SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Reltebon 5mg Prolonged-release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 5 mg oxycodone hydrochloride corresponding to 4.5 mg of oxycodone.

Excipient with known effect:

The prolonged-release tablets contain lactose monohydrate.

Each prolonged-release tablet contains 31.6 mg lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

Blue, round, biconvex tablets, 7 mm in diameter, with ‘OX 5’ debossed on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Reltebon is indicated in adults and adolescents aged 12 years and older.

4.2 Posology and method of administration

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

Posology
The dosage depends on the intensity of pain and the patient's individual susceptibility to the treatment. The following general dosage recommendations apply:

Adults and adolescents 12 years of age and older
Dose titration and adjustment

In general, the initial dose for opioid naïve patients is 10 mg oxycodone hydrochloride given at intervals of 12 hours. Some patients may benefit from a starting dose of 5 mg to minimize the incidence of side effects.

Patients already receiving opioids may start treatment with higher dosages taking into account their experience with former opioid therapies.

For doses not realisable/practicable with these strengths, other strengths are available.

According to well-controlled clinical studies 10-13 mg oxycodone hydrochloride correspond to approximately 20 mg morphine sulphate, both in the prolonged-release formulation.

Because of individual differences in sensitivity for different opioids, it is recommended that patients should start conservatively with Reltebon prolonged-release tablets after conversion from other opioids, with 50-75% of the calculated oxycodone dose.

Some patients who take Reltebon prolonged-release tablets following a fixed schedule need rapid release analgesics as rescue medication in order to control breakthrough pain. Reltebon prolonged-release tablets are not indicated for the treatment of acute pain and/or breakthrough pain. The single dose of the rescue medication should amount to 1/6 of the equianalgesic daily dose of Reltebon prolonged-release tablets. Use of the rescue medication more than twice daily indicates that the dose of Reltebon prolonged-release tablets needs to be increased. The dose should not be adjusted more often than once every 1-2 days until a stable twice daily administration has been achieved.

Following a dose increase from 10 mg to 20 mg taken every 12 hours dose adjustments should be made in steps of approximately one third of the daily dose. The aim is a patient- specific dosage which, with twice daily

administration, allows for adequate analgesia with tolerable undesirable effects and as little rescue medication as possible as long as pain therapy is needed.

Even distribution (the same dose mornings and evenings) following a fixed schedule (every 12 hours) is appropriate for the majority of the patients. For some patients it may be advantageous to distribute the doses unevenly. In general, the lowest effective analgesic dose should be chosen. For the treatment of non- malignant pain a daily dose of 40 mg is generally sufficient; but higher dosages may be necessary. Patients with cancer- related pain may require dosages of 80 to 120 mg, which in individual cases can be increased to up to 400 mg. If even higher doses are required, the dose should be decided individual balancing efficacy with the tolerance and risk of undesirable effects.

Use in non-malignant pain
Opioids are not first-line therapy for chronic non-malignant pain, nor are they recommended as the only treatment. Types of chronic pain which have been shown to be alleviated by strong opioids include chronic osteoarthritic pain and intervertebral disc disease.

Transferring patients between oral and parenteral oxycodone:
The dose should be based on the following ratio: 2 mg of oral oxycodone is equivalent to 1 mg of parenteral oxycodone. It must be emphasised that this is a guide to the dose required. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

Treatment goals and discontinuation
Before initiating treatment with Reltebon, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with oxycodone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

Duration of administration
Reltebon prolonged-release tablets should not be taken longer than necessary.

Paediatric population
There have been no studies in patients under 12 years of age, therefore oxycodone hydrochloride should not be used in patients under 12 years.

Controlled pharmacokinetic studies in elderly patients (aged over 65 years) have shown that, compared with younger adults, the clearance of oxycodone is only slightly reduced. No untoward adverse drug reactions were seen based on age, therefore adult doses and dosage intervals are appropriate.

Elderly patients
A dose adjustment is not usually necessary in elderly patients.

Patients with renal or hepatic impairment
The dose initiation should follow a conservative approach in these patients. The recommended adult starting dose should be reduced by 50% (for example a total daily dose of 10 mg orally in opioid naïve patients), and each patient should be titrated to adequate pain control according to their clinical situation.

Risk patients
Risk patients, for example patients with low body weight or slow metabolism of medicinal products, should initially receive half the recommended adult dose if they are opioid naïve. Dose titration should be performed in accordance with the individual clinical situation.

For instructions how to open the child resistant blisters, see section 6.6.

Method of administration

For oral use.

Reltebon prolonged-release tablets should be taken twice daily based on a fixed schedule at the dosage determined.

The prolonged-release tablets may be taken with or independent of meals with a sufficient amount of liquid. Reltebon prolonged release tablets must be swallowed whole and not broken, chewed or crushed.

4.3 Contraindications

- Hypersensitivity to oxycodone or to any of the excipients listed in section 6.1.

Oxycodone must not be used in any situation where opioids are contraindicated:

- Severe respiratory depression with hypoxia and/or hypercapnia.
- Severe chronic obstructive pulmonary disease.
- Cor pulmonale.
- Severe bronchial asthma.
- Elevated carbon dioxide levels in the blood.
- Paralytic ileus.
- Acute abdomen, delayed gastric emptying.
- Moderate to severe hepatic impairment
- Chronic constipation

4.4 Special warnings and precautions for use

Paediatric population
Reltebon prolonged-release tablets have not been studied in children younger than 12 years of age. The safety and efficacy of the tablets have not been demonstrated and the use in children younger than 12 years of age is therefore not recommended.

Elderly or debilitated patients
Caution must be exercised when administering oxycodone to the debilitated elderly, patients with severely impaired pulmonary function, patients with impaired hepatic or renal function, patients with myxoedema, hypothyroidism, Addison's disease, toxic psychosis, prostate hypertrophy, adrenocortical insufficiency, alcoholism, delirium tremens, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, hypotension, hypovolaemia, raised intracranial pressure, intracranial lesions, head injury (due to risk of increased intracranial pressure), reduced level of consciousness of uncertain origin, sleep apnoea or patients taking benzodiazepines, other CNS depressants (including alcohol) or MAO inhibitors (see section 4.5).

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 has to be administered with caution in patients with pancreatitis and diseases of the biliary tract.

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 fashion. Opioids may also cause worsening of pre-existing sleep apnoea (see section 4.8). 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 Reltebon prolonged-release tablets 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 Reltebon prolonged-release tablets concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).

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).

Reltebon prolonged-release tablets must be administered with caution in patients taking MAOIs or who have received MAOIs within the previous two weeks.
Reltebon prolonged-release tablets should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, Reltebon prolonged-release tablets should be discontinued immediately.

Pre-operative use
Reltebon prolonged release tablets are not recommended for pre-operative use or within the first 12-24 hours post operatively.

Patients undergoing abdominal surgery
As with all opioid preparations, oxycodone products should be used with caution following abdominal surgery as opioids are known to impair intestinal motility and should not be used until the physician is assured of normal bowel function.

Patients about to undergo additional pain-relieving procedures (e.g. surgery, plexus blockade) should not receive Reltebon prolonged-release tablets for 12 hours prior to the intervention. If further treatment with Reltebon prolonged-release tablets is indicated then the dosage should be adjusted to the new post-operative requirement.

Post-operative use
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).

Initial and long-term use
For appropriate patients who suffer with chronic non-malignant pain, opioids should be used as part of a comprehensive treatment programme involving other medications and treatment modalities. A crucial part of the assessment of a patient with chronic non-malignant pain is the patient's addiction and substance abuse history.

If opioid treatment is considered appropriate for the patient, then the main aim of treatment is not to minimise the dose of opioid but rather to achieve a dose, which provides adequate pain relief with a minimum of side effects.

Drug dependence, tolerance and potential for abuse

Opioid Use Disorder (abuse and dependence)
Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as oxycodone.

Repeated use of Reltebon may lead to Opioid Use Disorder (OUD). A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of Reltebon may result in overdose and/or death. The risk of developing OUD is increased in patients

with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with Reltebon and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician.

Patients will require monitoring for signs of drug-seeking 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 hydrochloride.

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.

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

Tablets must not be chewed or crushed
To avoid damage to the controlled release properties of the tablets the prolonged release tablets must be swallowed whole, and not broken, chewed or crushed. The administration of broken, chewed or crushed controlled release oxycodone tablets leads to rapid release and absorption of a potentially fatal dose of oxycodone (see section 4.9).

Alcohol
Concomitant use of alcohol and oxycodone hydrochloride prolonged-release tablets may increase the undesirable effects of oxycodone hydrochloride; concomitant use should be avoided.

Abuse of oral dosage forms by parenteral administration can be expected to result in serious adverse events, such as local tissue necrosis, infection, pulmonary granulomas, increased risk of endocarditis, and valvular heart injury, which may be fatal.

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

4.5 Interaction with other medicinal products and other forms of interaction

The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

Drugs which affect the CNS include, but are not limited to: other opioids, gabapentinoids such as pregabalin, anxiolytics, hypnotics and sedatives (including benzodiazepines), antipsychotics, antidepressants, phenothiazines, anaesthetics, muscle relaxants, antihypertensives and alcohol.

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.

Concomitant administration of oxycodone with anticholinergics or medicines with anticholinergic activity (e.g. tricyclic anti-depressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects. Oxycodone should be used with caution and the dosage may need to be reduced in patients using these medications.

MAO-inhibitors are known to interact with narcotic analgesics. MAO-inhibitors cause CNS-excitation or depression associated with hypertensive or hypotensive crisis (see section 4.4). Co-administration with monoamine oxidase inhibitors or within two weeks of discontinuation of their use should be avoided. Alcohol may enhance the pharmacodynamic effects of oxycodone; concomitant use should be avoided.

Oxycodone is metabolised mainly by CYP3A4, with a contribution from CYP2D6. The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs or dietary elements. Oxycodone doses may need to be adjusted accordingly.

CYP3A4 inhibitors, such as macrolide antibiotics (e.g. clarithromycin, erythromycin and telithromycin), azole-antifungals (e.g. ketoconazole, voriconazole, itraconazole, and posaconazole), protease inhibitors (e.g. boceprevir, ritonavir, indinavir, nelfinavir and saquinavir), cimetidine and grapefruit juice may cause a reduced clearance of oxycodone that could cause an increase of the plasma concentrations of oxycodone. Therefore the oxycodone dose may need to be adjusted accordingly.

Some specific examples are provided below:

- Itraconazole, a potent CYP3A4 inhibitor, administered 200 mg orally for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 2.4 times higher (range 1.5 - 3.4).

- Voriconazole, a CYP3A4 inhibitor, administered 200 mg twice-daily for four days (400 mg given as first two doses), increased the AUC of oral oxycodone. On average, the AUC was approximately 3.6 times higher (range 2.7 - 5.6).

- Telithromycin, a CYP3A4 inhibitor, administered 800 mg orally for four days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.8 times higher (range 1.3 – 2.3).

- Grapefruit Juice, a CYP3A4 inhibitor, administered as 200 ml three times a day for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.7 times higher (range 1.1 – 2.1).

CYP3A4 inducers, such as rifampicin, carbamazepine, phenytoin and St John´s Wort may induce the metabolism of oxycodone and cause an increased clearance of oxycodone that could cause a reduction of the plasma concentrations of oxycodone. The oxycodone dose may need to be adjusted accordingly.

Some specific examples are provided below:

- St John's Wort, a CYP3A4 inducer, administered as 300 mg three times a day for fifteen days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 50% lower (range 37-57%).

- Rifampicin, a CYP3A4 inducer, administered as 600 mg once-daily for seven days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 86% lower

Drugs that inhibit CYP2D6 activity, such as paroxetine and quinidine, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. Concurrent administration of quinidine resulted in an increase in oxycodone Cmax by 11%, AUC by 13%, and t½ elim. by 14%. Also, an increase in noroxycodone level was observed, (Cmax by 50%; AUC by 85%, and t½ elim. by 42%). The pharmacodynamic effects of oxycodone were not altered.

4.6 Fertility, pregnancy and lactation

Pregnancy

Reltebon prolonged release tablets tablets are not recommended for use in pregnancy nor during labour. There are limited data from the use of oxycodone in pregnant women.

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

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

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

Breastfeeding

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

4.7 Effects on ability to drive and use machines

Oxycodone may impair the ability to drive and use machines.

Oxycodone may modify patients' reactions to a varying extent depending on the dosage and individual susceptibility. Therefore, patients should not drive or operate machinery if affected.

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 under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
  - 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 and
  - It was not affecting your ability to drive safely

4.8 Undesirable effects

Adverse drug reactions are typical of full opioid agonists. Tolerance and dependence may occur (see Section 4.4). Constipation may be prevented with an appropriate laxative. If nausea and vomiting are troublesome, oxycodone may be combined with an anti-emetic.

The following frequency categories form the basis for classification of the 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
Frequency not known	Cannot be estimated from the available data

Body System	**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)**	**Frequency unknown (Cannot be estimated from the available data)**
Blood and lymphatic system disorders				lymphadenopathy	
Immune system			hypersensitivity		anaphylactic reaction, anaphylactoid

disorders					reaction.
Endocrine disorders			syndrome of inappropriate antidiuretic hormone secretion		
Metabolism and nutrition disorders		decreased appetite	dehydration		
Psychiatric disorders		anxiety, confusional state, depression, insomnia, nervousness. abnormal thinking, abnormal dreams	agitation, affect lability, euphoric mood, hallucinations, decreased libido, disorientation, mood altered, restlessness, dysphoria, depersonalisation, change in taste, hyperacousis		Aggression, drug dependence (see section 4.4)
Nervous system disorders	somnolence, dizziness, headache	tremor, lethargy, sedation	amnesia, convulsion, hypertonia, involuntary muscle contractions; hypoaesthesia; coordination disturbances; speech disorder, syncope, paraesthesia, dysgeusia, hypotonia		Hyperalgesia
Eye disorders			visual impairment, lacrimation disorder, miosis		
Ear and labyrinth disorders			vertigo		
Cardiac disorders			supraventricular tachycardia; palpitations (in the context of withdrawal syndrome)		
Vascular disorders			vasodilatation, facial flushing	hypotension, orthostatic	

				hypotension	
Respiratory, thoracic and mediastinal disorders		dyspnoea, bronchospasm, cough decreased	increased coughing; pharyngitis; rhinitis; voice changes, respiratory depression, hiccups		central sleep apnoea syndrome
Gastrointestinal disorders	constipation, nausea, vomiting	dry mouth, gastrointestinal disorders such as abdominal pain; diarrhoea; dyspepsia; loss of appetite	oral ulcers; gingivitis; stomatitis; flatulence, dysphagia, eructation, ileus gastritis	gum bleeding; increased appetite; tarry stool; tooth staining	dental caries
Hepato-biliary disorders			increased hepatic enzymes, biliary colic		cholestasis, spasm of sphincter of Oddi
Skin and subcutaneous tissue disorders	pruritus	skin eruptions including rash, in rare cases increased photosensitivity, in isolated cases urticaria or exfoliative dermatitis, hyperhidrosis	dry skin, exfoliative dermatitis	herpes simplex, urticaria	
Renal and urinary disorders		micturition disturbances (increased urge to urinate)	urinary retention, ureteral spasm	haematuria	
Reproductive system and breast disorders			reduced libido; erectile disfunction, hypogonadism		amenorrhoea
General disorders and administration site conditions		asthenia, fatigue	accidental injuries; pain (e.g. chest pain); oedema; migraine; drug tolerance, chills, malaise, peripheral oedema, thirst, pyrexia, drug withdrawal syndrome	weight changes (increase or decrease); cellulitis	drug withdrawal syndrome neonatal, opioid tolerance, opioid withdrawal syndrome

Description of selected adverse reactions

Opioid Tolerance and Opioid Withdrawal Syndrome
The frequency of opioid tolerance and the frequency of opioid withdrawal syndrome cannot be estimated from available evidence (e.g. clinical trials, spontaneous reporting, and the medical literature) and therefore is classified as " not known" (see section 4.8). 'Not known' should not be interpreted as an indication of the rarity of the occurrence of opioid tolerance and opioid withdrawal syndrome, but a reflection of the limitations in the available evidence that do not support a precise estimate of frequency.

Drug dependence
The frequency above regarding drug dependence reflects the current evidence, including cumulative data from clinical trials and additional post marketing sources, and indicates that the risk of drug dependence with opioids is highly variable depending upon: definition of drug dependence; duration of treatment; dose; individual patient risk factors; and clinical settings. 'Not known' should not be interpreted as an indication of the rarity of the occurrence of drug dependence, but a reflection of the limitations in the available evidence that do not support a precise estimate of frequency.

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system 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:
Acute overdose with oxycodone can be manifested by miosis, respiratory depression, hypotension and hallucinations. Circulatory failure and somnolence progressing to stupor or deepening coma, hypotonia, bradycardia, pulmonary oedema and death may occur in more severe cases. Toxic leukoencephalopathy has been observed with oxycodone 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.

The effects of overdosage will be potentiated by the simultaneous ingestion of alcohol or other psychotropic drugs.

Management:
Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation

The pure opioid antagonists such as naloxone are specific antidotes against symptoms from opioid overdose. Other supportive measures should be employed as needed.

In the case of massive overdosage, administer naloxone intravenously (0.4 to 2 mg for an adult and 0.01 mg/kg body weight for children) if the patient is in a coma or respiratory depression is present.

Repeat the dose at 2 minute intervals if there is no response. If repeated doses are required an infusion of 60% of the initial dose per hour is a useful starting point. A solution of 10 mg made up in 50 ml dextrose will produce 200 micrograms/ml for infusion using an IV pump (dose adjusted to the clinical response). Infusions are not a substitute for frequent review of the patient's clinical state. Intramuscular naloxone is an alternative in the event that IV access is not possible. As the duration of action of naloxone is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established. Naloxone is a competitive antagonist and large doses (4 mg) may be required in seriously poisoned patients.
For less severe overdosage, administer naloxone 0.2 mg intravenously followed by increments of 0.1 mg every 2 minutes if required.
The patient should be observed for at least 6 hours after the last dose of naloxone.
Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdosage.
Naloxone should be administered cautiously to persons who are known, or suspected, to be physically dependent on oxycodone. In such cases, an abrupt or complete reversal of opioid effects may precipitate pain and an acute withdrawal syndrome.

Additional/ other considerations:
Consider activated charcoal (50 g for adults, 10 -15 g for children), if a substantial amount has been ingested within 1 hour, provided the airway can be protected. It may be reasonable to assume that late administration of activated charcoal may be beneficial for prolonged release preparations; however there is no evidence to support this.

Reltebon prolonged-release tablets will continue to release and add to the oxycodone load for up to 12 hours after administration and the management of oxycodone overdosage should be modified accordingly. Gastric contents may therefore need to be emptied as this can be useful in removing unabsorbed drug, particularly when a prolonged release formulation has been taken.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids

ATC-Code: N02A A05

Oxycodone shows an affinity to kappa, mu and delta opioid receptors in the brain and spinal cord. It acts at these receptors as an opioid agonist without an antagonistic effect. The therapeutic effect is mainly analgesic and sedative. Compared to rapid-release oxycodone, given alone or in combination with other substances, the prolonged-release tablets provide pain relief for a markedly longer period without increased occurrence of undesirable effects.

Gastrointestinal System
Opioids may induce spasm of the sphincter of Oddi.

Endocrine system
Opioids 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 be manifest from these hormonal changes.

Other pharmacological effects
In- vitro and animal studies indicate various effects of natural opioids, such as morphine, on components of the immune system; the clinical significance of these findings is unknown. Whether oxycodone, a semisynthetic opioid, has immunological effects similar to morphine is unknown.

Clinical studies
The efficacy of Oxycodone prolonged-release tablets has been demonstrated in cancer pain, post-operative pain and severe non-malignant pain such as diabetic neuropathy, postherpetic neuralgia, low back pain and osteoarthritis. In the latter indication, treatment was continued for up to 18 months and proved effective in many patients for whom NSAIDs alone provided inadequate relief. The efficacy of Oxycodone prolonged-release tablets in neuropathic pain was confirmed by three placebo-controlled studies.

In patients with chronic non-malignant pain, maintenance of analgesia with stable dosing was demonstrated for up to three years.

5.2 Pharmacokinetic properties

Absorption:
The release of oxycodone from Reltebon prolonged-release tablets is biphasic with an initial relatively fast release providing an early onset of analgesia followed by a more controlled release, which determines the 12 hour duration of action.
Release of oxycodone from Reltebon prolonged-release tablets is independent of pH.
Reltebon prolonged-release tablets have an oral bioavailability comparable with conventional oral oxycodone, but the former achieve maximal plasma concentrations at about 3 hours rather than about 1 to

1.5 hours. Peak and trough concentrations of oxycodone from Reltebon prolonged-release tablets 10 mg administered 12-hourly are equivalent to those achieved from conventional oxycodone 5 mg administered 6-hourly.
All strengths of Reltebon prolonged-release tablets are bioequivalent in terms of both rate and extent of absorption.

The tablets must not be crushed, divided or chewed as this leads to rapid oxycodone release and absorption of a potentially fatal dose of oxycodone due to the damage of the prolonged release properties.

Distribution:
Following absorption, oxycodone is distributed throughout the entire body. Approximately 45% is bound to plasma protein.

Metabolism:
Oxycodone is metabolised in the liver via CYP3A4 and CYP2D6 to noroxycodone, oxymorphone and noroxymorphone, which are subsequently glucuronidated. Noroxycodone and noroxymorphone are the major circulating metabolites. Noroxycodone is a weak mu opioid agonist. Noroxymorphone is a potent mu opioid agonist; however, it does not cross the blood-brain barrier to a significant extent. Oxymorphone is a potent mu opioid agonist but is present at very low concentrations following oxycodone administration. None of these metabolites are thought to contribute significantly to the analgesic effect of oxycodone.

Elimination:
The mean apparent elimination half-life of oxycodone is 4.5 hours, which leads to steady-state being achieved in about one day. The active drug and its metabolites are excreted in urine

Elderly
The AUC in elderly subjects is 15% greater when compared with young subjects.

Gender
Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown.

Patients with renal impairment
Preliminary data from a study of patients with mild to moderate renal dysfunction show peak plasma oxycodone and noroxycodone concentrations approximately 50% and 20% higher, respectively and AUC values for oxycodone, noroxycodone and oxymorphone approximately 60%, 60% and 40% higher than normal subjects, respectively. There was an increase in $t_{½}$ of elimination for oxycodone of only 1 hour.

Patients with mild to moderate hepatic impairment

Patients with mild to moderate hepatic dysfunction showed peak plasma oxycodone and noroxycodone concentrations approximately 50% and 20% higher, respectively, than normal subjects. AUC values were approximately 95% and 75% higher, respectively. Oxymorphone peak plasma concentrations and AUC values were lower by 15% to 50%. The $t_{½}$ elimination for oxycodone increased by 2.3 hours.

5.3 Preclinical safety data

Reproductive and Development Toxicology

Oyxcodone had no effect on fertility or early embryonic development in male and female rats at doses as high as 8 mg/kg/d. Also, oxycodone did not induce any deformities in rats at doses as high as 8 mg/kg/d or in rabbits at doses as high as 125 mg/kg/d. Dose-related increases in developmental variations (increased incidences of extra (27) presacral vertebrae and extra pairs of ribs) were observed in rabbits when the data for individual foetuses were analysed. However, when the same data were analysed using litters as opposed to individual foetuses, there was no dose-related increase in developmental variations although the incidence of extra presacral vertebrae remained significantly higher in the 125 mg/kg/d group compared to the control group. Since this dose level was associated with severe pharmacotoxic effects in the pregnant animals, the foetal findings may have been a secondary consequence of severe maternal toxicity.

In a prenatal and postnatal development study in rats, maternal body weight and food intake parameters were reduced for doses $\geq$ 2 mg/kg/d compared to the control group. Body weights were lower in the F1 generation from maternal rats in the 6 mg/kg/d dosing group. There were no effects on physical, reflexological, or sensory developmental parameters or on behavioural and reproductive indices in the F1 pups (the NOEL for F1 pups was 2 mg/kg/d based on body weight effects seen at 6 mg/kg/d). There were no effects on the F2 generation at any dose in the study.

Genotoxicity

The results of *in-vitro* and *in-vivo* studies indicate that the genotoxic risk of oxycodone to humans is minimal or absent at the systemic oxycodone concentrations that are achieved therapeutically.

Oxycodone was not genotoxic in a bacterial mutagenicity assay or in an *in-vivo* micronucleus assay in the mouse. Oxycodone produced a positive response in the *in-vitro* mouse lymphoma assay in the presence of rat liver S9 metabolic activation at dose levels greater than 25 μg/mL. Two *in-vitro* chromosomal aberrations assays with human lymphocytes were conducted. In the first assay, oxycodone was negative without metabolic activation but was positive with S9 metabolic activation at the 24 hour time point but not at other time points or at 48 hour after exposure. In the second assay, oxycodone did not show any clastogenicity either with or without metabolic activation at any concentration or time point.

Carcinogenicity

Carcinogenicity was evaluated in a 2-year oral gavage study conducted in Sprague-Dawley rats. Oxycodone did not increase the incidence of tumours in male and female rats at doses up to 6 mg/kg/day. The doses were limited by opioid-related pharmacological effects of oxycodone.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose monohydrate

Hypromellose

Povidone K30

Stearic acid

Magnesium stearate

Colloidal anhydrous silica

Tablet coating

Polyvinyl alcohol

Titanium dioxide (E171)

Macrogol 3350

Talc

Blue Indigo Carmine Aluminium Lake (E132)

Iron oxide, yellow (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Blister packs:
Do not store above 25°C.

HDPE container:
Do not store above 30°C.

6.5 Nature and contents of container

Blister packs (PVC/Al) in cartons.

Pack sizes: 80 mg: 1, 20, 28, 30, 50, 56, 60, 98 and 100 prolonged-release tablets

White, round, HDPE tablet containers with LDPE caps.

Pack size: 98 and 100 prolonged-release tablets

White, round, child-resistant, HDPE tablet containers with LDPE caps.

Pack size: 98 and 100 prolonged-release tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Instructions for use of child resistant blisters:

1. Do not push the tablet directly out of the pocket
2. Separate one blister cell from the strip at the perforations
3. Carefully peel off the backing to open the pocket

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited
Sage House
319 Pinner Road
North Harrow
Middlesex

HA1 4HF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0998

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/04/2014

10 DATE OF REVISION OF THE TEXT

19/12/2025