

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dancex SR Plus 40 mg/20 mg Prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 40 mg of oxycodone hydrochloride (equivalent to 36mg oxycodone) and 20 mg of naloxone hydrochloride (as 21.8 mg naloxone hydrochloride dihydrate, equivalent to 18 mg naloxone).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet

Pink, oblong, biconvex prolonged-release tablet with break scores on both side, with a length of 14.2 mm, a width of 6.7 mm and a height of 3.6 - 4.6 mm. The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

The opioid antagonist naloxone is added to counteract opioid-induced constipation by blocking the action of oxycodone at opioid receptors locally in the gut.

Dancex SR Plus is indicated in adults.

4.2 Posology and method of administration

Posology

Analgesia

The analgesic efficacy of Dancex SR Plus is equivalent to oxycodone hydrochloride prolonged-release formulations.

The dose should be adjusted to the intensity of pain and the sensitivity of the individual patient. Unless otherwise prescribed, Dancex SR Plus should be administered as follows:

Adults

The usual starting dose for an opioid naive patient is 10 mg/5 mg of oxycodone hydrochloride/ naloxone hydrochloride at 12 hourly intervals.

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

Dancex SR Plus 5 mg/2.5 mg is intended for dose titration when initiating opioid therapy and individual dose adjustment.

The maximum daily dose of Dancex SR Plus is 160 mg oxycodone hydrochloride and 80 mg naloxone hydrochloride. The maximum daily dose is reserved for patients who have previously been maintained on a stable daily dose and who have become in need of an increased dose. Special attention should be given to patients with compromised renal function and patients with mild hepatic impairment if an increased dose is considered. For patients requiring higher doses, administration of supplemental prolonged-release oxycodone hydrochloride at the same time intervals should be considered, taking into account the maximum daily dose of 400 mg prolonged-release oxycodone hydrochloride. In the case of supplemental oxycodone hydrochloride dosing, the beneficial effect of naloxone hydrochloride on bowel function may be impaired.

After complete discontinuation of therapy with oxycodone/naloxone with a subsequent switch to another opioid a worsening of the bowel function can be expected.

Some patients taking these prolonged-release tablets according to a regular time schedule require immediate-release analgesics as "rescue" medication for breakthrough pain. Dancex SR Plus is a prolonged-release formulation and therefore not intended for the treatment of breakthrough pain. For the treatment of breakthrough pain, a single dose of "rescue medication" should approximate one sixth of the equivalent daily dose of oxycodone hydrochloride. The need for more than two "rescues" per day is usually an indication that the dose of Dancex SR Plus requires upward adjustment. This adjustment should be made every 1-2 days in steps of 5 mg/2.5 mg twice daily, or where necessary 10 mg/5 mg, oxycodone hydrochloride/naloxone hydrochloride until a stable dose is reached. The aim is to establish a patient-specific twice daily dose that will maintain adequate analgesia and make use of as little rescue medication as possible for as long as pain therapy is necessary.

Dancex SR Plus is taken at the determined dose twice daily according to a fixed time schedule. While symmetric administration (the same dose mornings and evenings) subject to a fixed time schedule (every 12 hours) is appropriate for the majority of patients, some patients, depending on the individual pain situation, may benefit from asymmetric dosing tailored to their pain pattern. In general, the lowest effective analgesic dose should be selected.

In non-malignant pain therapy, daily doses of up to 40 mg/20 mg oxycodone hydrochloride/naloxone hydrochloride are usually sufficient, but higher doses may be needed.

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

Analgesia

Elderly patients

As for younger adults the dose should be adjusted to the intensity of the pain or RLS symptoms and the sensitivity of the individual patient.

Patients with impaired hepatic function

A clinical trial has shown that plasma concentrations of both oxycodone and naloxone are elevated in patients with hepatic impairment. Naloxone concentrations were affected to a higher degree than oxycodone (see section 5.2). The clinical relevance of a relative high naloxone exposure in hepatic impaired patients is yet not known. Caution must be exercised when administering oxycodone/naloxone to patients with mild hepatic impairment (see section 4.4). In patients with moderate and severe hepatic impairment Dancex SR Plus is contraindicated (see section 4.3).

Patients with impaired renal function

A clinical trial has shown that plasma concentrations of both oxycodone and naloxone are elevated in patients with renal impairment (see section 5.2). Naloxone concentrations were affected to a higher degree than oxycodone. The clinical relevance of a relative high naloxone exposure in renal impaired patients is yet not known. Caution should be exercised when administering oxycodone/naloxone to patients with renal impairment (see section 4.4).

Paediatric population

The safety and efficacy of Dancex SR Plus in children aged below 18 years has not been established. No data are available.

Method of administration

Oral use.

These prolonged-release tablets are taken in the determined dose twice daily in a fixed time schedule.

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

Dancex SR Plus must be swallowed whole with sufficient liquid, and must not be divided, broken chewed or crushed (see section 4.4).

Treatment goals and discontinuation (Analgesia)

Before initiating treatment with Dancex SR Plus, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines.

During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with oxycodone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

Duration of use

Dancex SR Plus should not be administered for longer than absolutely necessary.

4.3 Contraindications

- Hypersensitivity to the active substances 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
- Non-opioid induced paralytic ileus
- Moderate to severe hepatic impairment

4.4 Special warnings and precautions for use

Caution must be exercised when administering oxycodone/naloxone to patients with:

- Severely impaired respiratory function
- Sleep apnoea
- CNS depressants co-administration (see below and section 4.5)
- Monoamine oxidase inhibitors (MAOIs, see below and section 4.5)
- Tolerance, physical dependence and withdrawal (see below)
- Psychological dependence [addiction], abuse profile and history of substance and/or alcohol abuse (see below)
- elderly or infirm
- head injury (due to the risk of increased intracranial pressure)
- epileptic disorder or predisposition to convulsions
- hypotension
- hypertension
- pancreatitis
- mild hepatic impairment
- renal impairment
- opioid-induced paralytic ileus
- myxoedema
- hypothyroidism
- Addison's disease (adrenal cortical insufficiency)
- prostate hypertrophy
- toxic psychosis
- alcoholism
- delirium tremens
- cholelithiasis
- pre-existing cardiovascular diseases

Respiratory depression

The major risk of opioid excess is respiratory depression.

Sleep-related breathing disorders

This medicinal product 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 manner. 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 product

Concomitant use of oxycodone/naloxone 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/naloxone 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).

MAO Inhibitors

Dancex SR Plus must be administered with caution in patients taking MAO Inhibitors or who have received MAO Inhibitors within the previous two weeks.

Hepatic or renal impairment

Caution must also be exercised when administering oxycodone/naloxone to patients with mild hepatic or renal impairment. Careful medical monitoring is particularly necessary for patients with severe renal impairment.

Diarrhoea

Diarrhoea may be considered as a possible effect of naloxone.

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 Plus can 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 Plus 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 Plus 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.

Discontinuation of treatment and withdrawal syndrome

Chronic administration of oxycodone/naloxone may lead to physical dependence. Withdrawal symptoms may occur upon the abrupt cessation of therapy. If therapy with oxycodone/naloxone is no longer required, it may be advisable to reduce the daily dose gradually in order to avoid the occurrence of withdrawal syndrome (see section 4.2).

Dancex SR Plus is not suitable for the treatment of withdrawal symptoms.

There is limited clinical experience with oxycodone/naloxone in the long-term treatment of RLS beyond 1 year (see section 4.2).

In order not to impair the prolonged-release characteristic of the prolonged-release tablets, the tablets must not be divided, broken, chewed or crushed. Breaking, chewing or crushing the prolonged-release tablets for ingestion leads to a faster release of the active substances and the absorption of a possibly fatal dose of oxycodone (see section 4.9).

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

Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore, a reduction of the dose or termination of therapy may be considered. Because of possible additive effects, caution should be advised when patients are taking other sedating medicinal products in combination with oxycodone/naloxone (see sections 4.5 and 4.7).

Alcohol

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

Paediatric population

Studies have not been performed on the safety and efficacy of oxycodone/naloxone in children and adolescents below the age of 18 years. Therefore, their use in children and adolescents under 18 years of age is not recommended.

Cancer

There is no clinical experience in patients with cancer associated to peritoneal carcinomatosis or with sub-occlusive syndrome in advanced stages of digestive and pelvic cancers. Therefore, the use of oxycodone/naloxone in this population is not recommended.

Surgery

Oxycodone/naloxone is 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 post-operative treatment with oxycodone/naloxone depends on a careful risk-benefit assessment for each individual patient.

Abuse

Any abuse of Dancex SR Plus by drug addicts is strongly discouraged.

If abused parenterally, intranasally or orally by individuals dependent on opioid agonists, such as heroin, morphine, or methadone, oxycodone/naloxone is expected to produce marked withdrawal symptoms - because of the opioid receptor antagonist characteristics of naloxone - or to intensify withdrawal symptoms already present (see section 4.9).

These tablets are intended for oral use only. Abusive parenteral injections of the prolonged-release tablet constituents (especially talc) can be expected to result in local tissue necrosis and pulmonary granulomas or may lead to other serious, potentially fatal undesirable effects.

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.

Long-term treatment

In patients under long-term opioid treatment, the switch to oxycodone/naloxone can initially provoke withdrawal symptoms or diarrhoea.

Hyperalgesia

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

Hepatobiliary disorders

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

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

Dancex SR Plus contains sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per prolonged-release tablet, 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).

Substances which depress the CNS include, but are not limited to: other opioids, gabapentinoids such as pregabalin, anxiolytics, hypnotics, sedatives (including benzodiazepines), antidepressants, antipsychotics, antihistamines and antiemetics.

Dancex SR Plus must be administered with caution in patients taking MAO Inhibitors or who have received MAO inhibitors within the previous two weeks.

Concomitant administration of oxycodone with anticholinergics or medications with anticholinergic activity (e.g. tri-cyclic antidepressants, antihistamines, anti-psychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects.

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.

Alcohol may enhance the pharmacodynamic effects of Dancex SR Plus; concomitant use should be avoided.

Clinically relevant changes in International Normalised Ratio (INR or Quick-value) in both directions have been observed in individuals if oxycodone and coumarin anticoagulants are co-applied.

Oxycodone is metabolised primarily via the CYP3A4 pathways and partly via the CYP2D6 pathway (see section 5.2). The activities of these metabolic pathways may be inhibited or induced by various co-administered medicinal products or dietary elements. Dancex SR Plus doses may need to be adjusted accordingly.

CYP3A4 inhibitors, such as macrolide antibiotics (e.g. clarithromycin, erythromycin, telithromycin), azole-antifungal agents (e.g. ketoconazole, voriconazole, itraconazole, posaconazole), protease inhibitors (e.g. ritonavir, indinavir, nelfinavir, saquinavir), cimetidine and grapefruit juice may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. A reduction in the dose of Dancex SR Plus and subsequent re-titration may be necessary.

CYP3A4 inducers, such as rifampicin, carbamazepine, phenytoin and St. John's Wort, may induce the metabolism of oxycodone and cause increased clearance of the active substance, resulting in a decrease in oxycodone plasma concentrations. Caution is advised, and further titration may be necessary to reach an adequate level of symptom control.

Theoretically, medicinal products that inhibit CYP2D6 activity, such as paroxetine, fluoxetine and quinidine, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. Concomitant administration with CYP2D6 inhibitors had an insignificant effect on the elimination of oxycodone and also had no influence on the pharmacodynamic effects of oxycodone.

In vitro metabolism studies indicate that no clinically relevant interactions are to be expected between oxycodone and naloxone. The likelihood of clinically relevant interactions between paracetamol, acetylsalicylic acid or naltrexone and the combination of oxycodone and naloxone in therapeutic concentrations is minimal.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no clinical data from the use of oxycodone/naloxone in pregnant women and during childbirth. Limited clinical data on the use of oxycodone during pregnancy in humans reveal no evidence of an increased risk of congenital abnormalities. For naloxone, insufficient clinical data on exposed pregnancies are available. However, systemic exposure of the women to naloxone after use of Dancex SR Plus is relatively low (see section 5.2).

Both oxycodone and naloxone pass into the placenta. Animal studies have not been performed with oxycodone and naloxone in combination (see section 5.3). Animal studies with oxycodone or naloxone administered as single active substances have not revealed any teratogenic or embryotoxic effects.

Long-term administration of oxycodone during pregnancy may lead to withdrawal symptoms in the newborn. If administered during childbirth, oxycodone may evoke respiratory depression in the newborn.

Dancex SR Plus should only be used during pregnancy if the benefit outweighs the possible risks to the unborn child or neonate.

Breast-feeding

Oxycodone passes into the breast milk. A milk-plasma concentration ratio of 3.4:1 was measured and oxycodone effects in the suckling infant are therefore conceivable. It is not known whether naloxone also passes into the breast milk. However, after use of Dancex SR Plus systemic naloxone levels are very low (see section 5.2).

A risk to the suckling child cannot be excluded in particular following intake of multiple doses of Dancex SR Plus by the breast-feeding mother.

Breast-feeding should be discontinued during treatment with Dancex SR Plus.

Fertility

No human data on the effect of oxycodone and naloxone on fertility are available. In rats, there was no effect on mating or fertility with Dancex SR Plus treatment (see Section 5.3).

4.7 Effects on ability to drive and use machines

Oxycodone/Naloxone has moderate influence on the ability to drive and use machines. This is particularly likely at the beginning of treatment with Dancex SR Plus, after dose increase or product rotation and if Dancex SR Plus is combined with other CNS depressant agents. Patients stabilised on a specific dose will not necessarily be restricted. Therefore, patients should consult with their physician as to whether driving or the use of machinery is permitted.

Patients being treated with Dancex SR Plus and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved (see also sections 4.4 and 4.5).

4.8 Undesirable effects

The following frequencies are the basis for assessing undesirable effects:

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 $< 1/10,000$

Not known cannot be estimated from the available data

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Undesirable effects in the treatment of pain

System organ class MedDRA	Common	Uncommon	Rare	Not known
Immune system disorders	-	Hypersensitivity	-	-
Metabolism and nutrition disorders	Decreased appetite up to loss of appetite			
Psychiatric disorders	Insomnia	Abnormal thinking Anxiety Confusion Depression Libido decreased	Drug dependence	Euphoric mood Hallucination Nightmares Aggression

		Nervousness Restlessness		
Nervous system disorders	Dizziness Headache Somnolence	Convulsions ¹ Disturbance in attention Dysgeusia Speech disorder Syncope Tremor Lethargy		Paraesthesia Sedation
Eye disorders		Visual impairment		
Ear and labyrinth disorders	Vertigo			
Cardiac disorders		Angina pectoris ² Palpitations	Tachycardia	
Vascular disorders	Hot flush	Blood pressure decreased Blood pressure increased		
Respiratory, thoracic and mediastinal disorders		Dyspnoea Rhinorrhoea Cough	Yawning	Respiratory depression Central sleep apnoea syndrome
Gastrointestinal disorders	Abdominal pain Constipation Diarrhoea Dry mouth Dyspepsia Vomiting Nausea Flatulence	Abdominal distention	Tooth disorder	Eructation
Hepatobiliary disorders		Hepatic enzymes increased Biliary colic		
Skin and subcutaneous tissue disorders	Pruritus Skin reactions Hyperhidrosis			
Musculoskeletal and connective tissue disorders		Muscle spasms Muscle twitching, Myalgia		
Renal and urinary disorders		Micturition urgency		Urinary retention
Reproductive system and breast disorders				Erectile dysfunction
General disorders and administration site conditions	Asthenia Fatigue	Drug withdrawal syndrome Chest pain Chills Malaise Pain Peripheral oedema Thirst		

Investigations		Weight decreased	Weight increased	
Injury, poisoning and procedural complications		Injury from accidents		

¹ particularly in persons with epileptic disorder or predisposition to convulsions

² particularly in patients with history of coronary artery disease

For the active substance oxycodone hydrochloride, the following additional undesirable effects are known

Due to its pharmacological properties, oxycodone hydrochloride may cause respiratory depression, miosis, bronchial spasm and spasms of nonstriated muscles as well as suppress the cough reflex.

System organ class MedDRA	Common	Uncommon	Rare	Not known
Infections and infestations	-	-	Herpes simplex	-
Immune system disorders				Anaphylactic reactions
Metabolism and nutrition disorders		Dehydration	Increased appetite	
Psychiatric disorders	Altered mood and personality changes Decreased activity Psychomotor hyperactivity	Agitation Perception disturbances (e.g. derealisation)		
Nervous system disorders		Concentration impaired Migraine Hypertonia Involuntary muscle contractions Hypoaesthesia Abnormal co-ordination		Hyperalgesia
Ear and labyrinth disorders		Hearing impaired		
Vascular disorders		Vasodilation		
Respiratory, thoracic and mediastinal disorders		Dysphonia		
Gastrointestinal disorders	Hiccups	Dysphagia Ileus Mouth ulceration Stomatitis	Melaena Gingival bleeding	Dental caries
Hepatobiliary disorders				Cholestasis <u>Sphincter of Oddi dysfunction</u>
Skin and subcutaneous tissue disorders		Dry skin	Urticaria	
Renal and urinary disorders	Dysuria			
Reproductive system and breast disorders		Hypogonadism		Amenorrhoea
General disorders and administration site conditions		Oedema Drug tolerance		Drug withdrawal syndrome neonatal

Drug dependence

Repeated use of Dancex SR Plus 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

Depending on the history of the patient, an overdose of oxycodone/naloxone may be manifested by symptoms that are either triggered by oxycodone (opioid receptor agonist) or by naloxone (opioid receptor antagonist).

Symptoms of oxycodone overdose include miosis, respiratory depression, somnolence progressing to stupor, hypotonia, bradycardia as well as hypotension. Coma, non-cardiogenic pulmonary oedema and circulatory failure may occur in more severe cases and may lead to a fatal outcome.

Toxic leukoencephalopathy has been observed with oxycodone overdose.

Symptoms of a naloxone overdose alone are unlikely.

Therapy of intoxication

Withdrawal symptoms due to an overdose of naloxone should be treated symptomatically in a closely-supervised environment.

Clinical symptoms suggestive of an oxycodone overdose may be treated by the administration of opioid antagonists (e.g. naloxone hydrochloride 0.4-2 mg intravenously). Administration should be repeated at 2-3 minute intervals, as clinically necessary. It is also possible to apply an infusion of 2 mg naloxone hydrochloride in 500 ml of 0.9% sodium chloride or 5% dextrose (0.004 mg/ml naloxone). The infusion should be run at a rate aligned to the previously administered bolus doses and to the patient's response.

Consideration may be given to gastric lavage.

Supportive measures (artificial ventilation, oxygen, vasopressors and fluid infusions) should be employed as necessary, to manage the circulatory shock accompanying an overdose. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation. Artificial ventilation should be applied if necessary. Fluid and electrolyte metabolism should be maintained.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics; opioids; natural opium alkaloids, ATC code: N02AA55

Mechanism of action

Oxycodone and naloxone have an affinity for kappa, mu and delta opiate receptors in the brain, spinal cord and peripheral organs (e.g. intestine). Oxycodone acts as opioid-receptor agonist at these receptors and binds to the endogenous opioid receptors in the CNS. By contrast, naloxone is a pure antagonist acting on all types of opioid receptors.

Pharmacodynamic effects

Because of the pronounced first-pass metabolism, the bioavailability of naloxone upon oral administration is <3%, therefore a clinically relevant systemic effect is unlikely. Due to the local competitive antagonism of the opioid receptor mediated oxycodone effect by naloxone in the gut, naloxone reduces the bowel function disorders that are typical for opioid treatment.

Clinical efficacy and safety

For effects of opioids on the endocrine system, see section 4.4.

Preclinical studies show differing effects of natural opioids on components of the immune system. The clinical significance of these findings is not known. It is not known whether oxycodone, a semi-synthetic opioid, has similar effects on the immune system to natural opioids.

Analgnesia

In a 12 weeks parallel group double-blinded study in 322 patients with opioid-induced constipation, patients who were treated with oxycodone hydrochloride/naloxone hydrochloride had on average one extra complete spontaneous (without laxatives) bowel movement in the last week of treatment, compared to patients who continued using similar doses of oxycodone hydrochloride prolonged release tablets ($p < 0.0001$). The use of laxatives in the first four weeks was significantly lower in the oxycodone/naloxone group compared to the oxycodone monotherapy group (31% versus 55%, respectively, $p < 0.0001$). Similar results were shown in a study with 265 non-cancer patients comparing daily doses of oxycodone hydrochloride/naloxone hydrochloride of 60 mg/30 mg to up to 80 mg/40 mg with oxycodone hydrochloride monotherapy in the same dose range.

5.2 Pharmacokinetic properties

Oxycodone hydrochloride

Absorption

Oxycodone has a high absolute bioavailability of up to 87% following oral administration.

Distribution

Following absorption, oxycodone is distributed throughout the entire body. Approximately 45% is bound to plasma protein. Oxycodone crosses the placenta and may be detected in breast milk.

Biotransformation

Oxycodone is metabolised in the gut and the liver to noroxycodone and oxymorphone and to various glucuronide conjugates. Noroxycodone, oxymorphone and noroxymorphone are produced via the cytochrome P450 system. Quinidine reduces the production of oxymorphone in man without substantially influencing the pharmacodynamics of oxycodone. The contribution of the metabolites to overall pharmacodynamic effect is insignificant.

Elimination

Oxycodone and its metabolites are excreted in both urine and faeces.

Naloxone hydrochloride

Absorption

Following oral administration, naloxone has a very low systemic availability of <3%.

Distribution

Naloxone passes into the placenta. It is not known, whether naloxone also passes into breast milk.

Biotransformation and elimination

After parenteral administration, the plasma half-life is approximately one hour. The duration of action depends upon the dose and route of administration, intramuscular injection producing a more prolonged effect than intravenous doses. It is metabolised in the liver and excreted in the urine. The principal metabolites are naloxone glucuronide, 6 β -naloxol and its glucuronide.

Oxycodone hydrochloride/naloxone hydrochloride combination (Dancex SR Plus)

Pharmacokinetic/pharmacodynamic relationships

The pharmacokinetic characteristics of oxycodone from Dancex SR Plus is equivalent to those of prolonged-release oxycodone hydrochloride tablets administered together with prolonged-release naloxone hydrochloride tablets.

All dose strengths of Dancex SR Plus are interchangeable.

After the oral administration of oxycodone hydrochloride/naloxone hydrochloride in maximum dose to healthy subjects, the plasma concentrations of naloxone are so low that it is not feasible to carry out a pharmacokinetic analysis. To conduct a

pharmacokinetic analysis naloxone-3-glucuronide as surrogate marker is used, since its plasma concentration is high enough to measure.

Overall, following ingestion of a high-fat breakfast, the bioavailability and peak plasma concentration (C_{max}) of oxycodone were increased by an average of 16% and 30% respectively compared to administration in the fasting state. This was evaluated as clinically not relevant, therefore Dancex SR Plus prolonged-release tablets may be taken with or without food (see section 4.2).

In vitro metabolism studies have indicated that the occurrence of clinically relevant interactions involving oxycodone hydrochloride/naloxone hydrochloride is unlikely.

Elderly patients

Oxycodone

For AUC_t of oxycodone, on average there was an increase to 118% (90% C.I.: 103, 135), for elderly compared with younger volunteers. For C_{max} of oxycodone, on average there was an increase to 114% (90% C.I.: 102, 127). For C_{min} of oxycodone, on average there was an increase to 128% (90% C.I.: 107, 152).

Naloxone

For AUC_t of naloxone, on average there was an increase to 182% (90% C.I.: 123, 270), for elderly compared with younger volunteers. For C_{max} of naloxone, on average there was an increase to 173% (90% C.I.: 107, 280). For C_{min} of naloxone, on average there was an increase to 317% (90% C.I.: 142, 708).

Naloxone-3-glucuronide

For AUC_t of naloxone-3-glucuronide, on average there was an increase to 128% (90% C.I.: 113, 147), for elderly compared with younger volunteers. For C_{max} of naloxone-3-glucuronide, on average there was an increase to 127% (90% C.I.: 112, 144). For C_{min} of naloxone-3-glucuronide, on average there was an increase to 125% (90% C.I.: 105, 148).

Patients with impaired hepatic function

Oxycodone

For AUC_{INF} of oxycodone, on average there was an increase to 143% (90% C.I.: 111, 184), 319% (90% C.I.: 248, 411) and 310% (90% C.I.: 241, 398) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers. For C_{max} of oxycodone, on average there was an increase to 120% (90% C.I.: 99, 144), 201% (90% C.I.: 166, 242) and 191% (90% C.I.: 158, 231) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers. For $t_{1/2Z}$ of oxycodone, on average there was an increase to 108% (90% C.I.: 70, 146), 176% (90% C.I.: 138, 215) and 183% (90% C.I.: 145, 221) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers.

Naloxone

For AUC_t of naloxone, on average there was an increase to 411% (90% C.I.: 152, 1112), 11518% (90% C.I.: 4259, 31149) and 10666% (90% C.I.: 3944, 28847) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers. For C_{max} of naloxone, on average there was an increase to 193% (90% C.I.: 115, 324), 5292% (90% C.I.: 3148, 8896) and 5252% (90% C.I.: 3124, 8830) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers. Due to insufficient amount of data available $t_{1/2Z}$ and the corresponding AUC_{INF} of naloxone were not calculated. The bioavailability comparisons for naloxone were therefore based on AUC_t values.

Naloxone-3-glucuronide

For AUC_{INF} of naloxone-3-glucuronide, on average there was an increase to 157% (90% C.I.: 89, 279), 128% (90% C.I.: 72, 227) and 125% (90% C.I.: 71, 222) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers. For C_{max} of naloxone-3-glucuronide, on average there was an increase to 141% (90% C.I.: 100, 197), 118% (90% C.I.: 84, 166) and a decrease to 98% (90% C.I.: 70, 137) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers. For $t_{1/2Z}$ of naloxone-3-glucuronide, on average there was an increase to 117% (90% C.I.: 72, 161), a decrease to 77% (90% C.I.: 32, 121) and a decrease to 94% (90% C.I.: 49, 139) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers.

Patients with impaired renal function

Oxycodone

For AUC_{INF} of oxycodone, on average there was an increase to 153% (90% C.I.: 130, 182), 166% (90% C.I.: 140, 196) and 224% (90% C.I.: 190, 266) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy volunteers. For C_{max} of oxycodone, on average there was an increase to 110% (90% C.I.: 94, 129), 135% (90% C.I.: 115, 159) and 167% (90% C.I.: 142, 196) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy volunteers. For $t_{1/2Z}$

of oxycodone, on average there was an increase to 149%, 123% and 142% for mild, moderate and severe renally impaired subjects, respectively, compared with healthy volunteers.

Naloxone

For AUC_t of naloxone, on average there was an increase to 2850% (90% C.I.: 369, 22042), 3910% (90% C.I.: 506, 30243) and 7612% (90% C.I.: 984, 58871) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy volunteers. For C_{max} of naloxone, on average there was an increase to 1076% (90% C.I.: 154, 7502), 858% (90% C.I.: 123, 5981) and 1675% (90% C.I.: 240, 11676) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy volunteers. Due to insufficient amount of data available t_{1/2Z} and the corresponding AUC_{INF} of naloxone were not calculated. The bioavailability comparisons for naloxone were therefore based on AUC_t values. The ratios may have been influenced by the inability to fully characterise the naloxone plasma profiles for the healthy subjects.

Naloxone-3-glucuronide

For AUC_{INF} of naloxone-3-glucuronide, on average there was an increase to 220% (90% C.I.: 148, 327), 370% (90% C.I.: 249, 550) and 525% (90% C.I.: 354, 781) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy subjects. For C_{max} of naloxone-3-glucuronide, on average there was an increase to 148% (90% C.I.: 110, 197), 202% (90% C.I.: 151, 271) and 239% (90% C.I.: 179, 320) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy subjects. For t_{1/2Z} of naloxone-3-glucuronide, on average there was no significant change between the renally impaired subjects and the healthy subjects.

Abuse

To avoid damage to the prolonged-release properties of the Dancex SR Plus prolonged-release tablets, the tablets must not be broken, crushed or chewed, as this leads to a rapid release of the active substances. However, the tablets can be divided into equal doses.

In addition, naloxone has a slower elimination rate when administered intranasally. Both properties mean that abuse of Dancex SR Plus will not have the effect intended. In oxycodone-dependent rats, the intravenous administration of oxycodone hydrochloride/naloxone hydrochloride at a ratio of 2:1 resulted in withdrawal symptoms.

5.3 Preclinical safety data

There are no data from studies on reproductive toxicity of the combination of oxycodone and naloxone. Studies with the single components showed that 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 foetuses 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. The standard oral reproduction toxicity studies with naloxone show that at high oral doses naloxone was not teratogenic and/or embryo/foetotoxic and does not affect perinatal/postnatal development. At very high doses (800 mg/kg/day) naloxone produced increased pup deaths in the immediate post-partum period at doses that produced significant toxicity in maternal rats (e.g. body weight loss, convulsions). However, in surviving pups, no effects on development or behaviour were observed.

Long-term carcinogenicity studies with oxycodone/naloxone in combination have not been performed. Carcinogenicity was evaluated in 2-year oral gavage study conducted in Sprague-Dawley rats. Oxycodone did not increase the incidence of tumors in male and female rats at doses up to 6 mg/kg/day. The doses were limited by opioid-related pharmacological effects of oxycodone.

For naloxone, a 24-months oral carcinogenicity study was performed in rats with doses up to 100 mg/kg/day and 6 month carcinogenicity study was performed in TgrasH2 mice at doses up to 200 mg/kg/day. The results of the two studies indicate that naloxone was not carcinogenic under these conditions.

Oxycodone and naloxone as single entities show 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/naloxone to humans at therapeutic concentrations may be ruled out with adequate certainty.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Polyvinyl acetate
Povidone K30
Sodium laurilsulfate
Silica, colloidal anhydrous
Cellulose, microcrystalline
Magnesium stearate

Tablet coating

Polyvinyl alcohol
Titanium dioxide (E 171)
Macrogol 3350
Talc
Iron oxide red (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years
Shelf life after first opening of the bottle:
3 months

6.4 Special precautions for storage

Blister:
Do not store above 25°C.

Bottles:
Do not store above 30°C.

6.5 Nature and contents of container

Blister

Child resistant aluminium/PVC/PE/PVDC perforated unit dose push-through blister.
Child resistant aluminium/PVC/PE/PVDC perforated unit dose peel-off blister.
Child resistant aluminium/PVC/PE/PVDC blister.

Bottle

HDPE bottles with child-resistant, tamper-evident screw cap made of PP.

Pack sizes

Unit-dose blister: 10x1 (hospital pack), 14x1, 20x1, 28x1, 30x1, 50x1, 56x1, 60x1, 98x1, 100x1 prolonged-release tablets.

Blister: 28, 56 and 84 prolonged-release tablets.

Bottles: 50 and 100 prolonged-release tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/250/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15th April 2016

Date of last renewal: 7th December 2020

10 DATE OF REVISION OF THE TEXT

August 2025