SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Carexil® 20mg Prolonged-release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 20 mg oxycodone hydrochloride equivalent to 17.9 mg oxycodone.

Excipient with known effect

Each prolonged-release tablet contains 60.3 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet

Blue, round, biconvex film coated prolonged-release tablets, diameter: 5.3 – 5.9 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Severe pain, which can be adequately managed only with opioid analgesics. Carexil® 20 mg Prolonged-release Tablets are indicated in adults and adolescents aged 12 years and older.

4.2 Posology and method of administration

Posology

The dose should be adjusted to the intensity of the pain and the sensitivity of the individual patient.

For doses not practicable with this medicinal product other strengths are available.

Adults and adolescents (12 years of age and older)

Carexil® 20 mg prolonged-release tablets should be taken twice daily based on a fixed schedule at the dose determined.

Starting dose

The usual starting dose for an opioid-naïve patient is 10 mg oxycodone hydrochloride per dose 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 of Carexil® 20 mg Prolonged-release Tablets taking into account their experience with former opioid therapies.

10 to 13 mg oxycodone hydrochloride correspond to approximately 20 mg of morphine sulphate, both in the prolonged-release formulation.

Dose adjustment

Some patients who take Carexil® 20 mg Prolonged-release Tablets following a fixed schedule need rapid release analgesics as rescue medication in order to control breakthrough pain. Carexil® 20 mg Prolonged-release Tablets is not intended for therapy of breakthrough pain. The single dose of the rescue medication should amount to 1/6 of the equianalgesic daily dose of Carexil® 20 mg Prolonged-release Tablets. Use of the rescue medication more than twice daily indicates that the dose of Carexil® 20 mg Prolonged-release Tablets needs to be increased. The dose should not be adjusted more often than once every 1-2 days until a stable 12-hourly administration has been achieved.

Following a dose increase from 10 mg to 20 mg oxycodone hydrochloride taken every 12 hours dose adjustments should be made in steps of approximately one third of the daily dose until the desired effect is obtained. The aim is a patient specific 12-hourly dose that will maintain adequate analgesia with acceptable undesirable effects and as little rescue medication as possible as long as pain control is necessary.

Even administration (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 beneficial to arrange 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 oxycodone hydrochloride is generally sufficient; but higher doses may be necessary.

Patients with cancer-related pain may require doses of 80 to 120 mg oxycodone hydrochloride, which in individual cases can be increased to up to 400 mg.

Duration of administration

Oxycodone should not be used for longer than necessary.

Special populations

Elderly

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

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 of oxycodone hydrochloride orally in opioid naïve patients), and each patient should be titrated to adequate pain control according to their clinical situation. In such cases Carexil® 20 mg Prolonged-release Tablets can be used.

Other patients at risk

Patients with low body weight or slow metabolisers, who are opioid-naïve should initially receive half the dose usually recommended for adults. Therefore, 10 mg of oxycodone hydrochloride per dose at intervals of 12 hours may not be suitable as a starting dose and in such cases o Carexil® 20 mg Prolonged-release Tablets can be used.

Paediatric population

Carexil® 20 mg Prolonged-release Tablets are not recommended for use in children under 12 years of age due to insufficient data on safety and efficacy.

Method of administration

Oral use.

The prolonged-release tablets may be taken with or without food with sufficient liquid.

Treatment goals and discontinuation

Before initiating treatment with Carexil, 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).

Carexil® 20 mg Prolonged-release Tablets must not be divided, broken, crushed or chewed.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- severe respiratory depression with hypoxia
- elevated carbon dioxide levels in the blood (hypercarbia)
- severe chronic obstructive lung disease
- cor pulmonale
- severe bronchial asthma
- paralytic ileus

4.4 Special warnings and precautions for use

The major risk of opioid excess is respiratory depression.

Caution should be exercised in

- elderly or debilitated patients,
- patients with severe impairment of pulmonary function, impaired hepatic or renal function,
- patients with myxedema,
- hypothyroidism,
- Addison's disease,
- prostatic hypertrophy,
- toxic psychosis,
- alcoholism, delirium tremens, known opioid dependence,
- diseases of the biliary tract,
- pancreatitis,
- obstructive and inflammatory bowel disorders,
- head injury (due to risk of increased intracranial pressure),

- hypotension,
- hypovolaemia,
- epilepsy or predisposition to convulsions,
- in patients taking sedative medicinal products such as benzodiazepines or other centrally depressant active substances including alcohol (see also section 4.5),
- in patients taking MAO inhibitors or within 2 weeks of discontinuation of their use (see also section 4.5)

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

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.

Risk from concomitant use of sedative medicinal products such as benzodiazepines or related medicinal products:

Concomitant use of oxycodone and sedative medicinal products such as benzodiazepines or related medicinal products may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicinal products should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe oxycodone concomitantly with sedative medicinal products, 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).

Tolerance and dependence

The patient may develop tolerance to the active substance with chronic use and require progressively higher doses to maintain pain control. Prolonged use of this medicinal product 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 symptoms of withdrawal. Withdrawal symptoms may include yawning, mydriasis, lacrimation, rhinorrhoea, tremor, hyperhidrosis, anxiety, agitation, convulsions, insomnia or myalgia.

Hyperalgesia that will not respond to a further dose increase of oxycodone may 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 Carexil® 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 Carexil® 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 Carexil 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 pharmaceutical forms by parenteral administration can be expected to result in serious adverse events, which may be fatal.

To avoid damage to the controlled-release properties of the prolonged-release tablets, the Carexil® 20 mg prolonged-release tablets must be swallowed whole and must not be divided, broken, crushed or chewed. The administration of broken, crushed or chewed tablets leads to rapid-release and absorption of a potentially fatal dose of oxycodone (see section 4.9).

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.

Surgical procedures

Carexil® 20 mg Prolonged-release Tablets are not recommended for pre-operative use or within the first 12-24 hours post-operatively. Depending on the type and extent of surgery, the anaesthetic procedure selected, other co-medication and the individual condition of the patient, the exact timing for initiating postoperative treatment with Carexil® 20 mg Prolonged-release

Tablets depends on a careful risk-benefit assessment for each individual patient.

Oxycodone-containing medicinal 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.

Alcohol

Concomitant use of alcohol and Carexil® 20 mg Prolonged-release Tablets may increase the undesirable effects of oxycodone; concomitant use should be avoided.

Empty matrix (tablets) may be seen in the stool.

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

4.5 Interaction with other medicinal products and other forms of interaction

Sedative medicinal products such as benzodiazepines or related medicinal products:

The concomitant use of opioids with sedative medicinal products such as benzodiazepines or related medicinal products 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).

Central nervous system depressant active substances are for example sedatives (including benzodiazepines), hypnotics, phenothiazines, neuroleptics, antidepressants, antihistamines, antiemetics) or other opioids.

Alcohol may enhance the pharmacodynamic effects of Carexil® 20 mg Prolonged-release Tablets; concomitant use should be avoided.

Concomitant administration of oxycodone with serotonin agents, such as a Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) may cause serotonin toxicity. The symptoms of serotonin toxicity may include mental-status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g. hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea). Oxycodone should be used with caution and the dose may need to be reduced in patients using these medicinal products.

Medicinal products with anticholinergic effects (e.g. tricyclic antidepressants, antihistamines, antiemetics, psychotropic medicinal products, muscle relaxants, medicinal products against Morbus Parkinson) may intensify the anticholinergic adverse drug reactions of oxycodone, such as constipation, dry mouth or dysfunction of urinary excretion.

Oxycodone should be used with caution in patients administered MAO-inhibitors or who have received MAO-inhibitors during the last two weeks.

A clinically relevant decrease or increase of INR (International Normalised Ratio) has been observed in individual cases in simultaneous use of oxycodone and coumarin anticoagulants.

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. In the following paragraphs these interactions are explained in detail.

CYP3A4 inhibitors, such as macrolide antibiotics (e.g. clarithromycin, erythromycin or telithromycin), azol-antifungals (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 of CYP3A4 enzyme inhibition are provided as follows:

- Itraconazole, a potent CYP3A4 inhibitor, administered 200 mg orally for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 2.4 times higher (range 1.5 - 3.4).
- Voriconazole, a CYP3A4 inhibitor, administered 200 mg twice-daily for four days (400 mg given as first two doses), increased the AUC of oral oxycodone. On average, the AUC was approximately 3.6 times higher (range 2.7 - 5.6).
- Telithromycin, a CYP3A4 inhibitor, administered 800 mg orally for four days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.8 times higher (range 1.3 – 2.3).
- Grapefruit juice, a CYP3A4 inhibitor, administered as 200 ml three times a day for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.7 times higher (range 1.1 – 2.1).

CYP3A4 inducers, such as rifampicin, carbamazepin, phenytoin or 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 of CYP3A4 enzyme induction are provided as follows:

- St Johns 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

Medicinal products that inhibit CYP2D6 activity, such as paroxetine or 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 breast-feeding.

Pregnancy
There are limited data from the use of oxycodone in pregnant women. Oxycodone passes 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. Withdrawal symptoms may be observed in the newborn of mothers undergoing treatment with oxycodone

Breast-feeding
Oxycodone may be excreted into breast milk and may cause sedation and respiratory depression in the breast-fed infant. Therefore, oxycodone should not be used in breast-feeding mothers.

Fertility
Human data are not available. Studies in rats have not shown any effects upon 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 medicinal products. Patients stabilised on a specific dose will not necessarily be restricted. Therefore, the physician should decide whether the patient is allowed to drive or 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:
    - o The medicine has been prescribed to treat a medical or dental problem and
    - o You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and

o It was not affecting your ability to drive safely.

4.8 Undesirable effects

Due to its pharmacological properties oxycodone can cause respiratory depression, miosis, bronchial spasm and spasm of the smooth muscles and may suppress the cough reflex.

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.

Opioids may cause severe hypotension in susceptible individuals.

The following frequency categories form the basis for classification of the undesirable effects:

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 infestations

Rare: herpes simplex

Immune system disorders:

Uncommon: hypersensitivity

Not known: anaphylactic reactions, anaphylactoid reactions

Metabolism and nutrition disorders

Common: decreased appetite up to loss of appetite

Uncommon: dehydration

Rare: increased appetite

Psychiatric disorders

Common: anxiety, confusional state, depression, decreased activity, restlessness, psychomotor hyperactivity, nervousness, insomnia, abnormal thinking

Uncommon: agitation, affect lability, euphoric mood, perception disturbances such as 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, convulsion (especially in persons with epileptic disorder or predisposition to convulsions), concentration impaired, migraine, hypertonia, involuntary muscle contractions, hypoaesthesia, coordination disturbances, speech disorder, syncope, paraesthesia, dysgeusia

Not known: hyperalgesia

Eye disorders

Uncommon: visual impairment, miosis

Ear and labyrinth disorders

Uncommon: hearing impaired,vertigo

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:	dyspnoea, bronchospasm
Uncommon:	respiratory depression, dysphonia, cough
Not known:	central sleep apnoea syndrome

Gastrointestinal disorders

Very common:	constipation, vomiting, nausea
Common:	abdominal pain, diarrhoea, dry mouth, hiccups, dyspepsia
Uncommon:	mouth ulceration, stomatitis, dysphagia, flatulence, eructation, ileus
Rare:	melaena, tooth disorders, 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

Paediatric population

The frequency, type and severity of adverse reactions in patients under 12 years of age is expected to be no different to those in adults and adolescents aged 12 years and above.

For infants born to mothers receiving oxycodone see section 4.6.

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 (www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store.

Drug dependence

Repeated use of [Nationally completed name] 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).

4.9 Overdose

Symptoms of intoxication

Acute overdose with oxycodone can be manifested by respiratory depression, somnolence progressing up to stupor or coma, hypotonia, miosis, bradycardia, hypotension, lung oedema and death.

Toxic leukoencephalopathy has been observed with oxycodone overdose.

Therapy of intoxication

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. 0.4 to 2 mg intravenously). Administration should be repeated at 2 to 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 in the management of circulatory shock accompanying overdose. 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

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, Carexil® 20 mg Prolonged-release Tablets provide pain relief for a markedly longer period without increased occurrence of undesirable effects.

Endocrine system

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

Gastrointestinal system

Opioids may induce spasm of the sphincter of Oddi.

5.2 Pharmacokinetic properties

Absorption

The absorption of oxycodone from Carexil® 20 mg Prolonged-release Tablets could be calculated biphasic with an initially relatively rapid half-life of 0.6 hours accounting for a minority of the active substance, and a slower half-life of 6.9 hours accounting for the majority of the active substance.

To avoid damage to the controlled-release properties of the prolonged-release tablets, the Carexil® 20 mg Prolonged-release Tablets must be swallowed whole and not be divided, broken, crushed or chewed. The administration of broken, crushed or chewed tablets leads to rapid-release and absorption of a potentially fatal dose of oxycodone (see section 4.9).

The relative bioavailability of Prolonged-release oxycodone are 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.

A fat-rich meal before the intake of the tablets does not affect the maximum concentration or the extent of absorption of oxycodone.

The absolute bioavailability of oxycodone is approximately two thirds relative to parenteral administration.

Distribution

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.

Biotransformation

Oxycodone is metabolised to noroxycodone and oxymorphone in the intestine and liver via the P450 cytochrome system ,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 bioequivalent in a dose proportional manner 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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.
Oyxcodone showed no effect on fertility and early embryonic development in male and female rats in doses of up to 8 mg/kg body weight and induced no malformation in rats in doses of up to 8 mg/kg and in rabbits in doses of 125 mg/kg bodyweight. However, in rabbits, when individual foetuses were used in statistical evaluation, a dose related increase in developmental variations was observed (increased incidences of 27 presacral vertebrae, extra pairs of ribs). When these parameters were statistically evaluated using litters, only the incidence of 27 presacral vertebrae was increased and only in the 125 mg/kg group, a dose level that produced severe pharmacotoxic effects in the pregnant animals. In a study on pre- and postnatal development in rats F1 body weights were lower at 6 mg/kg/d when compared to body weights of the control group at doses which reduced maternal weight and food intake (NOAEL 2 mg/kg body weight). There were neither effects on physical, reflexological, and sensory developmental parameters nor on behavioural and reproductive indices.
There were no effects on F2 generation.

Long-term studies on carcinogenicity have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Hydrogenated castor oil
Copovidone
Behenoyl polyoxyglycerides
Lactose monohydrate
Magnesium stearate
Maize starch
Colloidal anhydrous silica
Triglycerides, medium-chain

Tablet coating
Microcrystalline cellulose
Hypromellose
Stearic acid
Titanium dioxide (E 171)
Iron oxide red (E 172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

Bottles: Shelf life after first opening:

6 months

6.4 Special precautions for storage

Blisters: Do not store above 30°C.

HDPE-Bottles: This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Child resistant PVC/PE/PVDC-aluminium blisters consisting of a white opaque PVC/PE/PVDC laminated foil and an aluminium foil or HDPE-Bottles, closed with child resistant Twist-off cap (HDPE or PP) with or without a desiccant capsule of polyethylene (PE), containing silica gel as desiccant.

Pack sizes:

Blisters: 7, 10, 14, 20, 28, 30, 50, 56, 60, 98, 100, 100x1 and 112 prolonged-release tablets

Bottles: 100 and 250 prolonged-release tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Sandoz Limited
Park View, Riverside Way
Watchmoor Park
Camberley, Surrey
GU15 3YL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/0836

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22/09/2008

Date of latest renewal:

10 DATE OF REVISION OF THE TEXT

15/04/2025