SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Oxyargin 30 mg/15 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Oxyargin 30 mg/15 mg
Each prolonged-release tablet contains 30 mg of oxycodone hydrochloride (equivalent to 27 mg oxycodone) and 15 mg of naloxone hydrochloride (as 16.35 mg naloxone hydrochloride dihydrate, equivalent to 13.5 mg naloxone).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

Yellow, oblong, biconvex prolonged-release tablet with break scores on both sides, with a length of 12.2 mm, a width of 5.7 mm and a height of 3.3 - 4.3 mm.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

Oxyargin is indicated in adults.

4.2 Posology and method of administration

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with oxycodone in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4).

Posology

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 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 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.

Duration of use
Oxyargin should not be administered for longer than absolutely 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.

Treatment goals and discontinuation
Before initiating treatment with {product name}, 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).

Oxyargin 30 mg/15 mg
The tablet can be divided into equal doses. However, they must not be otherwise broken, chewed or crushed. Oxyargin must be swallowed with sufficient liquid.

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 or CNS depressants.

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 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).

Opioids, such as oxycodone hydrochloride, 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.

<u>Hepatobiliary disorders</u>
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.

<u>Hepatic or renal impairment</u>
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.

<u>Diarrhoea</u>
Diarrhoea may be considered as a possible effect of naloxone.

<u>Long-term treatment</u>
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).

Drug dependence, tolerance and potential for abuse

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 Oxyargin may 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 Oxyargin 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 Oxyargin 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.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Tolerance

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction.

The clinical need for analgesic treatment should be reviewed regularly.

Drug withdrawal syndrome

Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with oxycodone.

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

Hyperalgesia

Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

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 and must not be used for acute post-operative pain owing to the increased risk of persistent post-operative opioid use (PPOU) and opioid-induced ventilatory impairment (OIVI).

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 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.

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

Concomitant administration of oxycodone with serotonin agents, such as a Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) may cause serotonin toxicity. The symptoms of serotonin toxicity may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea). Oxycodone should be used with caution and the dosage may need to be reduced in patients using these medications.

Alcohol may enhance the pharmacodynamic effects of {Invented name}; 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. {Invented name} 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 {Invented name} 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 pain 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.

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

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.

If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Breastfeeding
Administration to nursing women is not recommended as oxycodone may be secreted in breast milk and may cause respiratory depression in the infant.

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 two sections: the treatment of pain and the active substance oxycodone hydrochloride.

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		Hypersensitivity			
Metabolism and nutrition disorders	Decreased appetite up to loss of appetite				
Psychiatric disorders	Insomnia	Abnormal thinking, Anxiety, Confusional state, Depression, Libido decreased, Nervousness, Restlessness			Euphoric mood, Hallucination, Nightmares, Aggression, Drug dependence (see section 4.4)
Nervous system disorders	Dizziness, Headache, Somnolence	Convulsions[1], Disturbance in attention,			Paraesthesia, Sedation

System Organ Class MedDRA	Common	Uncommon	Rare	Very rare	Not known
		Dysgeusia, Speech disorder, Syncope, Tremor, Lethargy			
Eye disorders		Visual impairment			
Ear and labyrinth disorders	Vertigo				
Cardiac disorders		Angina pectoris[2], Palpitations	Tachycardia		
Vascular disorders	Hot flush	Blood pressure decreased, Blood pressure increased			
Respiratory, thoracic and mediastinal disorders		Dyspnoea, Rhinorrhoea, Cough	Yawning		Respiratory depression
Gastrointestinal disorders	Abdominal pain, Constipation, Diarrhoea, Dry mouth, Dyspepsia, Vomiting, Nausea, Flatulence	Abdominal distention	Tooth disorder		Eructation
Hepatobiliary disorders		Hepatic enzymes increased, Biliary colic			Sphincter of Oddi dysfunction
Skin and subcutaneous tissue disorders	Pruritus, Skin reactions, Hyperhidrosis				
Musculoskeletal and connective tissue disorders		Muscle spasms, Muscle twitching, Myalgia			
Renal and urinary disorders		Micturition urgency			Urinary retention
Reproductive system and breast disorders					Erectile dysfunction
General disorders and administration site conditions	Asthenia, fatigue	Drug withdrawal syndrome, Chest pain, Chills, Malaise, Pain,			

System Organ Class MedDRA	Common	Uncommon	Rare	Very rare	Not known
		Oedema peripheral, 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)			
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

Description of selected adverse reactions

Drug dependence
Repeated use of {product name} can lead to drug dependence, even at therapeutic doses. The risk of
drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of
opioid treatment (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

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

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

Toxic leukoencephalopathy has been observed with oxycodone overdose.

Symptoms of a naloxone overdose alone are unlikely.

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

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

Consideration may be given to gastric lavage.

Supportive 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
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.

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 $AUC_{\square}$ 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 $AUC_{\square}$ 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 $AUC_{\square}$ 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.l.: 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 oxycodone had no effect on fertility and early embryonic development in male and female rats in doses of up to 8 mg/kg body weight and induced no malformations in rats in doses of up to 8 mg/kg and in rabbits in doses of 125 mg/kg bodyweight. However, in rabbits, when individual foetuses were used in statistical evaluation, a dose related increase in developmental variations was observed (increased incidences of 27 presacral vertebrae, extra pairs of ribs). When these parameters were statistically evaluated using litters, only the incidence of 27 presacral vertebrae was increased and only in the 125 mg/kg group, a dose level that produced severe pharmacotoxic effects in the pregnant animals. In a study on pre- and postnatal development in rats F1 body weights were lower at 6 mg/kg/d when compared to body weights of the control group at doses which reduced maternal weight and food intake (NOAEL 2 mg/kg body weight). There were neither effects on physical, reflexological, and sensory developmental parameters nor on behavioural and reproductive indices. The standard oral reproduction toxicity studies with naloxone show that at high oral doses naloxone was not teratogenic and/or embryo/foetotoxic, and does not affect perinatal/postnatal development. At very high doses (800 mg/kg/day) naloxone produced increased pup deaths in the immediate post-partum period at doses that produced significant toxicity in maternal rats (e.g. body weight loss, convulsions). However, in surviving pups, no effects on development or behaviour were observed.

Long-term carcinogenicity studies with oxycodone/naloxone in combination 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
Oxyargin 30 mg/15 mg prolonged-release tablets
Polyvinyl acetate
Povidone K30
Sodium lauryl sulphate

Silica, colloidal anhydrous
Cellulose, microcrystalline
Magnesium stearate

Tablet coating
Oxyargin 30 mg/15 mg
Polyvinyl alcohol,
Titanium dioxide (E171),
Iron oxide yellow (E 172),
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

Generics [UK] Ltd t/a Mylan

Station Close

Potters Bar

Herts EN6 1TL

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL No. 04569/1733

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