders
Uncommon: visual impairment, miosis

Ear and labyrinth disorders

Uncommon: hearing impaired, vertigo

Cardiac disorders
Uncommon: tachycardia, palpitations (in the context of withdrawal syndrome)

Vascular disorders
Uncommon: vasodilatation
Rare: hypotension, orthostatic hypotension

Respiratory, thoracic and mediastinal disorders
Common: dyspnoea, bronchospasm
Uncommon: respiratory depression, dysphonia, cough
Not known: central sleep apnoea syndrome

Gastrointestinal disorders
Very common: constipation, vomiting, nausea
Common: abdominal pain, diarrhoea, dry mouth, hiccups, dyspepsia
Uncommon: mouth ulceration, stomatitis, dysphagia, flatulence, eructation, ileus
Rare: melaena, tooth disorders, gingival bleeding
Not known: dental caries

Hepatobiliary disorders
Uncommon: increased hepatic enzymes
Not known: cholestasis, biliary colic, sphincter of Oddi dysfunction

Skin and subcutaneous tissue disorders
Very common: pruritus
Common: skin reaction/rash, hyperhidrosis
Uncommon: dry skin
Rare: urticaria

Renal and urinary disorders
Common: dysuria, micturition urgency
Uncommon: urinary retention

Reproductive system and breast disorders
Uncommon: erectile dysfunction, hypogonadism
Not known: amenorrhoea

General disorders and administration site conditions
Common: asthenic conditions, fatigue
Uncommon: chills, drug withdrawal syndrome, pain (e.g. chest pain), malaise, oedema, peripheral oedema, drug tolerance, thirst
Rare: weight increase, weight decrease
Not known: drug withdrawal syndrome neonatal

Injury, poisoning and procedural complications
Uncommon: injuries from accidents

Drug dependence
Repeated use of Dancex SR 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).

Paediatric population
The frequency, type and severity of adverse reactions in adolescents (12 to 18 years of age) appear similar to those in adults (see section 5.1).

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 national reporting system:
HPRA Pharmacovigilance; website: www.hpra.ie.

4.9 Overdose

Symptoms of intoxication
Acute overdose with oxycodone can be manifested by respiratory depression, somnolence progressing up to stupor or coma, hypotonia, miosis, bradycardia, hypotension, lung oedema and death.

Toxic leukoencephalopathy has been observed with oxycodone overdose.

Therapy of intoxication
A patent airway must be maintained. The pure opioid antagonists such as naloxone are specific antidotes against symptoms from opioid overdose. Other supportive measures should be employed as needed.

Opioid antagonists: Naloxone (e.g. 0.4 to 2 mg intravenously). Administration should be repeated at 2 to 3 minute intervals as necessary, or by an infusion of 2 mg in 500 ml of 0.9% sodium chloride or 5% dextrose (0.004 mg/ml naloxone). The infusion should be run at a rate related to the previously administered bolus doses and should be in accordance with the patient's response.

Other supportive measures: including artificial ventilation, oxygen, vasopressors, and fluid infusions in the management of circulatory shock accompanying overdose. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation. Fluid and electrolyte metabolism should be maintained.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics; Natural opium alkaloids
ATC code: N02AA05

Oxycodone shows an affinity to kappa, mu and delta opioid receptors in the brain, spinal cord and peripheral organs. It acts at these receptors as an opioid agonist without an antagonistic effect. The therapeutic effect is mainly analgesic and sedative. Compared to rapid-release oxycodone, given alone or in combination with other substances, oxycodone 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, the safety data obtained with oxycodone in clinical, pharmacodynamic and pharmacokinetic studies demonstrate that oxycodone is generally well tolerated in paediatric patients with adverse events affecting mainly the gastrointestinal and nervous system. Adverse events were consistent with the known safety profile of oxycodone as well as of other comparable strong opioids (see section 4.8 Undesirable effects).
There are no clinical trial data on longer term use in children aged 12 to 18 years.

5.2 Pharmacokinetic properties

Absorption
The absorption of oxycodone from Dancex SR prolonged-release tablets could be calculated biphasic with an initially relatively rapid half-life of 0.6 hours accounting for a minority of the active substance, and a slower half-life of 6.9 hours accounting for the majority of the active substance.

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

The relative bioavailability of prolonged-release oxycodone is comparable to that of rapid-release oxycodone with maximum plasma concentrations being achieved after approximately 3 hours after intake of the prolonged-release tablets compared to 1 to 1.5 hours. Peak plasma concentrations and oscillations of the concentrations of oxycodone from the prolonged-release and rapid-release formulations are comparable when given at the same daily dose at intervals of 12 and 6 hours, respectively.

A fat-rich meal before the intake of the tablets does not affect the maximum concentration or the extent of absorption of oxycodone.

The absolute bioavailability of oxycodone is approximately two thirds relative to parenteral administration.

Distribution
In *steady state,* thevolume 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 to 5 hours with *steady state* values being achieved after a mean of 1 day.

Biotransformation
Oxycodone is metabolised to noroxycodone and oxymorphone in the intestine and liver via the P450 cytochrome system, as well as to several glucuronide conjugates. *In vitro* studies suggest that therapeutic doses of cimetidine probably have no relevant effect on the formation of noroxycodone. In man, quinidine reduces the production of oxymorphone while the pharmacodynamic properties of oxycodone remain largely unaffected. The contribution of the metabolites to the overall pharmacodynamic effect is irrelevant.

Elimination
Oxycodone and its metabolites 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.

Linearity/non-linearity
Across the 10-80 mg dose range of prolonged-release oxycodone tablets linearity of plasma concentrations was demonstrated in terms of rate and extent of absorption.

5.3 Preclinical safety data

Reproductive and Developmental Toxicology
Oyxcodone showed no effect on fertility and early embryonic development in male and female rats in doses of up to 8 mg/kg body weight and induced no malformation in rats in doses of up to 8 mg/kg and in rabbits in doses of 125 mg/kg bodyweight. However, in rabbits, when individual fetuses were used in statistical evaluation, a dose related increase in developmental variations was observed (increased incidences of 27 presacral vertebrae, extra pairs 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 on pre- and postnatal development in rats F1 body weights were lower at 6 mg/kg/d when compared to body weights of the control group at doses which reduced maternal weight and food intake (NOAEL 2 mg/kg body weight). There were neither effects on physical, reflexological, and sensory developmental parameters nor on behavioural and reproductive indices.
There were no effects on F2 generation.

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 aberrations 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
Hydrogenated castor oil
Copovidone
Behenoyl macrogolglycerides
Lactose monohydrate
Magnesium stearate
Maize starch
Colloidal anhydrous silica
Triglycerides, medium-chain

Tablet coating
Microcrystalline cellulose
Hypromellose
Stearic acid
Titanium dioxide (E 171)

Iron oxide yellow (E 172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years
Shelf life after first opening:
Bottle: 6 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

The prolonged-release tablets are packed in child resistant PVC/PE/PVDC-aluminium blisters consisting of a white opaque PVC/PE/PVDC laminated foil and an aluminium foil or in HDPE–bottles, closed withchild resistant closure cap of polypropylene (PP) or HDPE, with or without a desiccant capsule of polyethylene (PE), containing silica gel as desiccant.

Pack sizes:
Blister: 10, 20, 28, 30, 40, 50, 56, 60, 100 and 112 prolonged-release tablets
Bottle: 50 and 100 prolonged-release tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/143/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24th September 2012

Date of last renewal: 8th August 2017

10 DATE OF REVISION OF THE TEXT

July 2025