

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nolxado 20 mg/10 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 20 mg of oxycodone hydrochloride equivalent to 18 mg oxycodone and 10 mg naloxone hydrochloride as 10.9 mg naloxone hydrochloride dihydrate, equivalent to 9 mg naloxone.

Excipient with known effect: lactose monohydrate

Each 20 mg/10 mg prolonged-release tablet contains 51.78 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet

Light pink, oval, slightly biconvex, film coated tablets prolonged-release engraved with “20” on one side of the tablet (dimensions: 9.5 mm x 4.5 mm).

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 bring relief from some side effects of oxycodone. Nolxado is indicated in adults.

4.2 Posology and method of administration

Posology

Analgesia

The analgesic efficacy of Nolxado is equivalent to oxycodone hydrochloride prolonged-release formulations.

The dosage should be adjusted to the intensity of pain and the sensitivity of the individual patient. Unless otherwise prescribed, Nolxado 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.

Lower strengths are available to facilitate dose titration when initiating opioid therapy and for individual dose adjustment.

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

The maximum daily dose of Nolxado 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 of Nolxado 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 of Nolxado, 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 Nolxado with a subsequent switch to another opioid a worsening of the bowel function can be expected.

Some patients taking Nolxado according to a regular time schedule require immediate-release analgesics as “rescue” medication for breakthrough pain. Nolxado 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 Nolxado requires upward adjustment. This adjustment should be made twice daily every 1-2 days. 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.

Nolxado is taken at the determined dosage 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.

Duration of use

Nolxado should not be administered for longer than absolutely necessary. If long-term treatment is necessary in view of the nature and severity of the illness, careful and regular monitoring is required to establish whether and to what extent further treatment is necessary.

When the patient no longer requires opioid therapy, it may be advisable to taper the dose gradually (see section 4.4).

Elderly patients

As for younger adults the dosage should be adjusted to the intensity of the pain 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 Nolxado to patients with mild hepatic impairment (see section 4.4). In patients with moderate and severe hepatic impairment Nolxado 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 Nolxado to patients with renal impairment (see section 4.4).

Paediatric population

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

Method of administration

Oral use.

Nolxado is taken in the determined dosage twice daily in a fixed time schedule.

The prolonged-release tablets may be taken with or without food with sufficient liquid. Nolxado must be swallowed whole, and not divided, broken, chewed or crushed.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Any situation where opioids are contraindicated,
- 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

The major risk of opioid excess is respiratory depression.

Caution must be exercised when administering Nolxado to elderly or infirm patients, patients with opioid-induced paralytic ileus, patients presenting severely impaired pulmonary function, patients with sleep apnoea, myxoedema, hypothyroidism, Addison's disease (adrenal cortical insufficiency), toxic psychosis, cholelithiasis, prostate hypertrophy, alcoholism, delirium tremens, pancreatitis, hypotension, hypertension, pre-existing cardiovascular diseases, head injury (due to the risk of increased intracranial pressure), epileptic disorder or predisposition to convulsions, or patients taking MAO inhibitors.

Caution must also be exercised when administering Nolxado to patients with mild hepatic or renal impairment. A careful medical monitoring is particularly necessary for patients with severe renal impairment.

Diarrhoea may be considered as a possible effect of naloxone.

In patients under long-term opioid treatment with higher doses of opioids, the switch to Nolxado can initially provoke withdrawal symptoms. Such patients may require specific attention.

Nolxado is not suitable for the treatment of withdrawal symptoms.

During long-term administration, the patient may develop tolerance to the medicinal product and require higher doses to maintain the desired effect. Chronic administration of Nolxado may lead to physical dependence. Withdrawal symptoms may occur upon the abrupt cessation of therapy. If therapy with Nolxado 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)

There is potential for development of psychological dependence (addiction) to opioid analgesics, including Nolxado. Nolxado should be used with particular care in patients with a history of alcohol and drug abuse. Oxycodone alone has an abuse profile similar to other strong agonist opioids.

In order not to impair the prolonged-release characteristic of the prolonged-release tablets, the prolonged-release tablets must be taken whole and must not be divided, broken, chewed or crushed. Dividing, 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).

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 Nolxado (see sections 4.5 and 4.7).

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

Studies have not been performed on the safety and efficacy of Nolxado 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.

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 Nolxado in this population is not recommended.

Nolxado 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 Nolxado depends on a careful risk-benefit assessment for each individual patient.

Any abuse of Nolxado by drug addicts is strongly discouraged. If abused parenterally, intranasally or orally by individuals dependent on opioid agonists, such as heroin, morphine, or methadone, Nolxado 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).

Nolxado consists of a dual-polymer matrix, 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.

The empty prolonged-release tablet matrix may be visible in the stool.

The use of Nolxado may produce positive results in doping controls. The use of Nolxado as a doping agent may become a health hazard.

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

4.5 Interaction with other medicinal products and other forms of interaction

Substances having a CNS-depressant effect (e.g. other opioids, sedatives, hypnotics, antidepressants, phenothiazines, neuroleptics, antihistamines and antiemetics) may enhance the CNS-depressant effect (e.g. respiratory depression) of Nolxado.

Alcohol may enhance the pharmacodynamic effects of Nolxado; concomitant use should be avoided.

Clinically relevant changes in International Normalized 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 drugs or dietary elements. Nolxado 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, saquinaver), 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 Nolxado 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 drug, 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 data from the use of Nolxado in pregnant women and during childbirth. Limited 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 Nolxado 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 drugs 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. Nolxado should only be used during pregnancy if the benefit outweighs the possible risks to the unborn child or neonate.

Breastfeeding

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 Nolxado 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 Nolxado by the breastfeeding mother. Breastfeeding should be discontinued during treatment with Nolxado.

Fertility

There are no data with respect to fertility.

4.7 Effects on ability to drive and use machines

Nolxado has moderate influence on the ability to drive and use machines. This is particularly likely at the beginning of treatment with Nolxado, after dose increase or product rotation and if Nolxado is combined with other CNS depressant agents. Patients stabilised on a specific dosage 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 Nolxado 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 (≥ 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)

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

Undesirable affects in the treatment of pain

<u>System organ class</u> <u>MedDRA</u>	<u>Common</u>	<u>Uncommon</u>	<u>Rare</u>	<u>Not known</u>
<u>Immune system disorders</u>		Hypersensitivity		
<u>Metabolism and nutrition disorders</u>	Decreased appetite up to loss of appetite			
<u>Psychiatric disorders</u>	Insomnia	Abnormal thinking Anxiety Confusion Depression Nervousness Restlessness		Euphoric mood Hallucination Nightmares
<u>Nervous system disorders</u>	Dizziness Headache Somnolence	Convulsions ¹ Disturbance in attention Speech disorder Syncope Tremor		Paraesthesia Sedation
<u>Eye disorders</u>		Visual impairment		
<u>Ear and labyrinth disorders</u>	Vertigo			
<u>Cardiac disorders</u>		Angina pectoris ² Palpitations	Tachycardia	
<u>Vascular disorders</u>	Hot flush	Blood pressure decreased Blood pressure increased		
<u>Respiratory, thoracic and mediastinal disorders</u>		Dyspnoea Rhinorrhoea Cough	Yawning	Respiratory depression
<u>Gastrointestinal</u>	Abdominal pain	Abdominal	Tooth disorder	Eructation

<u>disorders</u>	Constipation Diarrhoea Dry mouth Dyspepsia Vomiting Nausea Flatulence	distention		
<u>Hepatobiliary disorders</u>		Hepatic enzymes increased Biliary colic		
<u>Skin and subcutaneous tissue disorders</u>	Pruritus Skin reactions Hyperhidrosis			
<u>Musculoskeletal and connective tissue disorders</u>		Muscle spasms Muscle twitching, Myalgia		
<u>Renal and urinary disorders</u>		Micturition urgency		Urinary retention
<u>Reproductive system and breast disorders</u>				Erectile dysfunction
<u>General disorders and administration site conditions</u>	Asthenic conditions Fatigue	Chest pain, Chills, Drug withdrawal syndrome Malaise Pain Oedema peripheral		
<u>Investigations</u>		Weight decreased	Weight increased	
<u>Injury, poisoning and procedural complications</u>		Injuries 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.

<u>System organ class</u> <u>MedDRA</u>	<u>Common</u>	<u>Uncommon</u>	<u>Rare</u>	<u>Not known</u>
<u>Infections and infestations</u>			Herpes simplex	
<u>Immune system disorders</u>				Anaphylactic responses
<u>Metabolism and nutrition disorders</u>		Dehydration	Increased appetite	
<u>Psychiatric disorders</u>	Altered mood and personality	Agitation Perception		

	changes Decreased activity Psychomotor hyperactivity	disturbances (e.g. derealisation) Reduced libido Drug dependence		
<u>Nervous system disorders</u>		Concentration impaired Migraine Dysgeusia, Hypertonia, Involuntary muscle contractions Hypoaesthesia Abnormal co-ordination		
<u>Ear and labyrinth disorders</u>		Hearing impaired		
<u>Vascular disorders</u>		Vasodilation		
<u>Respiratory, thoracic and mediastinal disorders</u>		Dysphonia		
<u>Gastrointestinal disorders</u>	Hiccups	Dysphagia Ileus Mouth ulceration Stomatitis	Melaena, Gingival bleeding	
<u>Hepatobiliary disorders</u>				Cholestasis
<u>Skin and subcutaneous tissue disorders</u>		Dry skin	Urticaria	
<u>Renal and urinary disorders</u>	Dysuria			
<u>Reproductive system and breast disorders</u>				Amenorrhoea
<u>General disorders and administration site conditions</u>		Oedema Thirst Drug tolerance		

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms

Depending on the history of the patient, an overdose of Nolxado 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, skeletal muscle flaccidity, 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.

Symptoms of a naloxone overdose alone are unlikely.

Management

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

Opioids can influence the hypothalamic-pituitary-adrenal or gonadal axes. Among the changes observed are an increase of prolactin in the serum and a reduced level of cortisol and testosterone in the plasma. Clinical symptoms may occur because of these hormone changes.

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.

Analgesia

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 hydrochlorideAbsorption

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 (Nolxado)**Pharmacokinetic/pharmacodynamic relationships**

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

All dosage strengths of Nolxado are interchangeable.

After the oral administration of Nolxado 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 Nolxado prolonged-release tablets may be taken with or without food (see section 4.2).

In vitro drug metabolism studies have indicated that the occurrence of clinically relevant interactions involving Nolxado is unlikely.

Elderly**Oxycodone**

For AUC 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 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 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).

Hepatic impairment**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 AUCt 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 Cmax 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 t1/2Z and the corresponding AUCINF of naloxone were not calculated. The bioavailability comparisons for naloxone were therefore based on AUCt values.

Naloxone-3-glucuronide

For AUCINF 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 Cmax 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 t1/2Z 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.

Renal impairmentOxycodone

For AUCINF 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 Cmax 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 t1/2Z 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 AUCt 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 Cmax 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 t1/2Z and the corresponding AUCINF of naloxone were not calculated. The bioavailability comparisons for naloxone were therefore based on AUCt values. The ratios may have been influenced by the inability to fully characterize the naloxone plasma profiles for the healthy subjects.

Naloxone-3-glucuronide

For AUCINF 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 Cmax 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 t1/2Z 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 tablets, Nolxado must not be broken, crushed or chewed, as

this leads to a rapid release of the active substances. In addition, naloxone has a slower elimination rate when administered intranasally. Both properties mean that abuse of Nolxado 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 dosages 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 or oxycodone as a single entity have not been performed. For naloxone, a 24-months oral carcinogenicity study was performed in rats with naloxone doses up to 100 mg/kg/day. The results indicate that naloxone is 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 Nolxado to humans at therapeutic concentrations may be ruled out with adequate certainty.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Hydroxypropylcellulose
Ethylcellulose
Glycerol distearate
Lactose monohydrate
Talc (E553b)
Magnesium stearate (E470b)

Film coating

Poly vinyl alcohol
Titanium dioxide (E171)
Macrogol 3350
Talc (E553b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Child-resistant blister (PVC/PVDC white – paper/Alu foil): 10, 14, 20, 28, 30, 50, 56, 60, 90, 98, 100 or 112 prolonged-release tablets, in a box.

Perforated unit dose child-resistant peel-off blister (PVC/PVDC white -PET/Alu foil): 10x1, 14x1, 20x1, 28x1, 30x1, 50x1, 56x1, 60x1, 90x1, 98x1, 100x1 or 112x1 prolonged-release tablets, in a box.

Not all pack sizes may be marketed.

7 MARKETING AUTHORISATION HOLDER

HCS bvba
H. Kennisstraat 53
B 2650 Edegem
Belgium

8 MARKETING AUTHORISATION NUMBER

PA2096/005/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th May 2017

10 DATE OF REVISION OF THE TEXT