Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Armoneve 40 mg/20 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect: Each prolonged-release tablet contains 109.0 mg lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet

Yellow, capsule shaped tablets, with a nominal length of 14 mm and with a film coating, embossed “OXN” on one side and “40” on the other side.

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.

Armoneve is indicated in adults.

4.2 Posology and method of administration

Posology

Analgesia

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

The dosage should be adjusted to the intensity of pain and the sensitivity of the individual patient.

Armoneve should be administered as follows:

Adults

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

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

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

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

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

Some patients taking Armoneveaccording to a regular time schedule require immediate-release analgesics as “rescue” medication for breakthrough pain. Armoneve is a prolonged-release formulation and therefore not intended for the treatment of breakthrough pain. For the treatment of breakthrough pain, a single dose of “rescue medication” should approximate one sixth of the equivalent daily dose of oxycodone hydrochloride. The need for more than two “rescues” per day is usually an indication that the dosage requires upward adjustment. This adjustment should be made every 1-2 days in steps of 5 mg/2.5 mg oxycodone hydrochloride/naloxone hydrochloride twice daily, 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 used. is tablet mg 1.25 2.5 the when account into taken be should concentrations plasma peak corrected) (dose elevated>

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

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

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

Restless legs syndrome

Armoneve is indicated for patients suffering from RLS for at least 6 months. RLS symptoms should be present daily and during daytime (≥ 4 days/week). Armoneve should be used after failure of previous dopaminergic treatment. Dopaminergic treatment failure is defined as inadequate initial response, a response that has become inadequate with time, occurrence of augmentation or unacceptable tolerability despite adequate doses. Previous treatment with at least one dopaminergic medicinal product should have lasted in general 4 weeks. A shorter period might be acceptable in case of unacceptable tolerability with dopaminergic therapy.

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

Treatment of patients with restless legs syndrome with Armoneve should be under the supervision of a clinician with experience in the management of restless legs syndrome.
Armoneve should be administered as follows:

Adults

The usual starting dose is 5 mg/2.5 mg of oxycodone hydrochloride/naloxone hydrochloride at 12 hourly intervals.

Titration on a weekly basis is recommended in case higher doses are required. The mean daily dose in the pivotal study was 20mg/10mg 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.

Armoneve is taken at the determined dosage twice daily according to a fixed time schedule. While symmetric administration (the same dose mornings and evenings) subject to a fixed time schedule (every 12 hours) is appropriate for the majority of patients, some patients, depending on the individual situation, may benefit from asymmetric dosing tailored to the individual patient. 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 / Restless legs syndrome

Special populations

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

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

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

Method of administration

Oral use.

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

The prolonged-release tablets may be taken with or without food with sufficient liquid. The tablets must be swallowed whole, and not broken, chewed or crushed (see section 4.4).

Duration of use

Armoneve 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.

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
At least every three months during therapy with Armoneve patients should be clinically evaluated. Treatment should only be continued if Armoneve is considered effective and the benefit is considered to outweigh adverse effects and potential harms in individual patients.Prior to continuation of RLS treatment beyond 1 year a discharge regimen by gradually tapering down of Armoneve over a period of approximately one week should be considered to establish if continued treatment with Armoneve is indicated.

When a patient no longer requires opioid therapy cessation of treatment by tapering down over a period of approximately one week is recommended in order to reduce the risk of a withdrawal reaction (see section 4.4).

4.3 Contraindications

· Hypersensitivity to the active substances or to any of the excipients listed in section 6.1,
· Severe respiratory depression with hypoxia and/or hypercapnia,
· Severe chronic obstructive pulmonary disease,
· Cor pulmonale,
· Severe bronchial asthma,
· Non-opioid induced paralytic ileus,
· Moderate to severe hepatic impairment.

Additionally for restless legs syndrome:
· History of opioid abuse

4.4 Special warnings and precautions for use

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

Caution is advised in treating restless legs syndrome patients with additional sleep apnoea syndrome with these tablets due to the additive risk of respiratory depression. No data about the risk exist because in the clinical trial patients with sleep apnoea syndrome were excluded.

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

Diarrhoea may be considered as a possible effect of naloxone.

In patients under long-term opioid treatment, the switch to Armoneve can initially provoke withdrawal symptoms. Such patients may require specific attention.

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

There is no clinical experience with Armoneve in the long-term treatment of RLS beyond 1 year (see section 4.2).

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

In order not to impair the prolonged-release characteristic of the prolonged-release tablets, the prolonged-release tablets must be taken whole and must not be 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 Armoneve (see sections 4.5 and 4.7).

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

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 Armoneve in this population is not recommended.

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

Any abuse of Armoneve by drug addicts is strongly discouraged.

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

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

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

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

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

4.5 Interaction with other medicinal products and other forms of interactions

Substances having a CNS-depressant effect (e.g. other opioids, sedatives, hypnotics, anti-depressants, phenothiazines, neuroleptics, anti-histamines and anti-emetics) may enhance the CNS-depressant effect (e.g. respiratory depression) of Armoneve.

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

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

Oxycodone is metabolised primarily via the CYP3A4 pathways and partly via the CYP2D6 pathway (see section 5.2). The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs or dietary elements. Armoneve 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 Armoneve 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 Armoneve 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 Armoneve 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.

Armoneve 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 taking Armoneve systemic naloxone levels are very low (see section 5.2).

A risk to the breast-fed child cannot be excluded in particular following intake of multiple doses of Armoneve by the breastfeeding mother.

Breastfeeding should be discontinued during treatment with Armoneve.

Fertility

There are no data with respect to fertility.

4.7 Effects on ability to drive and use machines

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

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

4.8 Undesirable effects

The following frequencies are the basis for assessing undesirable effects:

Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)

Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

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

Immune system disorders
Uncommon: Hypersensitivity

Metabolism and nutrition disorders
Common: Decreased appetite up to loss of appetite

Psychiatric disorders
Common: Insomnia
Uncommon: Abnormal thinking, anxiety, confusional state, depression, libido decreased, nervousness, restlessness
Not known: Euphoric mood, hallucination, nightmares

Nervous system disorders
Common: Dizziness, headache, somnolence
Uncommon: Convulsions (particularly in persons with epileptic disorder or predisposition to convulsions), disturbance in attention, dysgeusia, speech disorder, syncope, tremor, lethargy
Not known: Paraesthesia, sedation

Eye disorders
Uncommon: Visual impairment

Ear and labyrinth disorders
Common: Vertigo

Cardiac disorders
Uncommon: Angina pectoris in particular in patients with history of coronary artery disease, palpitations
Rare: Tachycardia

Vascular disorders
Common: Hot flush
Uncommon: Blood pressure decreased, blood pressure increased

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea, rhinorrhoea, cough
Rare: Yawning
Not known: Respiratory depression

Gastrointestinal disorders
Common: Abdominal pain, constipation, diarrhoea, dry mouth, dyspepsia, vomiting, nausea, flatulence
Uncommon: Abdominal distension
Rare: Tooth disorder
Not known: Eructation

Hepatobiliary disorders
Uncommon: Hepatic enzymes increased, biliary colic

Skin and subcutaneous tissue disorders
Common: Pruritus, skin reactions, hyperhidrosis

Musculoskeletal and connective tissue disorders
Uncommon: Muscle spasms, muscle twitching, myalgia

Renal and urinary disorders
Uncommon: Micturition urgency
Not known: Urinary retention

Reproductive system and breast disorders
Not known: Erectile dysfunction

General disorders and administration site conditions
Common: Asthenia, fatigue
Uncommon: Chest pain, chills, drug withdrawal syndrome, malaise, pain, peripheral oedema, thirst,

Investigations
Uncommon: Weight decreased
Rare: Weight increased

Injury, poisoning and procedural complications
Uncommon: Injuries from accidents

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.

Infections and infestations
Rare:Herpes simplex

Immune system disorders
Not known: Anaphylactic responses

Metabolism and nutrition disorders
Uncommon: Dehydration
Rare: Increased appetite

Psychiatric disorders
Common: Altered mood and personality change, decreased activity, psychomotor hyperactivity
Uncommon: Agitation, perception disturbances (e.g. derealisation), drug dependence
Not known: Aggression

Nervous system disorders
Uncommon: Concentration impaired, migraine, hypertonia, involuntary muscle contractions, hypoaesthesia, abnormal coordination
Not known: Hyperalgesia

Ear and labyrinth disorders
Uncommon: Hearing impaired

Vascular disorders
Uncommon: Vasodilatation

Respiratory, thoracic and mediastinal disorders
Uncommon: Dysphonia

Gastrointestinal disorders
Common: Hiccups
Uncommon: Dysphagia, ileus, mouth ulceration, stomatitis
Rare: Melaena, gingival bleeding
Not known: Dental caries

Hepatobiliary disorders
Not known: Cholestasis

Skin and subcutaneous tissue disorders
Uncommon: Dry skin
Rare: Urticaria

Renal and urinary disorders
Common: Dysuria

Reproductive system and breast disorders
Uncommon: Hypogonadism
Not known: Amenorrhoea

General disorders and administration site conditions
Uncommon: Oedema, drug tolerance
Not known: Drug withdrawal syndrome neonatal

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 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 Armoneve 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 sodium chloride 9 mg/ml (0.9%) solution or glucose 50 mg/ml (5%) solution (0.004 mg/ml naloxone). The infusion should be run at a rate aligned to the previously administered bolus doses and to the patient's response.

Consideration may be given to gastric lavage.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics; Opioids; Natural opium alkaloids
ATC code: N02AA55

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

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

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

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

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

Restless legs syndrome
In a 12-week double-blind efficacy study, 150 patients with severe to very severe idiopathic restless legs syndrome at randomisation were treated with oxycodone hydrochloride/naloxone hydrochloride. Severe syndrome is defined as IRLS score between 21 and 30, and very severe as score between 31 and 40. Patients showed a clinically relevant and a statistically significant improvement in mean IRLS score compared to placebo during the entire treatment period with a decrease in the mean IRLS score of 5.9 points compared to placebo at week 12 (assuming an effect similar to placebo completers for patients who discontinued the study representing a very conservative approach).The onset of efficacy was demonstrated from as early as week 1 of treatment. Similar results were shown for the RLS symptom severity improvement (as measured by the RLS-6-Rating scale), in quality of life as measured by a QoL-RLS questionnaire, in sleep quality (measured by MOS sleep scale), and for the proportion of IRLS score remitters. No subject had a confirmed case of 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 metabolized in the gut and the liver to noroxycodone and oxymorphone and to various glucuronide conjugates. Noroxycodone, oxymorphone and noroxymorphone are produced via the cytochrome P450 system. Quinidine reduces the production of oxymorphone in man without substantially influencing the pharmacodynamics of oxycodone. The contribution of the metabolites to overall pharmacodynamic effect is insignificant.

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

Naloxone hydrochloride

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

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

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

Oxycodone hydrochloride / naloxone hydrochloride combination

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

All dosage strengths of Armoneve are interchangeable.

After the oral administration of Armoneve in maximum dose to healthy subjects, the plasma concentrations of naloxone are so low that it is not feasible to carry out a pharmacokinetic analysis. To conduct a pharmacokinetic analysis naloxone-3-glucuronide as surrogate marker is used, since its plasma concentration is high enough to measure.

Overall, following ingestion of a high-fat breakfast, the bioavailability and peak plasma concentration (C_{max}) of oxycodone were increased by an average of 16% and 30% respectively compared to administration in the fasting state. This was evaluated as clinically not relevant, therefore Armoneve 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 Armoneve is unlikely.

Elderly patients

Oxycodone
For AUCt 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 AUCt 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 AUCt 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 AUCt of naloxone, on average there was an increase to 411% (90% C.I.: 152, 1112), 11518% (90% C.I.: 4259, 31149) and 10666% (90% C.I.: 3944, 28847) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers. For C_{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 AUCtvalues.

Naloxone-3-glucuronide
For AUC_{INF} of naloxone-3-glucuronide, on average there was an increase to 157% (90% C.I.: 89, 279), 128% (90% C.I.: 72, 227) and 125% (90% C.I.: 71, 222) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy

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

Patients with impaired renal function

Oxycodone
For AUC_{INF} of oxycodone, on average there was an increase to 153% (90% C.I.: 130, 182), 166% (90% C.I.: 140, 196) and 224% (90% C.I.: 190, 266) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy volunteers. For C_{max} of oxycodone, on average there was an increase to 110% (90% C.I.: 94, 129), 135% (90% C.I.: 115, 159) and 167% (90% C.I.: 142, 196) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy volunteers. For $t_{1/2Z}$ of oxycodone, on average there was an increase to 149%, 123% and 142% for mild, moderate and severe renally impaired subjects, respectively, compared with healthy volunteers.

Naloxone
For AUCtof 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 AUCtvalues. The ratios may have been influenced by the inability to fully characterize 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 , the prolonged-release tablets 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 Armoneve will not have the effect intended. In oxycodone-dependent rats, the intravenous administration of oxycodone hydrochloride / naloxone hydrochloride at a ratio of 2:1 resulted in withdrawal symptoms.

5.3 Preclinical safety data

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

Long-term carcinogenicity studies with oxycodone/naloxone in combination or oxycodone as a single entity have not been performed. For naloxone, a 24-months oral carcinogenicity study was performed in rats with naloxone doses up to 100 mg/kg/day. The results indicate that naloxone is not carcinogenic under these conditions.

Oxycodone and naloxone as single entities show a clastogenic potential in *in vitro* assays. No similar effects were observed, however, under *in vivo* conditions, even at toxic doses. The results indicate that the mutagenic risk of Armoneve to humans at therapeutic concentrations may be ruled out with adequate certainty.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Povidone K30
Ethylcellulose
Stearyl alcohol
Lactose monohydrate
Talc
Magnesium stearate

Tablet coat:
Polyvinyl alcohol, partially hydrolysed
Titanium dioxide (E171)
Macrogol 3350
Talc
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blisters: 3 years
Bottles: 2 years Shelf life after first opening the bottle: 6 months

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Child resistant PVC/aluminium foil blisters

Pack sizes: 10, 14, 20, 28, 30, 50, 56, 60, 98 or 100 prolonged-release tablets
Hospital pack: 100 (10 x 10) prolonged-release tablets

HDPE bottles with a child-resistant PP closure:
Pack size: 100 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

Mundipharma Pharmaceuticals Limited
Millbank House
Arkle Road
Sandyford
Dublin 18
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1688/017/007

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 5th March 2018