Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Oxycodone hydrochloride Rowex 20 mg Hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 20 mg oxycodone hydrochloride, equivalent to 17.93 mg oxycodone.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard

Hard capsules of 14.4 mm in length with a light pink body imprinted with 20 and a brown cap imprinted with OXY.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Oxycodone hydrochloride Rowex is indicated in adults and adolescents of 12 years and older.

4.2 Posology and method of administration

Posology
The dose depends on the intensity of pain and the patient's individual response to the treatment. In general, the lowest effective analgesic dose should be chosen. The following general dose recommendations apply:

Adults and adolescents (12 years of age and older)
Starting dose
In general, the initial dose for opioid naïve patients is 5 mg oxycodone hydrochloride at intervals of 6 hours. Patients already receiving opioids may start treatment with higher doses (under consideration of their experience with former opioid therapies). In patients who have received oral morphine prior to oxycodone therapy, the daily dose is based on the fact that 10 to 13 mg of oral oxycodone hydrochloride are equivalent to approximately 20 mg of oral morphine sulphate. It should be noted that this is a guideline value for the required dose of hard capsules containing oxycodone hydrochloride. Treatment should be titrated to the adequate dose on an individual basis for each patient due to the inter-individual variability.

Dose adjustment
The dose should be increased with increasing pain intensity. If necessary, it should be carefully titrated, as frequent as once a day if necessary, to achieve adequate pain relief. The dose interval can simultaneously be reduced to 4 hours. The correct dose for an individual patient is the dose which controls the pain and is well tolerated throughout the dosing period.
A daily dose of up to 400 mg is adequate for most patients. However, some patients may require higher doses.

Oxycodone hydrochloride Rowex can be used to treat breakthrough pain in patients being given a prolonged-release formulation of oxycodone. The dose should be adjusted to the patient's requirements; however, the general rule is that a single dose should be equivalent to 1/8 - 1/6 of the daily dose of the prolonged-release formulation. The rescue medication must not be used more frequently than every 6 hours.
If the on-demand medication is needed more frequently than twice a day, a dose increase of the prolonged-release oxycodone preparation may be necessary. The goal is a patient-specific dose with the prolonged-release oxycodone preparation given twice a day, which provides adequate analgesia with tolerable undesirable effects and as little as possible rescue medication for as long as pain therapy is necessary.

Duration of use

Oxycodone hydrochloride Rowex should not be taken longer than necessary.

Elderly patients
The lowest possible dose should be administered after careful titration for pain control.

Patients with renal or hepatic impairment
The dose initiation should follow a conservative approach in these patients. The recommended starting dose for adults should be reduced by 50% (e.g. a total daily oral dose of 10 mg in patients not previously treated with opioids) and the dose should be titrated individually in each patient according to the clinical situation until adequate pain control is achieved. Therefore, the lowest recommended dose, i.e. 5 mg at intervals of 6 hours, may not be suitable as a starting dose.

Other patients at risk
Patients with low body weight or slow metabolisers should initially be given half the dose usually recommended for adults if they are opioid naïve.
Therefore, the lowest recommended dose, i.e. 5 mg at intervals of 6 hours, may not be suitable as a starting dose.

Paediatric population
The safety and efficacy of oxycodone in children under 12 years of age have not been established. Therefore, Oxycodone hydrochloride Rowex is not recommended for children under 12 years of age.

Method of administration
Oral use.
Oxycodone hydrochloride Rowex should be taken at the defined dose according to a fixed timetable, but not more frequently than every 4 to 6 hours.
For the treatment of breakthrough pain, Oxycodone hydrochloride Rowex should be taken as required.
The hard capsules can be taken with or without meals with plenty of liquid.
The medicinal product should not be taken with alcoholic beverages.

Treatment goals and discontinuation
Before initiating treatment with Oxycodone hydrochloride Rowex, 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 (COPD)
- Cor pulmonale
- Severe bronchial asthma
- Paralytic ileus

4.4 Special warnings and precautions for use

The major risk of opioid excess is respiratory depression.

Caution should be exercised in

- elderly or debilitated patients,
- patients with severe impairment of pulmonary function, impaired hepatic or renal function,
- patients with myxedema,
- hypothyroidism,
- Addison's disease,
- prostatic hypertrophy,

- toxic psychosis,
- alcoholism, delirium tremens, known opioid dependence,
- diseases of the biliary tract,
- pancreatitis,
- obstructive and inflammatory bowel disorders,
- head injury (due to risk of increased intracranial pressure),
- hypotension,
- hypovolaemia,
- epilepsy or predisposition to convulsions,
- in patients taking sedative medicinal products such as benzodiazepines or other centrally depressant active substances including alcohol (see also section 4.5)
- in patients taking MAO inhibitors or within 2 weeks of discontinuation of their use (see also section 4.5)

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

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).

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.

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.

Opioid Use Disorder (abuse and dependence)

Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as oxycodone.

Repeated use of Oxycodone hydrochloride Rowex may lead to Opioid Use Disorder (OUD). A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of Oxycodone hydrochloride Rowex 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 Oxycodone hydrochloride Rowex 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.

Oxycodone hydrochloride Rowex is indicated for oral use only. The contents of the capsule can trigger severe and potentially fatal events in cases of misuse involving parenteral venous injection.

Alcohol

Concomitant use of alcohol and Oxycodone hydrochloride Rowex may increase the undesirable effects of oxycodone such as somnolence or respiratory depression; concomitant use should be avoided.

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.

Surgical procedures
Oxycodone hydrochloride Rowex should only be used with caution before surgery and during the first 12-24 hours after surgery. 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 Oxycodone hydrochloride Rowex depends on a careful risk-benefit assessment for each individual patient.

Medicinal products containing oxycodone should only be used with caution after 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.

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

Oxycodone hydrochloride Rowex contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

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), hypnotics, phenothiazines, neuroleptics, antidepressants, antihistamines, antiemetics or other opioids.

Alcohol may enhance the pharmacodynamic effects of Oxycodone hydrochloride Rowex; 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, carbamazepin, 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.

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 only 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 medicinal products.

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 machines.

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.

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 responses, 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

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 Oxycodone hydrochloride Rowex 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 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 sodium chloride 9 mg/ml (0.9%) or glucose 50 mg/ml (5%) (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.

Endocrine system
See section 4.4.

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

5.2 Pharmacokinetic properties

Absorption
The absolute bioavailability for oxycodone is 42-87% after oral administration compared with parenteral application; maximum plasma concentration is achieved after 1 to 1.5 hours.

Distribution
The distribution volume for oxycodone at steady state is 2.6 l/kg and plasma protein binding is 38-45%.

Biotransformation
Oxycodone is metabolised to noroxycodone (CYP3A4) and oxymorphone (CYP2D6), as well as to several glucuronide conjugates, in the intestines and liver via the P450 cytochrome system. These metabolites make no relevant contribution to the overall pharmacodynamic effect.

Elimination
The plasma elimination half-life is 4 to 6 hours. Oxycodone and its metabolites are excreted in both urine and faeces. Oxycodone also crosses the placenta and may be detected in breast milk.

Linearity/non-linearity
The increase in plasma concentration is linear in the dose range of 5 to 20 mg after administration of the capsule formulation of oxycodone hydrochloride.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity.

Oxycodone 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.

Long-term studies on carcinogenicity have not been performed.

Oxycodone shows a clastogenic potential in *in vitro* assays. No similar effects were observed, however, under *in vivo* conditions, even at toxic doses. The results indicate that the mutagenic risk of oxycodone to humans at therapeutic concentrations may be ruled out with adequate certainty.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Content of capsule:
Microcrystalline cellulose
Magnesium stearate
Capsule shell:
Gelatine
Sodium laurilsulfate
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172)
Indigo carmine (E132)

Capsule printing ink:
Shellac
Iron oxide black (E172)
Potassium hydroxide (to adjust the pH)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Child-resistant white PVC/PVdC/Al/PE/paper perforated unit dose blisters.

Pack sizes: 20x1, 30x1, 50x1 and 100x1 hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/286/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8th December 2017

10 DATE OF REVISION OF THE TEXT

April 2023