SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Leveraxo 30 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Leveraxo 30 mg tablet contains 30 mg oxycodone hydrochloride equivalent to 26.9 mg oxycodone.

Excipient with known effect:

Each Leveraxo 30 mg tablet contains a maximum of 18 mg sucrose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet

Yellow, oblong, biconvex, film coated tablets with break scores on both sides. The height of the tablet is between 3.8 and 4.8 mm, the width is 5.3 mm and the length is 11.3 mm.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Leveraxo 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 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)

Dose titration

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 minimise the incidence of adverse reactions.

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

For doses not realisable/practicable with this medicinal product, other strengths and medicinal products 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 Leveraxo prolonged-release tablets after conversion from other opioids, with 50-75% of the calculated oxycodone dose.

Dose adjustment

Some patients who take Leveraxo following a fixed schedule need rapid release analgesics as rescue medication in order to control breakthrough pain. Leveraxo 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 Leveraxo. Use of the rescue medication more than twice daily indicates that the dose of Leveraxo 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 until the desired effect is achieved. 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 individually balancing efficacy with the tolerance and risk of undesirable effects.

Elderly patients
A dose adjustment is not usually necessary in elderly patients without clinically manifest impairment of hepatic or renal function.

Treatment goals and discontinuation
Before initiating treatment with Leveraxo, 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
Oxycodone should not be used for longer than necessary.

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.

Other patients at risk
Patients with low body weight or slow metabolisers, who are opioid naive should initially be treated with half the dose usually recommended for adults. Therefore the lowest recommended dosage in this SPC, i.e. 10 mg, may not be suitable as a starting dose and in such cases oxycodone hydrochloride 5 mg prolonged-release tablets can be used.

Paediatric population
Children under 12 years of age
Leveraxo should not be used in children under 12 years of age because of safety and efficacy concerns.

Method of administration
For oral use.
Leveraxo 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 (½ glass of water).

Leveraxo 5 mg prolonged-release tablets
Leveraxo must be swallowed whole, and must not be divided, broken, chewed or crushed.

Leveraxo 10 mg prolonged-release tablets
Leveraxo 20 mg prolonged-release tablets
Leveraxo 30 mg prolonged-release tablets
Leveraxo 40 mg prolonged-release tablets
Leveraxo 60 mg prolonged-release tablets
Leveraxo 80 mg prolonged-release tablets

Leveraxo can be divided into equal doses. However, do not chew or crush the tablet.

Leveraxo should not be used with alcoholic beverages.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Severe chronic obstructive lung disease
- Cor pulmonale
- Severe bronchial asthma
- Severe respiratory depression with hypoxia
- Elevated carbon dioxide levels in the blood (hypercarbia)
- Paralytic ileus

4.4 Special warnings and precautions for use

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, alcoholism, known opioid dependence, delirium tremens, diseases of the biliary tract, pancreatitis, obstructive and inflammatory intestinal disease,, hypotension, hypovolaemia, head injury (due to risk of increased intracranial pressure), epilepsy or seizure tendency and in patients taking MAO inhibitors.

In suspicion or in case of paralytic ileus administration of Leveraxo has to be stopped immediately.

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.

Surgical procedures

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

Respiratory- and cardiac depression

The major risk of opioid excess is respiratory depression. It is most likely to occur in elderly or debilitated patients.

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. 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 Leveraxo 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 Leveraxo 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).

Drug dependence, tolerance and potential for abuse

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

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

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

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

The clinical need for analgesic treatment should be reviewed regularly.

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

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

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia,

abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

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

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

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.

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

Patients will require monitoring for signs of drug-seeking behavior (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

Abuse of oral dosage forms by parenteral administration can be expected to result in serious adverse events. The tablet excipients may lead to necrosis of the local tissue, granulomas of the lung or other serious, potentially fatal events.

Leveraxo 5 mg prolonged-release tablets
To avoid damage to the controlled release properties of the prolonged release, tablets must be swallowed whole and must not be divided, broken, chewed or crushed. The administration of divided, broken, chewed or crushed controlled release oxycodone

tablets leads to a rapid release and absorption of a potentially fatal dose of oxycodone (see section 4.9).

Leveraxo 10 mg prolonged-release tablets
Leveraxo 20 mg prolonged-release tablets
Leveraxo 30 mg prolonged-release tablets
Leveraxo 40 mg prolonged-release tablets
Leveraxo 60 mg prolonged-release tablets
Leveraxo 80 mg prolonged-release tablets

To avoid damage to the controlled release properties of the prolonged release, Leveraxo tablets can be divided into equal doses. However, do not chew or crush the tablet. The administration of chewed or crushed controlled release oxycodone tablets leads to a rapid release and absorption of a potentially fatal dose of oxycodone (see section 4.9).

Leveraxo 60 mg prolonged-release tablets
Leveraxo 80 mg prolonged-release tablets
Leveraxo 60 mg & 80 mg prolonged-release tablets are not recommended for opioid-naive patients, because this strength may lead to a life-threatening respiratory depression.

Alcohol

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

Special patient groups

Hepatic impairment

Patients with severe hepatic impairment should be closely monitored.

Paediatric population

The safety and efficacy of oxycodone in children under 12 years of age have not been established. Leveraxo should not be used in children under 12 years of age because of safety and efficacy concerns.

'Anti-doping' warning

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

Excipients

This medicinal product contains sucrose and sodium. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. This medicine also 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

- There can be an enhanced central nervous system (CNS) depressant effect during concomitant therapy with medicinal products which affect the CNS, such as sedatives, for example benzodiazepines or related drugs, hypnotics, phenothiazines, neuroleptics, anaesthetics, antidepressants, antihistamines, antiemetics, muscle relaxants) and other opioids that may enhance the adverse drug reactions or alcohol, in particular respiratory depression, increased risk of sedation, coma and death. The dose and duration of concomitant use should be limited (see section 4.4).
- **Anticholinergics** (e.g. neuroleptics, antihistamines, antiemetics, antiparkinson medicinal products) can enhance the anticholinergic undesirable effects of oxycodone (such as constipation, dry mouth or micturition disorders).
- Oxycodone should be used with caution in patients administered **monoamine oxidase inhibitors** (MAOIs) or who have received MAO-inhibitors during the last two weeks.
- 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 serotoin 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.

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 medicinal products or dietary elements. The following paragraphs explain these interactions in more detail.

- **CYP3A4 inhibitors**, such as macrolide antibiotics (e.g. clarithromycin, erythromycin and telithromycin), azolantifungals (e.g. ketoconazole, voriconazole, itraconazole, or posaconazole), protease inhibitors (e.g. boceprevir, ritonavir, indinavir, nelfinavir or 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).
  - Strong **CYP2D6 inhibitors** may have an effect on the elimination of oxycodone. Medicinal products 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.
- Clinically relevant changes in International Normalised Ratio (INR, Quick) in both directions have been observed in individuals if **coumarin anticoagulants** are co-applied with oxycodone.

- Alcohol may enhance the pharmacodynamic effects of Leveraxo; concomitant use should be avoided.
- There are no studies investigating the effect of oxycodone on CYP catalysed metabolism of other active substances.

- **CYP3A4 inducers**, such as rifampicin, carbamazepin, 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.

4.6 Fertility, pregnancy and lactation

Use of this medicinal product should be avoided to the extent possible in patients who are pregnant or lactating.

Pregnancy
There are limited data from the use of oxycodone in pregnant women. Oxycodone crosses the placenta.
Infants born to mothers who have received opioids during the last 3 to 4 weeks before giving birth should be monitored for respiratory depression.
Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.
If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.
Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

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

Fertility
Human data are not available. In animal studies, oxycodone had no adverse effects on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Oxycodone may impair the ability to drive and use machines. This is particularly likely at the initiation of treatment with oxycodone, after dose increase or product rotation and if oxycodone is combined with other CNS depressant agents. In these circumstances Leveraxo has moderate to major influence on the ability to drive and use machines.

With stable therapy, a general ban on driving a vehicle is not necessary. In these circumstances Leveraxo has minor influence on the ability to drive and use machines. The treating physician must assess the individual situation.

4.8 Undesirable effects

Summary of the safety profile

Oxycodone can cause respiratory depression, miosis, bronchial spasms and spasms of the smooth muscles and can suppress the cough reflex. Tolerance and dependence may occur (see below).

The most frequently reported undesirable effects are nausea (especially at the beginning of treatment) and constipation.

Respiratory depression is the chief hazard of an opioid overdose and occurs most commonly in elderly or debilitated patients.

The adverse reactions considered at least possibly related to treatment are listed below by system organ class and absolute frequency. Frequencies are defined as:

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.

Infections and infestations

Rare: herpes simplex

Immune system disorders

Uncommon: hypersensitivity
Very rare: anaphylactic reaction, anaphylactoid reaction

Metabolism and nutrition disorders

Common: decreased appetite or loss of appetite
Uncommon: dehydration
Rare: increased appetite

Psychiatric disorders

Common: anxiety (altered mood and personality change), confusional state, depression, decreased activity, restlessness, psychomotor hyperactivity, nervousness. insomnia, abnormal thinking
Uncommon: agitation, affect lability, euphoric mood, perception disturbances

(hallucinations, derealisation), decreased libido, drug dependence (see section 4.4).
Not known: aggression

Nervous system disorders

Very common: somnolence, sedation, dizziness, headache
Common: tremor, lethargy
Uncommon: amnesia, convulsions (especially in persons with epileptic disorder or predisposition to convulsions), concentration impaired, migraine, hypertonia, involuntary muscle contractions, hypoaesthesia, abnormal coordination, speech disorder, syncope, paraesthesia, dysgeusia
Not known: hyperalgesia

Eye disorders

Uncommon: visual impairment, miosis

Ear and labyrinth disorders

Uncommon: vertigo, hearing impaired

Cardiac disorders

Uncommon: tachycardia, palpitations (in the context of withdrawal syndrome)

Vascular disorders

Uncommon: vasodilatation
Rare: hypotension, orthostatic hypotension

Respiratory, thoracic and mediastinal disorders

Common: dyspnea
Uncommon: respiratory depression, dysphonia, cough
Not Known: central sleep apnoea syndrome

Gastrointestinal disorders

Very common: constipation, nausea, vomiting
Common: abdominal pain, diarrhoea, dry mouth, hiccups, dyspepsia
Uncommon: mouth ulceration, stomatitis, dysphagia, flatulence, eructation, ileus
Rare: melaena, tooth disorder, gingival bleeding
Not known: dental caries

Hepatobiliary disorders

Uncommon: increased hepatic enzymes
Not known: cholestasis, biliary colic, sphincter of Oddi dysfunction

Skin and subcutaneous tissue disorders

Very common: pruritus
Common: skin reaction, rash, hyperhidrosis
Uncommon: dry skin

Rare: urticaria

Renal and urinary disorders

Common: dysuria, micturition urgency
Uncommon: urinary retention

Reproductive system and breast disorders

Uncommon: erectile dysfunction, hypogonadism
Not known: amenorrhoea

General disorders and administration site conditions

Common: asthenic conditions, fatigue
Uncommon: chills, drug withdrawal syndrome, pain (e.g. chest pain), malaise, oedema, peripheral oedema, drug tolerance, thirst
Rare: weight increase, weight decrease
Not known: drug withdrawal syndrome neonatal

Injury, poisoning and procedural complications

Uncommon: Injuries from accidents

Description of selected adverse reactions

Tolerance and dependence may develop with chronic use and a withdrawal syndrome may occur upon abrupt cessation of therapy. The opioid abstinence or withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, or increased blood pressure, respiratory rate or heart rate.

Drug dependence

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

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

Symptoms
Acute overdose with oxycodone can be manifested by respiratory depression, somnolence progressing to stupor or coma, hypotonia, miosis, bradycardia, hypotension, and death. In severe cases circulatory collapse and non-cardiogenic lung oedema may occur; abuse of high doses of strong opioids such as oxycodone can be fatal.

Toxic leukoencephalopathy has been observed with oxycodone overdose.

Management
A patent airway must be maintained.

The pure opioid antagonists such as naloxone are specific antidotes against symptoms from opioid overdose.

Other supportive measures should be employed as needed.

Opioid antagonists: Naloxone (e.g. naloxone 0.4-2 mg intravenously). Administration should be repeated at 2-3 minute intervals as necessary, or by an infusion of 2 mg in 500 ml of 0.9% sodium chloride or 5% dextrose (0.004 mg/ml naloxone). The infusion should be run at a rate related to the previously administered bolus doses and should be in accordance with the patient's response.

Other supportive measures: including artificial ventilation, oxygen, vasopressors and fluid infusions should be employed if circulatory shock occurs during treatment. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation. Fluid and electrolyte metabolism should be maintained.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics; Opioids; Natural opium alkaloids
ATC-Code: N02AA05

Mechanism of action
Oxycodone shows an affinity to kappa, mu and delta opioid receptors in the brain, spinal cord and peripheral organs. 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 can lead to spasms in the sphincter of Oddi.

5.2 Pharmacokinetic properties

Absorption
The relative bioavailability of Leveraxo is comparable to that of rapid release oxycodone with maximum plasma concentrations being achieved after approximately 3-5 hours after intake of the prolonged-release tablets compared to 1 to 1.5 hours. Peak plasma concentrations and oscillations of the concentrations of oxycodone from the prolonged-release and rapid-release formulations are comparable when given at the same daily dose at intervals of 12 and 6 hours, respectively.
A fat-rich meal before the intake of the tablets does not affect the maximum concentration or the extent of absorption of oxycodone.
The tablets must not be crushed or chewed as this leads to rapid oxycodone release due to the damage of the prolonged-release properties.

Distribution
The absolute bioavailability of oxycodone is approximately two thirds relative to parenteral administration. At a steady state, the volume of distribution of oxycodone amounts to 2.6 l/kg; a plasma protein binding to 38-45%; the elimination half-life to 4 to 6 hours and a plasma clearance to 0.8 l/min. The elimination half-life of oxycodone in prolonged-release tablets is 4-5 hours in steady state, which is achieved after a mean of 1 day.

Biotransformation
Oxycodone is metabolised in the intestine and liver via the P450 cytochrome system to noroxycodone and oxymorphone as well as to several glucuronide conjugates. In vitro studies suggest that therapeutic doses of cimetidine probably have no relevant effect on the formation of noroxycodone. In man, quinidine reduces the production of oxymorphone while the pharmacodynamic properties of oxycodone remain largely unaffected. The contribution of the metabolites to the overall pharmacodynamic effect is irrelevant.

Elimination
Oxycodone and its metabolites are excreted via urine and faeces. Oxycodone crosses the placenta and is found in breast milk.

Linearity/non-linearity
Across the 5-80 mg dose range of prolonged release oxycodone tablets linearity of plasma concentrations was demonstrated in terms of rate and extent of absorption.

5.3 Preclinical safety data

In rat studies, oxycodone had no effect on fertility and embryonic development. However, in rabbits, at dose levels which produced maternal toxicity, a dose related increase in developmental variations was observed (increased number of presacral vertebrae, extra pairs of ribs). In a rat study on pre- and post-natal development, there were neither effects on physical, reflexological, and sensory developmental parameters nor on behavioural and reproductive indices

Data from genotoxicity studies with oxycodone reveal no special hazard for humans. Long-term studies on carcinogenicity have not been performed.

Oxycodone showed a clastogenic potential in some *in vitro* investigations. However, under *in vivo* conditions such findings were not observed, even at toxic doses. The

results indicate that the mutagenic risk of oxycodone to humans at therapeutic concentrations may be ruled out with adequate certainty.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Sugar spheres (sucrose, maize starch)

Hypromellose

Talc

Ethyl cellulose

Hydroxypropylcellulose

Propylene glycol

Carmellose sodium

Cellulose, microcrystalline

Magnesium stearate (Ph. Eur.)

Silica, colloidal anhydrous

Tablet coating:

Polyvinyl alcohol

Titanium dioxide (E171)

Iron oxide yellow (E172)

Macrogol 3350

Talc

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

Child resistant white opaque PVC/PE/PVDC-aluminium perforated unit dose blisters.
HDPE bottles with PP child-resistant closure.

Pack sizes:
10x1, 14x1, 20x1, 28x1, 30x1, 50x1, 56x1, 60x1, 98x1, 100x1 prolonged-release tablets in blister.
10, 20, 30, 50, 100 prolonged-release tablets in HDPE bottles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Generics (U.K.) Limited T/A Viatris,
Station Close,
Potters Bar,
EN6 1TL,
United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 04569/1653

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/05/2024

10 DATE OF REVISION OF THE TEXT

13/04/2026