Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dancex SR 5 mg Prolonged-Release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 5 mg oxycodone hydrochloride equivalent to 4.5 mg oxycodone.

Excipient with known effect :
Each prolonged-release tablet contains 34.0 mg lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet
Blue, round, biconvex prolonged-release tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of administration

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 and older
Dose titration and adjustement
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 to minimize the incidence of side effects.

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 medicinal product other strengths and medicinal products 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 Dancex SR prolonged-release tablets after conversion from other opioids, with 50-75% of the calculated oxycodone dose.

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 prolonged-release tablets are 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 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 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.

Method of administration
For oral use.

Dancex SR prolonged-release tablets 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. Dancex SR prolonged release tablets must be swallowed whole, not chewed.

Duration of administration
Dancex SR prolonged-release tablets should not be taken longer than necessary. If long-term treatment is necessary due to the type and severity of the illness careful and regular monitoring is required to determine whether and to what extent treatment should be continued.
Discontinuation of treatment
When a patient no longer requires therapy with oxycodone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

Children under 12 years of age
Dancex SR prolonged-release tablets are not recommended for children under 12 years of age.

Older people
The lowest dose should be administered with careful titration to pain control.
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.

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

Dancex SR prolonged-release tablets should not be used with alcoholic beverages.

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
- severe chronic obstructive lung disease
- cor pulmonale
- severe bronchial asthma
- paralytic ileus

4.4 Special warnings and precautions for use

The major risk of opioid excess is respiratory depression.

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).

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.

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.

Abuse and misuse

Oxycodone has an abuse profile similar to other strong agonist opioids. Oxycodone may be sought and abused by people with latent or manifest addiction disorders. There is potential for development of psychological dependence (addiction) to opioid analgesics, including oxycodone. Dancex SR should be used with particular care in patients with a history of alcohol and drug abuse.

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

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).

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.

Alcohol

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

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

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 interactions

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 Dancex SR; concomitant use should be avoided.

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 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

Breastfeeding
Oxycodone may be secreted in breast milk and may cause respiratory depression in the newborn. Oxycodone should, therefore, not be used in breastfeeding mothers.

4.7 Effects on ability to drive and use machines

Oxycodone can impair alertness and reactivity to such an extent that the ability to drive and operate machinery is affected or ceases altogether. With stable therapy, a general ban on driving a vehicle is not necessary. The treating physician must assess the individual situation.

4.8 Undesirable effects

Oxycodone can cause respiratory depression, miosis, bronchial spasms and spasms of the smooth muscles and can suppress the cough reflex.

The adverse reactions considered at least possibly related to treatment are listed below by system organ class and absolute frequency. Frequencies are defined as:

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)

Blood and lymphatic system disorders
Rare: lymphadenopathy

Endocrine disorders
Uncommon: syndrome of inappropriate antidiuretic hormone secretion

Immune system disorders:
Uncommon: hypersensitivity.
Not known: anaphylactic responses.

Metabolism and nutrition disorders
Common: decreased appetite
Uncommon: dehydration

Psychiatric disorders
Common: anxiety, confusional state, depression, nervousness and insomnia, abnormal thinking
Uncommon: agitation, affect lability, euphoric mood, hallucinations, decreased libido, drug dependence (see section 4.4), hyperacousis
Not known: aggression

Nervous system disorders
Very common: somnolence, dizziness, headache
Common: tremor
Uncommon: amnesia, convulsion, hypertonia, both increased and decreased muscle tone, involuntary muscle contractions, hypaesthesia, coordination disturbances, speech disorder, syncope, paraesthesia, dysgeusia,
Rare: muscle spasm
Not known: hyperalgesia

Eye disorders
Uncommon: visual impairment, miosis

Ear and labyrinth disorders
Uncommon: vertigo

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

Vascular disorder
Uncommon: vasodilatation.
Rare: hypotension, orthostatic hypotension.

Respiratory, thoracic and mediastinal disorders
Common: dyspnoea, brochospasm
Uncommon: respiratory depression, increased coughing, pharyngitis, rhinitis, voice changes

Gastrointestinal disorders
Very common: constipation, nausea, vomiting
Common: dry mouth, abdominal pain, diarrhoea, dyspepsia
Uncommon: dysphagia, oral ulcers, gingivitis, stomatitis, flatulence, eructation, ileus
Rare: gum bleeding, increased appetite, tarry stool, tooth staining and damage
Not known: dental caries

Hepato-biliary disorders
Uncommon: increased hepatic enzymes
Not known: cholestasis, biliary colic

Skin and subcutaneous tissue disorders
Very common: pruritus
Common: skin eruptions including rash, in rare cases increased photosensitivity, in isolated cases exfoliative dermatitis, hyperhidrosis
Uncommon: dry skin, herpes simplex
Rare: urticaria

Renal and urinary disorders
Common: increased urge to urinate
Uncommon: urinary retention
Rare: haematuria

Reproductive system and breast disorders
Uncommon: erectile dysfunction
Not known: amenorrhoea
General disorders and administration site conditions
Common: asthenic conditions
Uncommon: chills, accidental injuries, pain (e.g. chest pain), oedema, peripheral oedema, migraine, drug withdrawal syndrome, malaise, drug tolerance, thirst
Rare: weight changes (increase or decrease), cellulitis

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 preferably through the online reporting option accessible from the IMB homepage. A downloadable report form is also accessible from the IMB website, which may be completed manually and submitted to the IMB via 'freepost', in addition to the traditional post-paid 'yellow card' option.

FREEPOST
Pharmacovigilance Section
Irish Medicines Board
Kevin O'Malley House
Earlsfort Centre
Earlsfort Terrace
Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: http://www.imb.ie/
email: imbpharmacovigilance@imb.ie

4.9 Overdose

Symptoms and intoxication

Miosis, respiratory depression, somnolence, reduced skeletal muscle tone and drop in blood pressure. In severe cases circulatory collapse, stupor, coma, bradycardia and non-cardiogenic lung oedema may occur; abuse of high doses of strong opioids such as oxycodone can be fatal.

Therapy of intoxications

Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation

In the event of overdosing intravenous administration of an opiate antagonist (e.g. 0.4-2 mg intravenous naloxone) may be indicated. 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.

Gastric lavage can be taken into consideration. Consider activated charcoal (50 g for adults, 10 -15 g for children), if a substantial amount has been ingested within 1 hour, provided the airway can be protected. It may be reasonable to assume that late administration of activated charcoal may be beneficial for prolonged release preparations; however there is no evidence to support this.

For speeding up the passage a suitable laxative (e.g. a PEG based solution) may be useful.

Supportive measures (artificial respiration, oxygen supply, administration of vasopressors and infusion therapy) should, if necessary, be applied in the treatment of accompanying circulatory shock. Upon cardiac arrest or cardiac arrhythmias cardiac massage or defibrillation may be indicated. If necessary, assisted ventilation as well as maintenance of water and electrolyte balance.

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.

5.2 Pharmacokinetic properties

Absorption
The relative bioavailability of Oxycodone Hydrochloride prolonged-release tablets 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 tablets must not be crushed or chewed as this leads to rapid oxycodone release due to the damage of the prolonged release properties.

Distribution
The absolute bioavailability of oxycodone is approximately two thirds relative to parenteral administration. 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 values being achieved after a mean of 1 day.

Biotransformation
Oxycodone is metabolised in the intestine and liver via the P450 cytochrome system to noroxycodone and oxymorphone 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.

Linearity/non-linearity
The 5, 10 and 20 mg prolonged-release tablets are bioequivalent in a dose proportional manner with regard to the amount of active substance absorbed as well as comparable with regard to the rate of absorption.

5.3 Preclinical safety data

In animal studies oyxcodone had 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 malformations 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.
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 Hydrochloride prolonged-release tablets to humans at therapeutic concentrations may be ruled out with adequate certainty.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Hydrogenated castor oil
Copovidone
Behenoyl polyoxyglycerides
Lactose monohydrate
Magnesium stearate
Maize starch
Colloidal anhydrous silica
Triglycerides, medium-chain

Tablet coating
Microcrystalline cellulose
Hypromellose
Stearic acid
Titanium dioxide (E 171)
Indigo carmine aluminium salt

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

HDPE-Twist-off containers
Shelf life after first opening: 6 months

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Child resistant PVC/PE/PVDC-aluminium blisters consisting of a white opaque PVC/PE/PVDC laminated foil and an aluminium foil

Alternatively the prolonged-release tablets are packed in HDPE-Twist-off containers, closed with child resistant Twist-off cap (HDPE or PP) with or without a desiccant capsule of polyethylene (PE), containing silica gel as desiccant.

Pack sizes:
7, 10, 14, 20, 28, 30, 50, 56, 60, 98, 100, 100x1 and 112 prolonged-release tablets in blister
100 and 250 prolonged-release tablets in HDPE bottle

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Newtown

Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/143/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristion: 1st August 2008

Date of last renewal: 28th April 2013

10 DATE OF REVISION OF THE TEXT

October 2019