1 NAME OF THE MEDICINAL PRODUCT

Oxycodone hydrochloride/Naloxone hydrochloride 5 mg/2.5 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 5 mg of oxycodone hydrochloride, equivalent to 4.5 mg oxycodone, and 2.5 mg naloxone hydrochloride as 2.75 mg of 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.

Blue, 9.6x4.8mm, elliptic, biconvex coated tablet, engraved with “5” on one 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.

Oxycodone hydrochloride/Naloxone hydrochloride is indicated in adults

4.2 Posology and method of administration

Posology

Analgesia

The analgesic efficacy of Oxycodone hydrochloride/Naloxone hydrochloride is equivalent to oxycodone hydrochloride prolonged-release formulations.

The dosage should be adjusted to the intensity of pain and the sensitivity of the individual patient. Unless otherwise prescribed, Oxycodone hydrochloride/Naloxone hydrochloride 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.

Patients already receiving opioids may be started on higher doses of Oxycodone hydrochloride/Naloxone hydrochloride depending on their previous opioid experience.
Oxycodone hydrochloride/Naloxone hydrochloride 5 mg/2.5 mg is intended for dose titration when initiating opioid therapy and individual dose adjustment.
The maximum daily dose of these tablets is 160 mg oxycodone hydrochloride and 80 mg naloxone hydrochloride. The maximum daily dose is reserved for patients who have previously been maintained on a stable daily dose and who have become in need of an increased dose. Special attention should be given to patients with compromised renal function and patients with mild hepatic impairment if an increased dose is considered. For patients requiring higher doses, administration of supplemental prolonged-release oxycodone hydrochloride at the same time intervals should be considered, taking into account the maximum daily dose of 400 mg prolonged-release oxycodone hydrochloride. In the case of supplemental oxycodone hydrochloride dosing, the beneficial effect of naloxone hydrochloride on bowel function may be impaired.
After complete discontinuation of therapy with these tablets with a subsequent switch to another opioid a worsening of the bowel function can be expected.
Some patients taking these prolonged-release tablets according to a regular time schedule require immediate-release analgesics as “rescue” medication for breakthrough pain. Oxycodone hydrochloride/Naloxone hydrochloride 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 twice daily, or where ¨necessary 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.
Oxycodone hydrochloride/Naloxone hydrochloride 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.

<u>Restless legs syndrome</u>

Oxycodone hydrochloride/Naloxone hydrochloride is indicated for patients suffering from RLS for at least 6 months. RLS symptoms should be present daily and during daytime (≥ 4 days/week). Oxycodone hydrochloride/Naloxone hydrochloride 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 Oxycodone hydrochloride/Naloxone hydrochloride should be under the supervision of a clinician with experience in the management of restless legs syndrome.

Unless otherwise prescribed, Oxycodone hydrochloride/Naloxone hydrochloride 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.

Oxycodone hydrochloride/Naloxone hydrochloride 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

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 these tablets to patients with mild hepatic impairment (see section 4.4). In patients with moderate and severe hepatic impairment Oxycodone hydrochloride/Naloxone hydrochloride is contraindicated (see section 4.3).

Renal impairment
A clinical trial has shown that plasma concentrations of both oxycodone and naloxone are elevated in patients with renal impairment (see section 5.2). Naloxone concentrations were affected to a higher degree than oxycodone. The clinical relevance of a relative high naloxone exposure in renal impaired patients is yet not known. Caution should be exercised when administering these tablets to patients with renal impairment (see section 4.4).

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

Method of administration

Oral use.

These prolonged-release tablets are taken in the determined dosage twice daily in a fixed time schedule.

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

Duration of use

These tablets should not be administered for longer than absolutely necessary.

If long-term pain 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 Oxycodone hydrochloride/Naloxone hydrochloride patients should be clinically evaluated. Treatment should only be continued if Oxycodone hydrochloride/Naloxone hydrochloride 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 Oxycodone hydrochloride/Naloxone hydrochloride over a period of approximately one week should be considered to establish if continued treatment with Oxycodone hydrochloride/Naloxone hydrochloride 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

Caution must be exercised when administering these tablets to patients with:

- Impaired respiratory function,
- Sleep apnoea,
- CNS depressants co-administration (see below and section 4.5)
- Monoamine oxidase inhibitors (MAOIs, see below and section 4.5)
- Tolerance, physical dependence and withdrawal (see below)
- Psychological dependence [addiction], abuse profile and history of substance and/or alcohol abuse (see below)
- Elderly or infirm
- Head injury, intracranial lesions or increased intracranial pressure,
- Reduced level of consciousness of uncertain origin
- Epileptic disorder or predisposition to convulsions
- Hypotension
- Hypertension
- Pancreatitis
- Mild hepatic impairment
- Renal impairment
- Opioid-induced paralytic ileus
- Myxoedema
- Hypothyroidism
- Addison's disease (adrenal cortical insufficiency)
- Prostate hypertrophy
- Toxic psychosis
- Alcoholism
- Delirium tremens
- Cholelithiasis
- Pre-existing cardiovascular diseases

Respiratory depression

The primary risk of opioid excess is respiratory depression.

Sleep-related breathing disorders

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

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

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

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

MAOIs

Oxycodone hydrochloride/Naloxone hydrochloride must be administered with caution in patients taking MAOIs or who have received MAOIs within the previous two weeks.

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 these tablets to patients with mild hepatic or renal impairment. Careful medical monitoring is particularly necessary for patients with severe renal impairment.

Diarrhoea may be considered as a possible effect of naloxone.

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 Oxycodone hydrochloride/Naloxone hydrochloride may lead to Opioid Use Disorder (OUD). Abuse or intentional misuse of Oxycodone hydrochloride/Naloxone hydrochloride 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.

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 Oxycodone hydrochloride/Naloxone hydrochloride in the long-term treatment of RLS beyond 1 year (see section 4.2).

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 Oxycodone hydrochloride/Naloxone hydrochloride (see sections 4.5 and 4.7).

Concomitant use of alcohol and Oxycodone hydrochloride/Naloxone hydrochloride may increase the undesirable effects of Oxycodone hydrochloride/Naloxone hydrochloride; concomitant use should be avoided.

Studies have not been performed on the safety and efficacy of Oxycodone hydrochloride/Naloxone hydrochloride in children and adolescents below the age of 18 years. Therefore, their use in children and adolescents under 18 years of age is not recommended.

There is no clinical experience in patients with cancer associated to peritoneal carcinomatosis or with sub-occlusive syndrome in advanced stages of digestive and pelvic cancers. Therefore, the use of these tablets in this population is not recommended.

These tablets are not recommended for pre-operative use or within the first 12-24 hours post-operatively. Depending on the type and extent of surgery, the anaesthetic procedure selected, other co-medication and the individual condition of the patient,

the exact timing for initiating post-operative treatment with these tablets depends on a careful risk-benefit assessment for each individual patient.

Any abuse of these tablets by drug addicts is strongly discouraged.

If abused parenterally, intranasally or orally by individuals dependent on opioid agonists, such as heroin, morphine, or methadone, these tablets areexpected to produce marked withdrawal symptoms - because of the opioid receptor antagonist characteristics of naloxone - or to intensify withdrawal symptoms already present (see section 4.9).

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

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

Opioids such as oxycodone may influence the hypothalamic-pituitary-adrenal or –gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical symptoms may manifest from these hormonal changes.

The use of Oxycodone hydrochloride/Naloxone hydrochloride may produce positive results in doping controls. The use of Oxycodone hydrochloride/Naloxone hydrochloride as a doping agent may become a health hazard.

Oxycodone hydrochloride/Naloxone hydrochloride contains less than 1 mmol sodium (23 mg) per dosage unit, 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).

Substances having a CNS-depressant effect (e.g. other opioids, gabapentinoids such as pregabalin, anxiolytics, sedatives (including benzodiazepines), hypnotics, antidepressants, antipsychotics,phenothiazines, neuroleptics, anti-histamines and anti-emetics) may enhance the CNS-depressant effect (e.g. respiratory depression) of Oxycodone hydrochloride/Naloxone hydrochloride.

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 Oxycodone hydrochloride/Naloxone hydrochloride, 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. Oxycodone hydrochloride/Naloxone hydrochloride doses may need to be adjusted accordingly.

CYP3A4 inhibitors, such as macrolide antibiotics (e.g. clarithromycin, erythromycin, telithromycin), azole-antifungal agents (e.g. ketoconazole, voriconazole, itraconazole, posaconazole), protease inhibitors (e.g. ritonavir, indinavir, nelfinavir, saquinavir), cimetidine and grapefruit juice may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. A reduction in the dose of these tablets and subsequent re-titration may be necessary.

CYP3A4 inducers, such as rifampicin, carbamazepine, phenytoin and St. John's Wort, may induce the metabolism of oxycodone and cause increased clearance of the drug, resulting in a decrease in oxycodone plasma concentrations. Caution is advised and further titration may be necessary to reach an adequate level of symptom control.

Theoretically, medicinal products that inhibit CYP2D6 activity, such as paroxetine, fluoxetine and quinidine, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. Concomitant administration with CYP2D6 inhibitors had an insignificant effect on the elimination of oxycodone and also had no influence on the pharmacodynamic effects of oxycodone.

In vitro metabolism studies indicate that no clinically relevant interactions are to be expected between oxycodone and naloxone. The likelihood of clinically relevant interactions between paracetamol, acetylsalicylic acid or naltrexone and the combination of oxycodone and naloxone in therapeutic concentrations is minimal. 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).

Substances having a CNS-depressant effect (e.g. other opioids, gabapentinoids such as pregabalin, anxiolytics, sedatives (including benzodiazepines), hypnotics, antidepressants, antipsychotics,phenothiazines, neuroleptics, anti-histamines and anti-emetics) may enhance the CNS-depressant effect (e.g. respiratory depression) of Oxycodone hydrochloride/Naloxone hydrochloride.

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 Oxycodone hydrochloride/Naloxone hydrochloride, 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.

Oxycodone hydrochloride/Naloxone hydrochloride doses may need to be adjusted accordingly.

CYP3A4 inhibitors, such as macrolide antibiotics (e.g. clarithromycin, erythromycin, telithromycin), azole-antifungal agents (e.g. ketoconazole, voriconazole, itraconazole, posaconazole), protease inhibitors (e.g. ritonavir, indinavir, nelfinavir, saquinavir), cimetidine and grapefruit juice may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. A reduction in the dose of these tablets and subsequent re-titration may be necessary.

CYP3A4 inducers, such as rifampicin, carbamazepine, phenytoin and St. John's Wort, may induce the metabolism of oxycodone and cause increased clearance of the drug, resulting in a decrease in oxycodone plasma concentrations. Caution is advised and further titration may be necessary to reach an adequate level of symptom control.

Theoretically, medicinal products that inhibit CYP2D6 activity, such as paroxetine, fluoxetine and quinidine, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. Concomitant administration with CYP2D6 inhibitors had an insignificant effect on the elimination of oxycodone and also had no influence on the pharmacodynamic effects of oxycodone.

In vitro metabolism studies indicate that no clinically relevant interactions are to be expected between oxycodone and naloxone. The likelihood of clinically relevant interactions between paracetamol, acetylsalicylic acid or naltrexone and the combination of oxycodone and naloxone in therapeutic concentrations is minimal.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of Oxycodone hydrochloride/Naloxone hydrochloride in pregnant women and during childbirth. Limited data on the use of oxycodone during pregnancy in humans reveal no evidence of an increased risk of congenital abnormalities. For naloxone, insufficient clinical data on exposed pregnancies are available. However, systemic exposure of the women to naloxone after use of these tablets is relatively low (see section 5.2). Both oxycodone and naloxone pass into the placenta. Animal studies have not been performed with oxycodone and naloxone in combination (see section 5.3). Animal studies with oxycodone or naloxone administered as single drugs have not revealed any teratogenic or embryotoxic effects.

Long-term administration of oxycodone during pregnancy may lead to withdrawal symptoms in the newborn. If administered during childbirth, oxycodone may evoke respiratory depression in the newborn.

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

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 these tablets systemic naloxone levels are very low (see section 5.2).

A risk to the suckling child cannot be excluded in particular following intake of multiple doses of these tablets by the breastfeeding mother.

Breastfeeding should be discontinued during treatment with Oxycodone hydrochloride/Naloxone hydrochloride.

Fertility

There are no data with respect to fertility.

4.7 Effects on ability to drive and use machines

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

Patients being treated with Oxycodone hydrochloride/Naloxone hydrochloride 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).

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while you have this medicine in your body over a specified limit unless you have a defence (called the 'statutory defence').
- This defence applies when:
  - The medicine has been prescribed to treat a medical or dental problem; and
  - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine.
- Please note that it is still an offence to drive if you are unfit because of the medicine (i.e. your ability to drive is being affected)

Details regarding a new driving offence concerning driving after drugs have been taken in the UK may be found here: https://www.gov.uk/drug-driving-law.

4.8 Undesirable effects

The following frequencies are the basis for assessing undesirable effects:

Term	Frequency

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 in the 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	Drug dependence		Euphoric mood, Hallucination, Nightmares Aggression
Nervous system disorders	Dizziness, Headache, Somnolence	Convulsions[1], Disturbance in attention, Dygeusia, Speech disorder, Syncope, Tremor, Lethargy			Paraesthesia, Sedation
Eye disorders		Visual impairment			
Ear and labyrinth disorders	Vertigo				
Cardiac disorders		Angina pectoris[2], Palpitations	Tachycardia		

System organ class MedDRA	Common	Uncommon	Rare	Very rare	Not known
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			
Skin and subcutaneous tissue disorders	Pruritus, Skin reactions, Hyperhydrosis				
Musculoskeletal and connective tissue disorders		Muscle spasm, 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	Chest pain, Chills, Drug withdrawal syndrome, Malaise,			

System organ class MedDRA	Common	Uncommon	Rare	Very rare	Not known
		Pain, Peripheral oedema, Thirst			
Investigations		Weight decreased	Weight increased		
Injury, poisoning and procedural complications		Injury from accidents			

1 particulary in persons with epileptic disorder or predisposition to convulsions

2 in 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 spam 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 responses
Metabolism and nutritional disorders		Dehydration	Increased appetite		
Psychiatric disorders	Altered mood and personality change, Decreased activity, Psychomotor hyperactivity	Agitation, Perception disturbances (e.g. derealisation),			

System organ class MedDRA	Common	Uncommon	Rare	Very rare	Not known
Nervous system disorders		Concentration impaired, Migraine, Hypertonia, Involuntary muscle contractions, Hypoaesthesia, Abnormal co-ordination			Hyperalgesia
Ear and labyrinth disorders		Hearing impaired			
Vascular disorders		Vasodilatation			
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 disorder		Dry skin	Urticaria		
Renal and urinary disorders	Dysuria				
Reproductive system and breast disorders		Hypogonadism			Amenorrhoea
General disorders and application site conditions		Oedema, Drug tolerance			Drug withdrawal syndrome neonatal

Undesirable effects in the treatment of restless leg syndrome

The list below reflects the adverse drug reactions seen with Oxycodone hydrochloride /Naloxone hydrochloride in a 12-week, randomised, placebo-controlled clinical trial

comprising a total of 150 patients on Oxycodone hydrochloride/Naloxone hydrochloride and 154 patients on placebo with daily dosages between 10 mg/5 mg and 80 mg/40 mg oxycodone hydrochloride/naloxone hydrochloride. Adverse drug reactions associated with these tablets in pain and not observed in RLS study population were added with the frequency of not known.

System organ class MedDRA	Very common	Common	Uncommon	Rare	Very rare	Not known
Immune system disorders						Hypersensitivity
Metabolism and nutritional disorders		Decreased appetite up to loss of appetite				
Psychiatric disorders		Insomnia, depression	Libido decreased, sleep attacks			Abnormal thinking, anxiety, confusional state, nervousness, restlessness, euphoric mood, hallucination, nightmares, drug dependence, aggression
Nervous system disorders	Headache, somnolence	Dizziness, disturbance in attention, tremor, paraesthesia	Dysgeusia			Convulsions (particularly in persons with epileptic disorder or predisposition to convulsions), sedation, speech disorder, syncope, lethargy
Eye disorders		Visual impairment				
Ear and labyrinth disorders		Vertigo				
Cardiac disorders						Angina pectoris (in particular in patients with history of coronary artery disease), palpitations, tachycardia
Vascular disorders		Hot flush, blood pressure decreased, blood pressure increased				
Respiratory, thoracic and mediastinal disorders			Dyspnoea			Cough, rhinorrhoea, respiratory depression, yawning

System organ class MedDRA	Very common	Common	Uncommon	Rare	Very rare	Not known
Gastrointestinal disorders	Constipation, nausea	Abdominal pain, dry mouth, vomiting	Flatulence			Abdominal distension, diarrhoea, dyspepsia, eructation, tooth disorder
Hepatobiliary disorders		Hepatic enzymes increased (alanine aminotransferase increased, gamma-glutamyltransferase increased)				Biliary colic
Skin and subcutaneous tissue disorder	Hyperhidrosis	Pruritus, skin reactions				
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 application site conditions	Fatigue	Chest pain, chills, thirst, pain	Drug withdrawal syndrome, oedema peripheral,			Malaise, asthenia
Investigation						Weight decreased, weight increased
Injury, poisoning and procedural complications			Injuries from accidents			

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the 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

Symptoms of intoxication

Depending on the history of the patient, an overdose of Oxycodone hydrochloride/Naloxone hydrochloride 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: Analgesics; Opioids; Natural opium alkaloids.

ATC code: N02A A55.

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.

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 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 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 (Oxycodone hydrochloride/Naloxone hydrochloride)

Pharmacokinetic/pharmacodynamic relationships

The pharmacokinetic characteristics of oxycodone from Oxycodone hydrochloride/Naloxone hydrochloride are equivalent to those of prolonged-release oxycodone hydrochloride tablets administered together with prolonged-release naloxone hydrochloride tablets.

All dosage strengths of Oxycodone hydrochloride/Naloxone hydrochloride 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 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 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 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□ 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□ values. The ratios may have been influenced by the inability to fully characterize the naloxone plasma profiles for the healthy subjects.

Naloxone-3-glucuronide

For 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 hydrochloride/Naloxone hydrochloride 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 hydrochloride/Naloxone hydrochloride 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 fetuses 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/fetotoxic, 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 hydrochloride/Naloxone hydrochloride 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 Oxycodone hydrochloride/Naloxone hydrochloride to humans at therapeutic concentrations may be ruled out with adequate certainty.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Hypromellose

Polyvinyl acetate

Povidone

Sodium laurilsulfate

Cellulose microcrystalline

Silicon dioxide

Colloidal anhydrous silica

Magnesium stearate.

Tablet coat:

Polyvinyl alcohol

Titanium dioxide (E171)

Macrogol 3350

Talc

Brillant blue FCF aluminum lake (E133)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Peelable, child resistant perforated unit dose blister: Polyamide-Aluminium-PVC / Aluminium-PET foil blister.

Pack sizes:

10x1, 14x1, 20x1, 28x1, 30x1, 50x1, 56x1, 60x1, 98x1, 100x1, and 100x1 (Hospital pack) 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

Ethypharm

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92213 Saint Cloud cedex

France

8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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