SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Oxylan 80 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Oxylan 80 mg prolonged-release tablets

1 film-coated tablet contains 80 mg oxycodone hydrochloride corresponding to 71.72 mg oxycodone.

Excipient with known effect:

Soya lecithin……0.525 mg per tablet

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Prolonged-release tablet

Oxylan 80 mg prolonged-release tablets

Pale green, round and biconvex film-coated tablets.

Diameter: 11.1 mm

Thickness: 4.7 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

Posology

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.

Switching from morphine to oxycodone

The inter-patient variability requires that each patient be carefully adjusted to the dose that is appropriate for them. At the beginning of the change, a dose that is lower than the dose equivalent may be recommended. Patients who received oral morphine prior to oxycodone therapy should receive their daily dose based on the following ratio: 10 mg oral oxycodone is equivalent to 20 mg oral morphine

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. It is therefore possible that the lowest single dose recommended in this SmPC, i.e. 10 mg, is not suitable as a starting dose. In these cases Oxylan 5 mg prolonged-release tablets can be used.

Other risk patients

In patients with low body weight or slow metabolism of drugs who are also opioid-naive, the recommended starting dose should be reduced to half the normally recommended starting dose for adults. It is therefore possible that the lowest single dose recommended in this SmPC, i.e. 10 mg, is not suitable as a starting dose. In these cases Oxylan 5 mg prolonged-release tablets can be used.

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, soya, peanut, 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,
- severely impaired respiratory function,
- impaired hepatic function,
- impaired renal function,
- sleep apnoea,
- myxoedema, hypothyroidism,
- concomitant use of centrally depressant substances (see below and 4.5),
- Addison's disease (adrenal insufficiency),
- intoxication psychosis (e.g. alcohol),
- prostatic hypertrophy,
- alcoholism, known opioid dependence,
- psychological dependence [addiction], abuse profile and history of substance and/or alcohol abuse (see below)
- delirium tremens,
- head injury, increased intracranial pressure,
- impaired consciousness of unknown cause,
- hypotension,
- hypovolaemia,
- epileptic disorder or predisposition to convulsions,
- pancreatitis,
- diseases of the biliary tract, biliary or ureteric colic,
- obstructive or inflammatory intestinal diseases,
- constipation,
- disturbances of circulatory regulation,
- in patients taking MAO inhibitors (see below and section 4.5).

With the occurrence or suspicion of paralytic ileus, oxycodone should be immediately discontinued.

Respiratory depression

The major 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. 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 Oxylan 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 Oxylan concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation.

In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

MAOIs

Oxycodone should be administered with caution to patients taking MAOIs or who have received MAOIs within the last two weeks.

Tolerance, physical dependence, withdrawal symptoms and tapering off

The patient may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain control.

Oxylan prolonged-release tablets have a primary dependence potential.

Prolonged use of Oxylan prolonged-release tablets may lead to physical dependence and a withdrawal syndrome may occur upon abrupt cessation of therapy. When a patient no longer requires therapy with oxycodone, it may be advisable to taper the dose gradually to prevent withdrawal symptoms.

Withdrawal symptoms may include yawning, mydriasis, lacrimation, rhinorrhoea, tremor, hyperhidrosis, anxiety, agitation, convulsions, insomnia, and myalgia.

Hyperalgesia

Hyperalgesia that will not respond to a further dose increase of oxycodone may very rarely occur, particularly in high doses. An oxycodone dose reduction or change to an alternative opioid may be required.

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 prolonged-release tablets 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.

Parenteral abuse

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

Opioids are not first-line therapy for chronic non-malignant pain, nor are they recommended as the only treatment. Opioids should be used as part of a comprehensive treatment programme involving other medications and treatment modalities. Patients with chronic non-malignant pain should be monitored for signs of dependence or substance abuse. The attainment of treatment goals should be regularly checked in accordance with pain management guidelines. If appropriate, the dose is to be adjusted. In case the treatment objectives are not met, discontinuation of therapy should be considered.

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. 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.

Depending on the type and extent of the surgical procedure, the selected anesthetic method, other concomitant medication and the individual condition of the patient, the time of postoperative use of Oxylan prolonged-release tablets must be determined after carefully weighing the benefit and risk in each individual case.

The safety of Oxylan prolonged-release tablets used pre-operatively has not been established and can therefore not be recommended.

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.

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. Oxylan prolonged-release tablets should be used with particular care in patients with a history of alcohol and drug abuse.

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

Centrally depressant drugs
There can be an enhanced CNS depressant effect during concomitant therapy with drugs which affect the CNS: gabapentinoids such as pregabalin,sedatives, hypnotics, antipsychotics, anaesthetics, phenothiazines, neuroleptic drugs, antidepressants, muscle relaxants, antihistamines, antiemetics and other opioids which may enhance the adverse drug reactions, especially 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, antiparkinson medicines) can enhance the anticholinergic undesirable effects of oxycodone (such as constipation, dry mouth or micturition disorders).

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.

Interactions via the CYP system
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

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

Fertility

No human data on the effect of oxycodone on fertility are available. Studies in rats have not shown any effects upon fertility (see section 5.3).

Pregnancy

There are limited data from the use of oxycodone in pregnant women. Infants born to mothers who have received opioids during the last 3 to 4 weeks before giving birth should be monitored for respiratory depression. Withdrawal symptoms may be observed in the newborns of mothers undergoing treatment with oxycodone.

Breast-feeding

Oxycodone may be secreted in breast milk and may cause sedation and respiratory depression in the newborn. Oxycodone should, therefore, not be used in breastfeeding mothers.

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 changes in therapy, and if oxycodone is combined with alcohol or other CNS depressants.

With stable therapy, a general ban on driving a vehicle is not necessary. The treating physician must assess the individual situation.

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 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 predominantly in elderly or debilitated patients. Opioids may cause severe hypotension in susceptible individuals.

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)

Infections and parasitic diseases
Rare: Herpes simplex

Immune system disorders:
Uncommon: hypersensitivity
Not known: anaphylactic responses

Blood and lymphatic system disorders
Rare: lymphadenopathy

Endocrine disorders
Uncommon: syndrome of inappropriate antidiuretic hormone secretion

Metabolism and nutrition disorders
Common: decreased appetite
Uncommon: dehydration
Rare: increased appetite

Psychiatric disorders
Common: anxiety, confusion, depression, decreased activity, restlessness, psychomotor hyperactivity, insomnia, nervousness, abnormal thinking
Uncommon: agitation, affect lability, euphoric mood, dysphoria, perception disturbances (e.g hallucinations, depersonalisation), 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, seizures (particularly (particularly in epileptic patients or patients with tendency to convulsions), impaired concentration, migraine, increased muscle tone, hypoaesthesia, involuntary muscle contraction, impaired coordination, speech disorders, syncope, paraesthesia, dysgeusia
Not known: hyperalgesia

Eye disorders
Uncommon: visual impairment, miosis

Ear and labyrinth disorders
Uncommon: hearing impairment, vertigo

Cardiac disorders
Uncommon: palpitation (in the context of withdrawal syndrome), supraventricular tachycardia

Vascular disorders
Uncommon: vasodilatation
Rare: hypotension, orthostatic hypotension

Respiratory, thoracic and mediastinal disorder
Common: dyspnoea, bronchospasm
Uncommon: respiratory depression, increased coughing
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, mouth ulcerations, gingivitis, stomatitis, flatulence, eructation, ileus
Rare: melaena, gingival bleeding, tooth dirsorders
Not known: dental caries

Hepatobiliary disorders
Uncommon: increase hepatic enzymes
Not known: cholestasis, biliary colic, 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

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, hypoganadism
Not known: amenorrhoea

General disorders and administration site conditions
Common: asthenia, tiredness
Uncommon: chills, malaise, pain (e.g. chest pain), oedema, peripheral oedema, physical dependence with withdrawal symptoms, drug tolerance,

thirst
Rare: weight changes (increase or decrease), cellulitis
Not known: drug withdrawal syndrome neonatal

Injury, poisoning and procedural complications
Uncommon: injuries from accidents

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 national reporting system:

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard

4.9 Overdose

Symptoms

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.

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

Reproductive and Developmental Toxicology

Oxycodone had no effect on fertility or early embryonic development in male and female rats at doses as high as 8 mg/kg/day. Also, oxycodone did not induce any malformation in rats at doses as high as 8 mg/kg/day or in rabbits at doses as high as 125 mg/kg/day 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/day 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 ≥2 mg/kg/day compared to the control group. Body weights were lower in the F1 generation from maternal rats in the 6 mg/kg/day 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/day based on body weight effects seen at 6 mg/kg/day). 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 48 hours 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

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

Lecithin (soya) (E 322)

Iron oxide yellow (E 172)

Iron oxide black (E 172)

Indigo carmine, aluminium lake (E 132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 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.

5, 10 and 20 mg only: Tablet containers of 100 and 250 prolonged-release tablets. The tablet containers are for use in hospitals and dose-dispensing pharmacies only.

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 21597/0065

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/05/2010 / 31.03.2013

10 DATE OF REVISION OF THE TEXT

25/02/2025