

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Nolxado 40 mg/20 mg prolonged-release tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect: lactose monohydrate

Each 40 mg/20 mg prolonged-release tablet contains 103.55 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Prolonged-release tablet

Brownish yellow, capsule shaped, slightly biconvex, film coated prolonged-release tablets engraved with "40" on one side of the tablet (dimensions: 14.0 mm x 6.0 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, these tablets 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 depending on their previous opioid experience.

The maximum daily dose of these tablets 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 these tablets 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. 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 dosage requires upward adjustment. This adjustment should be made 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.

#### 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 these tablets 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 these tablets 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.

These prolonged-release tablets are 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. These tablets must be swallowed whole, and not broken, chewed or crushed (see section 4.4).

### Treatment goals and discontinuation

Before initiating treatment with Nolxado, 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

These tablets 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 these tablets 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, intracranial lesions or increased intracranial pressure, reduced level of consciousness of uncertain origin
- 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 primary risk of opioid excess is respiratory depression.

### *Sleep-related breathing disorders*

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

### *Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:*

Concomitant use of opioids, including oxycodone hydrochloride and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Nolxado concomitantly with sedative medicines, 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).

### MAOIs

Nolxado must be administered with caution in patients taking MAOIs or who have received MAOIs within the previous two weeks.

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

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 Nolxado 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 Nolxado 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 Nolxado 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

Repeated use of Nolxado may lead to physical dependence and a withdrawal syndrome may occur upon abrupt cessation of therapy. If therapy 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).

Nolxado is not suitable for the treatment of withdrawal symptoms.

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 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).

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 these tablets in this population is not recommended.

These tablets are not recommended for pre-operative use or within the first 12-24 hours post-operatively. Depending on the type and extent of surgery, the anaesthetic procedure selected, other co-medication and the individual condition of the patient, the exact timing for initiating post-operative treatment with these tablets depends on a careful risk-benefit assessment for each individual patient.

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

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 manifest from these hormonal changes.

In patients under long-term opioid treatment the switch to Nolxado may initially provoke withdrawal symptoms or diarrhoea.

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.

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, total lactase deficiency or glucose-galactose malabsorption should not take Nolxado.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs 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).

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

Nolxado must be administered with caution in patients taking MAOIs or who have received MAOIs within the previous two weeks.

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 dosage may need to be reduced in patients using these medications.

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.

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, 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 these tablets 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 these tablets 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. These tablets 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 taking these tablets 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 these tablets by the breast-feeding mother.

Breast-feeding should be discontinued during treatment with Nolxado.

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 oxycodone/naloxone treatment (see section 5.3).

**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, after dose increase or product rotation and if these tablets are 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 ( $\geq 1/10$ )
- 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 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 Confusional	Drug dependence (see section 4.4)	Euphoric mood Hallucination Nightmares

		state Depression Libido decreased Nervousness Restlessness		Aggression
<u>Nervous system disorders</u>	Dizziness Headache Somnolence	Convulsions <sup>1</sup> Disturbance in attention Dysgeusia Speech disorder Syncope Tremor Lethargy		Paraesthesia Sedation
<u>Eye disorders</u>		Visual impairment		
<u>Ear and labyrinth disorders</u>	Vertigo			
<u>Cardiac disorders</u>		Angina pectoris <sup>2</sup> 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 Central sleep apnoea syndrome
<u>Gastrointestinal disorders</u>	Abdominal pain Constipation Diarrhoea Dry mouth Dyspepsia Vomiting Nausea Flatulence	Abdominal distention	Tooth disorder	Eructation
<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>	Asthenia Fatigue	Chest pain, Chills, Drug withdrawal syndrome Malaise Pain Oedema		



		peripheral Thirst		
<u>Investigations</u>		Weight decreased	Weight increased	
<u>Injury, poisoning and procedural complications</u>		Injuries from accidents		

<sup>1</sup> particularly in persons with epileptic disorder or predisposition to convulsions

<sup>2</sup> 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 reaction
<u>Metabolism and nutrition disorders</u>		Dehydration	Increased appetite	
<u>Psychiatric disorders</u>	Altered mood and personality changes Decreased activity Psychomotor hyperactivity	Agitation Perception disturbances (e.g. derealisation)		
<u>Nervous system disorders</u>		Concentration impaired Migraine Hypertonia Involuntary muscle contractions Hypoaesthesia Abnormal co-ordination		Hyperalgesia
<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	Dental caries
<u>Hepatobiliary disorders</u>				Cholestasis Sphincter of Oddi dysfunction
<u>Skin and subcutaneous tissue disorders</u>		Dry skin	Urticaria	
<u>Renal and urinary disorders</u>	Dysuria			
<u>Reproductive system and breast disorders</u>		Hypogonadism		Amenorrhoea
<u>General disorders and administration site conditions</u>		Oedema Drug tolerance		Drug withdrawal syndrome neonatal

### Drug dependence

Repeated use of Nolxado 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 HPRA Pharmacovigilance. Website: [www.hpra.ie](http://www.hpra.ie).

## **4.9 Overdose**

### Symptoms of intoxication

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, 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 upon 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.

### 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 metabolized 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 $\beta$ -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<sub>max</sub>) 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 patients

##### Oxycodone

For AUC<sub>T</sub> of oxycodone, on average there was an increase to 118% (90% C.I.: 103, 135), for elderly compared with younger volunteers. For C<sub>max</sub> of oxycodone, on average there was an increase to 114% (90% C.I.: 102, 127). For C<sub>min</sub> of oxycodone, on average there was an increase to 128% (90% C.I.: 107, 152).

##### Naloxone

For AUC<sub>T</sub> of naloxone, on average there was an increase to 182% (90% C.I.: 123, 270), for elderly compared with younger volunteers. For C<sub>max</sub> of naloxone, on average there was an increase to 173% (90% C.I.: 107, 280). For C<sub>min</sub> of naloxone, on average there was an increase to 317% (90% C.I.: 142, 708).

##### Naloxone-3-glucuronide

For AUC<sub>T</sub> 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<sub>max</sub> of naloxone-3-glucuronide, on average there was an increase to 127% (90% C.I.: 112, 144). For C<sub>min</sub> 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<sub>INF</sub> 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<sub>max</sub> 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<sub>1/2Z</sub> 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 C<sub>max</sub> 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<sub>1/2Z</sub> 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 C<sub>max</sub> 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<sub>1/2Z</sub> 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 functionOxycodone

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 C<sub>max</sub> 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<sub>1/2Z</sub> 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 C<sub>max</sub> 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<sub>1/2Z</sub> 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 C<sub>max</sub> 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<sub>1/2Z</sub> 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, Naloxado 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 Naloxado 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 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 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

3 years.

### 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 tablet, in a box.

Not all pack sizes may be marketed.

### **7 MARKETING AUTHORISATION HOLDER**

KRKA, d.d., Novo mesto  
Šmarješka cesta 6  
8501 Novo mesto  
Slovenia

### **8 MARKETING AUTHORISATION NUMBER**

PA1347/085/003

### **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

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Date of last renewal: 24<sup>th</sup> March 2022

### **10 DATE OF REVISION OF THE TEXT**

October 2024