Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Oxyargin 5 mg /2.5 mg prolonged release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 5 mg of oxycodone hydrochloride (equivalent to 4.5 mg oxycodone) and 2.5 mg of naloxone hydrochloride (as 2.74 mg naloxone hydrochloride dihydrate, equivalent to 2.25 mg naloxone).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

White, round, biconvex prolonged-release tablet with a diameter of 4.7 mm and a height of 2.9 - 3.9 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

Second line symptomatic treatment of patients with severe to very severe idiopathic restless legs syndrome after failure of dopaminergic therapy.

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

Oxyargin is indicated in adults.

4.2 Posology and method of administration

Posology

Analgesia
The analgesic efficacy of Oxyargin 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, Oxyargin should be administered as follows:

Adults
The usual starting dose for opioid naive patients 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 Oxyargin depending on their previous opioid experience.

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

The maximum daily dose of Oxyargin is 160 mg oxycodone hydrochloride and 840 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 of Oxyargin, 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 Oxyargin with a subsequent switch to another opioid a worsening of the bowel function can be expected.

Some patients taking Oxyargin according to a regular time schedule require immediate-release analgesics as "rescue" medication for breakthrough pain. Oxyargin 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 Oxyargin requires upward adjustment. This adjustment should be made every 1-2 days in steps of twice daily 5 mg/2.5 mg, or where necessary 2.5 mg/1.25 mg or 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. Slightly elevated (dose corrected) peak plasma concentrations should be taken into account when the 2.5 mg/1.25 mg tablet is used.

Oxyargin 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.

Restless legs syndrome (RLS)
Oxyargin is indicated in patients who have been suffering from RLS for at least 6 months. The symptoms of RLS should be present daily and during daytime (on at least 4 days of the week). Oxyargin should be used after previous dopaminergic therapy has failed. Failure of dopaminergic therapy is defined as an inadequate initial response, a response that has become inadequate over time, incidence of an augmentation or unacceptable intolerance despite appropriate dose. Previous treatment with at least one dopaminergic medicinal product should have been carried out for at least 4 weeks. A shorter duration of treatment may be justifiable in the event of unacceptable intolerance to dopaminergic treatment.

The dose should be adjusted to the sensitivity of the individual patient.

Treatment of restless legs syndrome with Oxyargin should be supervised by aclinician with experience in the management of restless legs syndrome.

Unless prescribed otherwise, Oxyargin should be administered as follows:

Adults
The usual starting dose is 5 mg/2.5 mg oxycodone hydrochloride/naloxone hydrochloride every 12 hours.

Titration on a weekly basis is recommended in case higher doses are required. The mean daily dose in the pivotal study was 20 mg/10 mg oxycodone hydrochloride/naloxone hydrochloride. Some patients may benefit from higher daily doses up to a maximum of 60 mg/30 mg oxycodone hydrochloride/naloxone hydrochloride..

The fixed dose of Oxyargin is taken twice a day at fixed intervals. Whilst symmetrical administration (the same dose mornings and evenings) at fixed intervals (every 12 hours) is appropriate for the majority of patients, some patients may possibly benefit – depending on the individual situation – from an asymmetrical dosing regimen tailored to their individual needs. In general, the lowest effective dose should be selected.

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

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

Restless legs syndrome
During treatment with Oxyargin, the patient should be clinically monitored at least every three months. The treatment should only be continued if Oxyargin is considered to be effective and the benefit is assumed to outweigh the undesirable effects and

potential harm for the respective patient. Before continuing treatment for RLS beyond one year, consideration should be given to a washout period in which Oxyargin is gradually reduced over a period of about one week in order to examine whether further treatment with Oxyargin is necessary.

If the patient does not require opioid treatment anymore, it is advisable to withdraw the medicinal product gradually, over about a week, in order to reduce the risk of a withdrawal reaction (see section 4.4).

Analgesia/restless legs syndrome

Duration of use
Oxyargin 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.

Paediatric population

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

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

Method of administration
For oral use.

Oxyargin is taken in the determined dose twice daily in a fixed time schedule.

The prolonged-release tablets may be taken with or without food with sufficient liquid.
Oxyargin must be swallowed whole with sufficient liquid, and must not be 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.

In addition for restless legs syndrome:
- history of opioid abuse.

4.4 Special warnings and precautions for use

Respiratory depression

The major risk of opioid excess is respiratory depression. Caution must be exercised when administering Oxyargin 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.

In patients with restless legs syndrome who also suffer from sleep apnoea syndrome, treatment with Oxyargin should be used with caution due to the additive risk of respiratory depression. There are no data relating to this risk as patients with sleep apnoea syndrome were excluded from the clinical study.

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

Concomitant use of Oxyargin 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 Oxyargin 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).

Hepatic or renal impairment

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

Diarrhoea

Diarrhoea may be considered as a possible effect of naloxone.

Long-term treatment

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

Oxyargin 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 Oxyargin may lead to physical dependence. Withdrawal symptoms may occur upon the abrupt cessation of therapy. If therapy with Oxyargin 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 no clinical experience with Oxyargin in the long-term treatment of RLS beyond 12 months (see section 4.2).

Psychological dependence (addiction)

There is potential for development of psychological dependence (addiction) to opioid analgesics, including Oxyargin. Oxyargin 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 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 Oxyargin (see sections 4.5 and 4.7).

Alcohol

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

Paediatric population
Studies have not been performed on the safety and efficacy of Oxyargin 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 Oxyargin in this population is not recommended.

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

Abuse
Any abuse of Oxyargin by drug addicts is strongly discouraged.

If abused parenterally, intranasally or orally by individuals dependent on opioid agonists, such as heroin, morphine, or methadone, Oxyargin 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).

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.

Doping
Athletes must be aware that this medicine may cause a positive reaction to 'anti-doping' tests. The use of Oxyargin as a doping agent may become a health hazard.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

Substances having a CNS-depressant effect (e.g. other opioids, sedatives such as benzodiazepines or related drugs, hypnotics, antidepressants, phenothiazines, neuroleptics, antihistamines and antiemetics) may enhance the CNS-depressant effect increasing the risk of sedation, respiratory depression, coma and deathwhen used concomitantly withOxyargin. The dose and duration of concomitant use should be limited (see section 4.4).

Alcohol may enhance the pharmacodynamic effects of Oxyargin; 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 drugs or dietary elements. Oxyargin 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 Oxyargin 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 Oxyargin 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 Oxyargin 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.

Oxyargin 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 oxycodone/naloxone 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 Oxyargin by the breastfeeding mother.

Breastfeeding should be discontinued during treatment with Oxyargin.

Fertility
There are no data with respect to fertility.

4.7 Effects on ability to drive and use machines

Oxyargin has moderate influence on the ability to drive and use machines. This is particularly likely at the beginning of treatment with Oxyargin, after dose increase or product rotation and if Oxyargin 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 Oxyargin 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 sections 4.4 and 4.5).

4.8 Undesirable effects

Undesirable effects are presented below in three sections: the treatment of pain, the active substance oxycodone hydrochloride and the treatment of restless legs syndrome.

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 effects for treatment of pain

System organ class MedDRA	Common	Uncommon	Rare	Very rare	Not known
Immune system disorders		Hyper-sensitivity			
Metabolism and nutrition disorders	Decreased appetite up to loss of appetite				
Psychiatric disorders	Insomnia	Restlessness Abnormal thinking Anxiety Confusional state Depression Reduced libido Nervousness			Euphoric mood Hallucination Nightmares
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	Decrease in blood pressure Increase in blood pressure			
Respiratory, thoracic and mediastinal disorders		Dyspnoea Rhinorrhoea Cough	Yawning		Respiratory depression
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				
Musculo-skeletal 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	Asthenic conditions 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] particular 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**	**Very 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) Drug dependence			Aggression
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
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

Undesirable effects for treatment of restless legs syndrome

The following section contains the undesirable effects observed during treatment with oxycodone/naloxone in a 12-week, randomised, placebo-controlled clinical study with a total of 150 patients on oxycodone/naloxone and 154 patients on placebo. The daily dose ranged from 10 mg/5 mg to 80 mg/40 mg oxycodone hydrochloride/naloxone hydrochloride. Adverse drug reactions associated with treatment with oxycodone/naloxone for pain but not seen in the RLS study population are listed in the frequency group "Not known".

System organ class MedDRA	**Very Common**	**Common**	**Uncommon**	**Not known**
Immune system disorders				Hypersensitivity reactions
Metabolism and nutrition disorders		Decreased appetite up to anorexia		
Psychiatric disorders		Insomnia, depression	Decreased lipido, sleep attacks	Abnormal thinking, anxiety, confusional state, nervousness, restlessness, euphoric mood, hallucinations, nightmares
Nervous system disorders	Headache, somnolence	Dizziness, disturbance in attention, tremor, paraesthesia	Dysgeusia	Convulsions (especially in patients with epileptic disorder or predisposition to seizures), sedation, speech disorders, syncope, lethargy
Eye disorders		Visual disturbances		
Ear and labyrinth disorders		Vertigo		
Cardiac disorders				Angina pectoris, especially in patients with history of coronary heart disease, palpitations, tachycardia
Vascular disorders		Hot flushes, drop in blood pressure, increase in blood pressure		
Respiratory, thoracic and mediastinal			Dyspnoea	Cough, rhinorrhoea, respiratory depression, yawning

disorders				
Gastrointestinal disorders	Constipation, nausea	Abdominal pain, dry mouth, vomiting	Flatulence	Abdominal distension, diarrhoea, dyspepsia, eructation, tooth disorder
Hepatobiliary disorders		Increase in hepatic enzymes (alanine aminotransferase, gamma-glutamyltransferase)		Biliary colic
Skin and subcutaneous tissue disorders	Hyperhidrosis	Pruritus, skin reactions		
Musculoskeletal and connective tissue disorders				Muscle cramps, muscle twitching, myalgia
Renal and urinary disorders				Urge to urinate, urinary retention
Reproductive system and breast disorders			Erectile dysfunction	
General disorders and administration site conditions	Fatigue	Chest pain, chills, thirst, pain	Drug withdrawal symptoms, peripheral oedema	Malaise Asthenia
Investigations				Weight decreased Weight increased
Injury, poisoning and procedural complications			Injuries due to accidents	

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 of intoxication
Depending on the history of the patient, an overdose of Oxycodone/Naloxone Oxyargin 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.

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 measure (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: Nervous system; 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.

Restless legs syndrome
In a 12-week, double-blind efficacy study, 150 patients with severe to very severe idiopathic restless legs syndrome were treated with oxycodone hydrochloride/naloxone hydrochloride after randomisation. Severe syndrome was defined as an IRLS score between 21 and 30 and very severe syndromes as a score between 31 and 40. A clinically relevant and statistically significant improvement in the mean IRLS score was seen in the patients throughout treatment compared to placebo. In week 12, the decrease in the mean IRLS score compared to placebo was 5.9 points (assuming a comparable effect in patients who discontinued the study to patients on placebo who completed the study, which represents a very conservative approach). The onset of efficacy was demonstrated from as early as week 1 of treatment. Comparable results were seen for the improvement in severity of RLS symptoms (measured by the RLS-6 scale), the quality of life (measured by a QoL-RLS-questionnaire) and quality of sleep (measured by the MOS sleep scale), and for the proportion of patients with an improvement in IRLS score. None of the patients experienced a confirmed augmentation during the study.

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, 6β-naloxol and its glucuronide.

Oxycodone hydrochloride/naloxone hydrochloride combination
Pharmacokinetic/pharmacodynamic relationships
The pharmacokinetic characteristics of oxycodone from oxycodone hydrochloride/naloxone hydrochloride is equivalent to those of prolonged-release oxycodone hydrochloride tablets administered together with prolonged-release naloxone hydrochloride tablets.

All dose strengths of Oxyargin 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 valid 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 oxycodone hydrochloride/naloxone hydrochloride 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 oxycodone hydrochloride/naloxone hydrochloride is unlikely.

Elderly patients
Oxycodone
For AUC_{τ} 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_{τ} 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 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 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 tablets, Oxycodone/Naloxone Oxyargin 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 Oxycodone/Naloxone Oxyargin 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 oyxcodone had no effect on fertility and early embryonic development in male and female rats in doses of up to 8 mg/kg body weight and induced no malformations in rats in doses of up to 8 mg/kg and in rabbits in doses of 125 mg/kg bodyweight. However, in rabbits, when individual 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 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 Oxyargin 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 lauryl sulphate
Silica, colloidal anhydrous
Cellulose, microcrystalline
Magnesium stearate

Tablet coating
Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol 3350
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister:
36 months

Bottles:
36 months.
Shelf life after first opening: 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 blisters.

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

Pack sizes
Blister: 10, 14, 20, 28, 30, 50, 56, 60, 90, 98, 100 prolonged-release tablets
Bottle: 50, 100, 250 prolonged-release tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

McDermott Laboratories Ltd t/a Gerard Laboratories
35/36 Baldoyle Industrial Estate
Grange Road
Dublin 13
Ireland

8 MARKETING AUTHORISATION NUMBER

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10 DATE OF REVISION OF THE TEXT

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