SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Oxylan 15 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 film-coated tablet contains 15 mg oxycodone hydrochloride corresponding to 13.45 mg oxycodone.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet

Grey, round and biconvex prolonged-release tablets.

Diameter: 8.1 mm

Thickness: 4.0 mm

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Oxylan is indicated in adults and adolescents (from 12 years and older) for the treatment of severe pain, which can be adequately managed only with opioid analgesics.

4.2 Posology and method of administration

DOSAGE

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).
The dosage depends on the pain intensity and the patient's individual susceptibility to the treatment.
For doses not realisable/practicable with this strength, other strengths of this medicinal product are available.

The following general dosage recommendations apply:

Adults and adolescents 12 years 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 adverse reactions.

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

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 Oxycodone hydrochloride prolonged-release tablets after conversion from other opioids, with 50-75% of the calculated oxycodone dose.

Some patients who take Oxycodone hydrochloride prolonged-release tablets following a fixed schedule need rapid-release analgesics as rescue medication in order to control breakthrough pain. Oxycodone hydrochloride 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 Oxycodone hydrochloride prolonged-release tablets. Use of the rescue medication more than twice daily indicates that the dose of Oxycodone hydrochloride 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 in the morning and in the evening) 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 against tolerance and the risk of undesirable effects.

Elderly patients
Elderly patients without clinical manifestation of impaired liver and/or kidney function usually do not require dose adjustments.

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 his/her clinical situation.

Paediatric population
Opioids must only be used for appropriate indications and prescribed by a specialist experienced in managing severe pain in children, with careful assessments of the benefits and risks.

Children below the age of 12 years
The safety and efficacy of oxycodone in children below 12 years of age has not yet been established. No data are available.

METHOD OF ADMINISTRATION
Oral use.

Oxylan 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. Oxylan prolonged-release tablets must be swallowed whole, and they must not be chewed, divided or crushed.

Treatment goals and discontinuation
Before initiating treatment with Oxylan prolonged-release tablets, 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
Oxylan prolonged-release tablets should not be taken longer than necessary.

4.3 Contraindications

Hypersensitivity to oxycodone hydrochloride, or to any of the excipients.

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
- paralytic ileus
- acute abdomen, delayed gastric emptying

4.4 Special warnings and precautions for use

Caution should be exercised in

- elderly or debilitated patients,
- patients with severe impairment of lung, liver or kidney function,
- myxoedema, hypothyroidism,
- Addison's disease (adrenal insufficiency),
- intoxication psychosis (e.g. alcohol),
- prostatic hypertrophy,
- alcoholism, known opioid dependence,
- delirium tremens,
- pancreatitis,
- diseases of the biliary tract, biliary or ureteric colic,
- conditions with increased brain pressure,
- disturbances of circulatory regulation,
- epilepsy or seizure tendency and
- in patients taking MAO inhibitors.

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.

Respiratory depression
The major risk of opioid excess is respiratory depression.

Caution must be exercised when administering oxycodone to the debilitated elderly; patients with severely impaired pulmonary function, 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, head injury (due to risk of increased intracranial pressure) or patients taking MAO inhibitors.

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 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 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

For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).

Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse.

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.

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.

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 Oxylan 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 Oxylan 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 Oxylan 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
Abuse of oral dosage forms by parenteral administration can be expected to result in serious adverse events, which may be fatal.

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

Surgical procedures

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. The use of oxycodone prolonged-release tablets is not recommended prior to and during the first 12-24 hours after surgical procedures. 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). If further treatment with oxycodone is indicated, the dose should be adjusted to the new post-operative requirements.
Special care should be taken when oxycodone is used in patients undergoing bowel-surgery. Opioids should only be administered post-operatively when the bowel function has been restored.
The safety of Oxylan prolonged-release tablets used pre-operatively has not been established and can therefore not be recommended.

Children
Oxycodone hydrochloride 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.

Patients with severe hepatic impairment
Patients with severe hepatic impairment should be closely monitored.

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.

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

Anti-Doping Warning
The use of Oxylan may produce positive results in doping controls.
Use of Oxylan as a doping agent may become a health hazard.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per prolonged-release tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Alcohol may enhance the pharmacodynamic effects of Oxylan prolonged-release tablets; concomitant use should be avoided.

Central nervous system depressants (e.g. sedatives, hypnotics, antipsychotics, anaesthetics, antidepressants, muscle relaxants, antihistamines, antiemetics) and other

opioids can enhance the adverse reactions of oxycodone, in particular respiratory depression.

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.

Sedative medicines such as benzodiazepines or related drugs
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).

Anticholinergics (e.g. antipsychotics, antihistamines, antiemetics, anti-parkinson medicines) can enhance the anticholinergic undesirable effects of oxycodone (such as constipation, dry mouth or micturition disorders).

Cimetidine can inhibit the metabolism of oxycodone.

Monoaminoxidase (MAO) inhibitors are known to interact with opioid analgesics, producing CNS excitation or depression with hyper- or hypotensive crisis (see section 4.4).). Oxycodone should be used with caution in patients administered MAO-inhibitors or who have received MAO-inhibitors during the last two weeks (see section 4.4).

Clinically relevant changes in International Normalized Ratio (INR) in both directions have been observed in individuals if **coumarin anticoagulants** are co- applied with Oxylan prolonged-release tablets.

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.

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

Some specific examples are provided below:

- Itraconazole, a potent CYP3A4 inhibitor, administered as 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 as 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 as 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 which could result in a reduction of oxycodone plasma concentrations.
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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Breast-feeding

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

4.7 Effects on ability to drive and use machines

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

Oxycodone can cause respiratory depression, miosis, bronchial spasms and spasms of the smooth muscles and can suppress the cough reflex.

Drug dependence
Repeated use of Oxylan prolonged-release tablets 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).

The adverse reactions considered at least possibly related to treatment are listed below by system organ class and absolute frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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

<u>Immune system disorders:</u>
Uncommon: hypersensitivity
Not known: anaphylactic responses

<u>Blood and lymphatic system disorders</u>
Rare: lymphadenopathy

<u>Endocrine disorders</u>
Uncommon: syndrome of inappropriate antidiuretic hormone secretion

<u>Metabolism and nutrition disorders</u>

Common: decreased appetite
Uncommon: dehydration

Psychiatric disorders
Common: anxiety, confusional state, depression, insomnia, nervousness, abnormal thinking Uncommon: agitation, affect lability, euphoric mood, hallucinations, decreased libido, drug dependence (see section 4.4)
Not known: aggression, drug dependence (see section 4.4)

Nervous system disorders
Very common: somnolence, dizziness, headache
Common: asthenia, paraesthesia
Uncommon: increased or decreased muscle tone, tremor, involuntary muscle contractions, hypaesthesia, coordination disturbances, malaise, vertigo
Rare: seizures, particularly in epileptic patients or patients with tendency to convulsions, muscle spasm

Eye disorders
Uncommon: visual impairment, miosis

Ear and labyrinth disorders
Uncommon: vertigo

Cardiac disorders
Common: lowering of blood pressure, rarely accompanied by secondary symptoms such as palpitations, syncope, bronchospasm
Uncommon: palpitation (in the context of withdrawal syndrome), supraventricular tachycardia

Vascular disorders
Uncommon: vasodilatation
Rare: hypotension, orthostatic hypotension

Respiratory, thoracic and mediastinal disorders
Common: dyspnoea
Uncommon: respiratory depression, increased coughing, pharyngitis, rhinitis, voice changes
Not known: central sleep apnoea syndrome

Gastrointestinal disorders
Very common: constipation, nausea, vomiting
Common: dry mouth, rarely accompanied by thirst and difficulty swallowing; abdominal pain, diarrhoea, dyspepsia
Uncommon: dysphagia, oral ulcers, gingivitis, stomatitis, flatulence, eructation, ileus
Rare: gingival bleeding, increased appetite, tarry stool,
Not known: dental caries

Hepatobiliary disorders
Not known: sphincter of Oddi dysfunction

Skin and subcutaneous tissue disorders
Very common: pruritus
Common: rash, hyperhidrosis
Uncommon: dry skin
Rare: urticaria, manifestations of herpes simplex, increased photosensitivity
Very rare: exfoliative dermatitis

Renal and urinary disorders
Uncommon: micturition disturbances (urinary retention, but also increased urge to urinate)
Rare: haematuria

Reproductive system and breast disorders
Uncommon: reduced libido, erectile dysfunction
Not known: amenorrhoea

General disorders and administration site conditions
Common: sweating, asthenic conditions
Uncommon: chills, malaise, accidental injuries, pain (e.g. chest pain), oedema, peripheral oedema, migraine, physical dependence with withdrawal symptoms, drug tolerance, thirst
Rare: weight changes (increase or decrease), cellulitis
Not known: drug withdrawal syndrome neonatal

Paediatric population
The frequency, type and severity of adverse reactions in adolescents (12 to 18 years of age) appear similar to those in adults (see section 5.1).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

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. Acute overdose with oxycodone can be manifested by miosis, respiratory depression, somnolence progressing to stupor or coma, hypotonia, drop in blood pressure and death. In severe cases circulatory collapse, bradycardia 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.

Therapy

Primary attention must be given to the establishment of a patent airway and institution of assisted or controlled ventilation.

Pure opioid antagonist such as naloxone (0.4 - 2 mg intravenous) serve as specific antidotes in the treatment of opioid overdose. Administration of single doses must be repeated depending on the clinical situation at intervals of 2 to 3 minutes. Intravenous infusion of 2 mg of naloxone in 500 ml isotonic saline or 5% dextrose solution (corresponding to 0.004 mg naloxone/ml) is possible. The rate of infusion should be adjusted to the previous bolus injections and the response of the patient.

Gastric lavage can be taken into consideration. The administration of activated charcoal (50 g for adults, 10 -15 g for children) should be considered within 1 hour, 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.

For speeding up the passage a suitable laxative (e.g. a PEG-based solution) may be useful.

Supportive measures (artificial respiration, oxygen supply, administration of vasopressors and infusion therapy) should, if necessary, be applied in the treatment of accompanying circulatory shock. Upon cardiac arrest or cardiac arrhythmias, cardiac massage or defibrillation may be indicated. If necessary, assisted ventilation as well as maintenance of water and electrolyte balance.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids ATC code: N02AA05.

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.

Paediatric population

Overall, the safety data obtained with oxycodone in clinical, pharmacodynamic and pharmacokinetic studies demonstrate that oxycodone is well tolerated in paediatric patients with only minor adverse events affecting mainly the gastrointestinal and nervous system. All of the adverse events reported were consistent with the known safety profile of oxycodone as well as of other comparable strong opioids (see section 4.8).
There is no clinical trial data on longer term use in children aged 12 to 18 years.

5.2 Pharmacokinetic properties

Absorption

The relative bioavailability of Oxylan prolonged-release tablets is comparable to that of rapid-release oxycodone with maximum plasma concentrations being achieved after approximately 3 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.

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

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

Metabolism

Oxycodone is metabolised in the intestine and liver via the cytochrome P450 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

The 5, 10 and 20 mg prolonged-release tablets are dose-proportional with regard to the amount of active substance absorbed as well as comparable with regard to the rate of absorption.

5.3 Preclinical safety data

There is insufficient data on the reproduction toxicity properties of oxycodone and there is no data available on fertility and postnatal effects following intrauterine exposure. Oxycodone did not cause malformations in rats and rabbits at dosages which were 1.5 to 2.5 times the human dose of 160 mg/day, based on mg/kg basis.

Long-term studies on carcinogenicity have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Kollidon SR (consisting of poly(vinylacetate), povidone (K = 27.0 – 32.4), sodium lauryl sulphate, silica)
Cellulose, microcrystalline
Colloidal anhydrous silica
Magnesium stearate, vegetable

Tablet coating
Polyvinyl alcohol
Talc (E 553b)
Titanium dioxide (E 171)
Macrogol 3350
Iron oxide black (E 172)
Iron oxide red (E 172)
Iron oxide yellow (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

PVC/PVdC/aluminium blisters containing 7, 10, 14, 20, 28, 30, 50, 56, 60, 72, 98, and 100 prolonged-release tablets.
Unit-dose blisters of 30x1, 50x1, 56x1, 60x1, 72x1, 98x1, and 100x1 prolonged-release tablets.

Not all pack sizes will be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

G.L. Pharma GmbH

Schlossplatz 1

8502 Lannach

Austria

8 MARKETING AUTHORISATION NUMBER(S)

PL 21597/0094

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/09/2023

10 DATE OF REVISION OF THE TEXT

06/03/2025