

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 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 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 oxycodone hydrochloride 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
- acute abdomen, delayed gastric emptying
- elevated carbon dioxide levels in the blood

4.4 Special warnings and precautions for use

Dancex SR prolonged-release tablets have not been studied in children younger than 12 years of age. The safety and efficacy of the tablets have not been demonstrated and the use in children younger than 12 years of age is therefore not recommended.

Caution is required in elderly or debilitated patients, in patients with severe impairment of lung, liver or kidney function, myxoedema, hypothyroidism, Addison's disease, adrenocortical insufficiency, intoxication psychosis (e.g. alcohol), prostatic hypertrophy, alcoholism, known opioid dependence, delirium tremens, pancreatitis, inflammatory bowel disorders, diseases of the biliary tract, biliary or ureteric colic, conditions with increased brain pressure, disturbances of circulatory regulation (e.g. hypotension, hypovolaemia), epilepsy or seizure tendency and in patients taking MAO inhibitors.

As with all opioid preparations, oxycodone 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.

Patients with severe hepatic impairment should be closely monitored.

Respiratory depression is the most significant risk induced by opioids and is most likely to occur in elderly or debilitated patients. The respiratory depressant effect of oxycodone can lead to increased carbon dioxide concentrations in blood and hence in cerebrospinal fluid. In predisposed patients opioids can cause severe decrease in blood pressure.

Long-term use of Dancex SR prolonged-release tablets can cause the development of tolerance which leads to the use of higher doses in order to achieve the desired analgesic effect. There is a cross-tolerance to other opioids. Chronic use of Dancex SR prolonged-release tablets can cause 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 a withdrawal syndrome. Withdrawal symptoms may include yawning, mydriasis, lacrimation, rhinorrhoea, tremor, hyperhidrosis, anxiety, agitation, convulsions and insomnia.

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.

Dancex SR prolonged-release tablets have a primary dependence potential. However, when used as directed in patients with chronic pain the risk of developing physical or psychological dependence is markedly reduced or needs to be assessed in a differentiated manner. There are no data available on the actual incidence of psychological dependence in chronic pain patients. In patients with a history of alcohol and drug abuse the medicinal product must be prescribed with special care.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Dancex SR prolonged-release tablets.

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

In case of abusive parenteral venous injection the tablet excipients may lead to necrosis of the local tissue, granulomas of the lung or other serious, potentially fatal events. To avoid damage to the controlled release properties of the tablets the prolonged release tablets must not be chewed or crushed. The administration of chewed or crushed tablets leads to rapid release and absorption of a potentially fatal dose of oxycodone (see section 4.9).

Concomitant use of alcohol and Dancex SR prolonged-release tablets may increase the undesirable effects of Dancex SR prolonged-release tablets; concomitant use should be avoided.

Dancex SR prolonged-release tablets is not recommended for pre-operative use or within the first 12-24 hours postoperatively.

4.5 Interaction with other medicinal products and other forms of interaction

Central nervous system depressants (e.g. sedatives, hypnotics, phenothiazines, neuroleptics, anaesthetics, antidepressants, muscle relaxants, antihistamines, antiemetics) and other opioids or alcohol can enhance the adverse reactions of oxycodone, in particular respiratory depression. MAO-inhibitors causes CNS-excitation or depression associated with hypertensive or hypotensive crisis (see section 4.4). Oxycodone should be used with caution in patients administered MAO-inhibitors or who have received MAO-inhibitors during the last two weeks (see section 4.4).

Alcohol may enhance the pharmacodynamic effects of Dancex SR prolonged-release tablets; concomitant use should be avoided.

Anticholinergics (e.g. neuroleptics, antihistamines, antiemetics, antiparkinson medicinal products) can enhance the anticholinergic undesirable effects of oxycodone (such as constipation, dry mouth or micturition disorders).

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.

CYP3A4 inhibitors, such as macrolide antibiotics (e.g. clarithromycin, erythromycin and telithromycin), azol-antifungals (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 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, carbamazepin, 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 John's Wort, a CYP3A4 inducer, administered as 300 mg three times a day for fifteen days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 50% lower (range 37-57%).
- Rifampicin, a CYP3A4 inducer, administered as 600 mg once-daily for seven days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 86% lower

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

Clinically relevant changes in International Normalized Ratio (INR) in both directions have been observed in individuals if coumarin anticoagulants are co-applied with Dancex SR prolonged release tablets.

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 ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Very rare ($\leq 1/10,000$)

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), hyperacusis

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), cellulitisReporting 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

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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: Natural opium alkaloids
ATC-Code: N02A A05

Oxycodone shows an affinity to kappa, mu and delta opioid receptors in the brain and spinal cord. 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, the prolonged-release tablets provide pain relief for a markedly longer period without increased occurrence of undesirable effects.

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 oxycodone 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

This medicinal product does not require any special storage conditions.

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
Bantry
Co. Cork

8 MARKETING AUTHORISATION NUMBER

PA0711/143/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st August 2008

Date of last renewal: 28th April 2013

10 DATE OF REVISION OF THE TEXT

September 2013