# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Myloxifin 5 mg/2.5 mg prolonged-release tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Myloxifin 5 mg/2.5 mg

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.

Myloxifin 5 mg/2.5 mg

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.

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

Myloxifin is indicated in adults.

### 4.2 Posology and method of administration

Posology

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).

**Analgesia**
The analgesic efficacy of Myloxifin 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, Myloxifin 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.

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

Patients already receiving opioids may be started on higher doses of Oxycodone/Naloxone Myloxifin depending on their previous opioid experience.

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

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

Some patients taking Myloxifin according to a regular time schedule require immediate-release analgesics as “rescue” medication for breakthrough pain. Myloxifin 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 Myloxifin 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.>

Myloxifin 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.

**Analgesia**

*Paediatric population*

The safety and efficacy of Myloxifin 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 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 Myloxifin to patients with mild hepatic impairment (see section 4.4). In patients with moderate and severe hepatic impairment Myloxifin 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 Myloxifin to patients with renal impairment (see section 4.4).

Method of administration
For oral use.

These prolonged-release tablets are 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.

Myloxifin 5 mg/2.5 mg
Myloxifin must be swallowed whole with sufficient liquid, and must not be divided, broken, chewed or crushed.

Duration of use
Myloxifin 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).

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).

## 4.3 Contraindications

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

  moderate to severe hepatic impairment.

## 4.4 Special warnings and precautions for use

Respiratory depression

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

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

Hepatobiliary disorders
Oxycodone may cause dysfunction and spasm of the sphincter of Oddi, thus increasing the risk of biliary tract symptoms and pancreatitis. Therefore, oxycodone / naloxone has to be administered with caution in patients with pancreatitis and diseases of the biliary tract.

Diarrhoea
Diarrhoea may be considered as a possible effect of naloxone.

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. Iatrogenic addiction following therapeutic use of opioids is known to occur.
Repeated use of Myloxifin may lead to Opioid Use Disorder (OUD). Abuse or intentional misuse of Myloxifin 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).

Patients will require monitoring for signs of drug-seeking behaviour (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.

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

Myloxifin is not suitable for the treatment of withdrawal symptoms.
Alcohol
Concomitant use of alcohol and Myloxifin may increase the undesirable effects of Myloxifin; concomitant use should be avoided.

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

Surgery
Do not use 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 Myloxifin by drug addicts is strongly discouraged.

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

These tablets 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.

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

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

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

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

Alcohol may enhance the pharmacodynamic effects of Myloxifin; 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. Myloxifin 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 Myloxifin 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

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.

There are no data from the use of Myloxifin 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 Myloxifin 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.

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

Breastfeeding

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

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 Myloxifin by the breastfeeding mother.

Breastfeeding should be discontinued during treatment with Myloxifin.

Fertility
There are no data with respect to fertility.

## 4.7 Effects on ability to drive and use machines

Myloxifin has moderate influence on the ability to drive and use machines. This is particularly likely at the beginning of treatment with Myloxifin, after dose increase or product rotation and if Myloxifin 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 Myloxifin 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 4.5 and 4.7).

## 4.8 Undesirable effects

Undesirable effects are presented below in three sections: the treatment of pain, 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 | | Hyper-sensitivity | | | |

| System organ class MedDRA | Common | Uncommon | Rare | Very rare | Not known |
|---|---|---|---|---|---|
| disorders | | | | | |
| Metabolism and nutrition disorders | Decreased appetite up to loss of appetite | | | | |
| Psychiatric disorders | Insomnia | Restlessness, Abnormal thinking, Anxiety, Confusion state, Depression, libido decreased, Nervousness | | | Euphoric mood, Hallucination, Nightmares, Drug dependence (see section 4.4.) |
| 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 | | | Sphincter of Oddi dysfunction |

| System organ class MedDRA | Common | Uncommon | Rare | Very rare | Not known |
|---|---|---|---|---|---|
| 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, 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<br>Decreased activity<br>Psychomotor hyperactivity | Agitation,<br>Perception disturbances (e.g. derealisation),<br>Drug dependence | | | Aggression |
| Nervous system disorders | | Concentration impaired,<br>Migraine,<br><br>Hypertonia ,<br>Involuntary muscle contractions,<br>Hypoaesthesia,<br>Abnormal co-ordination | | | Hyperalgesia |
| Ear and labyrinth disorders | | Hearing impaired | | | |
| Vascular disorders | | Vasodilation | | | |
| Respiratory, thoracic and mediastinal disorders | | Dysphonia | | | |
| Gastrointestinal disorders | Hiccups | Dysphagia,<br>Ileus,<br>Mouth ulceration,<br>Stomatitis | Melaena,<br>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 | | | Amenorrhoe |
| General disorders and administration site conditions | | Oedema,<br>Drug tolerance | | | 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 the MHRA Yellow Card Scheme, Website: 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 Myloxifin 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.

## 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 (Myloxifin)

*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 Myloxifin 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□ of oxycodone, on average there was an increase to 118% (90% C.I.: 103, 135), for elderly compared with younger volunteers. For $C_{max}$ of oxycodone, on average there was an increase to 114% (90% C.I.: 102, 127). For $C_{min}$ of oxycodone, on average there was an increase to 128% (90% C.I.: 107, 152).

*Naloxone*

For AUC□ of naloxone, on average there was an increase to 182% (90% C.I.: 123, 270), for elderly compared with younger volunteers. For $C_{max}$ of naloxone, on average there was an increase to 173% (90% C.I.: 107, 280). For $C_{min}$ of naloxone, on average there was an increase to 317% (90% C.I.: 142, 708).

*Naloxone-3-glucuronide*

For AUC□ of naloxone-3-glucuronide, on average there was an increase to 128% (90% C.I.: 113, 147), for elderly compared with younger volunteers. For $C_{max}$ of naloxone-3-glucuronide, on average there was an increase to 127% (90% C.I.: 112, 144). For $C_{min}$ of naloxone-3-glucuronide, on average there was an increase to 125% (90% C.I.: 105, 148).

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 $t_{1/2Z}$ 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 $AUC_t$ 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 Myloxifin 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 Myloxifin 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 Myloxifin to humans at therapeutic concentrations may be ruled out with adequate certainty.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Tablet core

Myloxifin 5 mg/2.5 mg

Polyvinyl acetate

Povidone K30

Sodium lauryl sulphate

Silica, colloidal anhydrous

Cellulose, microcrystalline

Magnesium stearate

Tablet coating

Myloxifin 5 mg/2.5 mg

Polyvinyl alcohol,

Titanium dioxide (E171),

Macrogol 3350,

Talc

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

Blister:

3 years

Bottles:

3 years

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

Ridge Pharma Limited
Merlin House
Brunel Road
Theale
Reading RG7 4AB
United Kingdom

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 48804/0013

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

15/07/2020

## 10 DATE OF REVISION OF THE TEXT

30/01/2025