SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Oxycodone Teva 5 mg capsules, hard
Oxycodone Teva 10 mg capsules, hard
Oxycodone Teva 20 mg capsules, hard

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Oxycodone Teva 5 mg capsules:
Each capsule contains 5 mg oxycodone hydrochloride corresponding to 4.48 mg oxycodone.
Oxycodone Teva 10 mg capsules:
Each capsule contains 10 mg oxycodone hydrochloride corresponding to 8.96 mg oxycodone.
Oxycodone Teva 20 mg capsules:
Each capsule contains 20 mg oxycodone hydrochloride corresponding to 17.93 mg oxycodone.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard (capsule)

Oxycodone Teva 5 mg capsules:
Hard capsules, 14.4 mm in length, with a dark pink body marked with ‘5’ and a brown cap marked with ‘OXY’.
Oxycodone Teva 10 mg capsules:
Hard capsules, 14.4 mm in length, with a white body marked with ‘10’ and a brown cap marked with ‘OXY’.
Oxycodone Teva 20 mg capsules:
Hard capsules, 14.4 mm in length, with a light pink body marked with ‘20’ and a brown cap marked with ‘OXY’.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oxycodone Teva 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 intensity of pain and the patient’s individual susceptibility to the treatment. The correct dosage per individual patient is the lowest dose which sufficiently controls the pain with no or tolerable side effects.

The following general dose recommendations apply:

Adults and adolescents (from 12 years and older)

The dosage must be adjusted individually according to the patient's condition and taking into account any previous pain treatment.

Starting dose
The starting dose for adult patients who have not previously received opioids is 5 mg oxycodone hydrochloride given at intervals of 6 hours, but a higher starting dose may be required depending on the patient's need for pain control.
The starting dose for adolescents (from 12 years and older) who have not previously received opioids or who have severe pain that is not controlled with weak opioids is 5 mg oxycodone hydrochloride every 6 hours.

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

Switching from morphine
Patients receiving oral morphine before oxycodone therapy should have their daily dose based on the following ratio: 10 mg of oral oxycodone is equivalent to 20 mg of oral morphine. It should be noted that this is a guide to the dose of oxycodone hydrochloride capsules required. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

Dose adjustment
If the pain responds to opioids, the dose can be increased every day until the required effect is achieved or unacceptable side effects occur. The dosing interval can be reduced to every 4 hours if necessary, but the dose should not be taken more than 6 times per day. The correct dose for any individual patient is that which controls the pain and is well tolerated throughout the dosing period.

The majority of patients will not require a daily dose greater than 400 mg. However, a few patients may require higher doses.

In patients receiving a prolonged-release formulation of oxycodone, Oxycodone Teva may be used to control breakthrough pain. The dose should be adjusted according to the patient's need but as a general rule the single dose should amount to 1/8 to 1/6 of the daily dose of the prolonged-release formulation. If the addition of a short-acting opioid for breakthrough pain is needed more than twice daily, it may indicate that the prolonged-release formulation needs to be increased.

Treatment goals and discontinuation
Before initiating treatment with Oxycodone Teva, 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 treatment
Oxycodone should not be taken longer than necessary. See section 4.4 regarding the need for close monitoring for development of dependence and abuse.

Special populations

Paediatric population
Opioids must only be used for the management of severe pain in children after careful assessment 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.

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

Renal or hepatic impairment
The plasma concentration of oxycodone is higher in patients with impaired renal or liver function compared to patients with normal renal and liver function. The dose initiation should follow a conservative approach in these patients. The recommended adult starting dose should be reduced by 50% (for example a total daily dose of 10 mg orally in opioid naïve patients), and each patient should be titrated to adequate pain control according to their clinical situation (see section 4.4 and 5.2).

Other patients at risk
Risk patients, for example patients with low body weight or slow metabolism of medicinal products, should initially receive half the recommended adult dose if they are opioid naïve.
Therefore the lowest recommended dose, i.e. 5 mg, may not be suitable as a starting dose.
Dose titration should be performed in accordance with the individual clinical situation and using the appropriate formulation as available.

Method of administration
Oral use.
Oxycodone Teva should be administered using a fixed schedule at the dose determined but not more often than every 4 to 6 hours.
The capsules may be taken with or without food with a sufficient amount of liquid.

The medicinal product should not be taken with alcoholic beverages.

4.3 Contraindications

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

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

4.4 Special warnings and precautions for use

Oxycodone has to be administered with caution in patients
- with severely impaired respiratory function,
- with sleep apnoea,
- taking benzodiazepines or other CNS depressants (including alcohol; see below and section 4.5),
- taking monoamine oxidase inhibitors (MAOIs, see below and section 4.5),
- with signs of Opioid Use Disorder (see below),
- with tolerance and withdrawal (see below),
- debilitated or elderly,
- with head injury (due to risk of increased intracranial pressure),
- with hypotension,
- with hypovolaemia,
- with epileptic disorder or predisposition to convulsions,

- with pancreatitis,
- with obstructive and inflammatory intestinal disease,
- with impaired hepatic function,
- with impaired renal function,
- with myxoedema,
- with hypothyroidism,
- with Addison's disease (adrenal insufficiency),
- with prostatic hypertrophy,
- with alcoholism,
- with toxic psychosis,
- with delirium tremens,
- with constipation,
- with diseases of the biliary tract, biliary or ureteric colic.

The dose may need to be reduced.

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

Respiratory depression
The primary risk of opioid excess is respiratory depression. Respiratory depression is most likely to occur in elderly or debilitated patients. The respiratory depressant effect of oxycodone can lead to increased carbon dioxide concentrations in blood and hence in cerebrospinal fluid. In predisposed patients opioids can cause severe decrease in blood pressure.

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 opioids, including oxycodone 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 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 must be administered with caution in patients taking MAOIs or who have received MAOIs within the previous two weeks (see section 4.5).

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 Oxycodone Teva 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 Oxycodone Teva 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 Oxycodone Teva 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.

Tolerance and withdrawal
The patient may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain control. Prolonged use of oxycodone 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 and insomnia.

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.

Chronic non-malignant pain
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 program involving other medications and treatment modalities. Patients with chronic non-malignant pain should be monitored for signs of dependence or substance abuse.

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

Abusive parenteral venous injection
In case of abusive parenteral venous injection the capsule content may lead to serious, potentially fatal events.

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.

Surgical procedures
Oxycodone should be used with caution pre-operatively and within the first 12-24 hours post-operatively.
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.

Endocrine effects
Opioids, such as oxycodone, 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.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

Alcohol may enhance the pharmacodynamic effects of oxycodone; concomitant use should be avoided.

MAO-inhibitors are known to interact with narcotic analgesics. MAO-inhibitors cause CNS-excitation or depression associated with hypertensive or hypotensive crisis (see section 4.4). 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).

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

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

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, which may lead to altered plasma concentrations of oxycodone. Oxycodone doses may therefore need to be adjusted.

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

Some specific examples are provided below:

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

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

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

- St John's Wort, a CYP3A4 inducer, administered as 300 mg three times a day for fifteen days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 50% lower (range 37-57%).
- Rifampicin, a CYP3A4 inducer, administered as 600 mg once-daily for seven days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 86% lower

Drugs that inhibit CYP2D6 activity, such as paroxetine, fluoxetine and quinidine, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. However, co-administration with inhibitors of CYP2D6 has resulted in only a minor effect on oxycodone elimination and no influence on the pharmacodynamic effects of oxycodone.

The effect of other relevant isoenzyme inhibitors on the metabolism of oxycodone is not known. Potential interactions should be taken into account. The potential effect of oxycodone on cytochrome P450-enzymes has not been studied in vitro or in vivo.

Clinically relevant changes in International Normalised Ratio (INR) in both directions have been observed in individuals if coumarin anticoagulants are co-applied with oxycodone.

4.6 Fertility, pregnancy and lactation

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

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 newborn of mothers undergoing treatment with oxycodone.

Oxycodone crosses the placenta. Animal studies with oxycodone have not shown any teratogenic or embryotoxic effects. Oxycodone should only be used during pregnancy if the benefit outweighs the potential risks to the unborn child or neonate.

Breastfeeding
Oxycodone may be excreted in human breast milk and may cause respiratory depression in the breastfed child. Therefore, oxycodone should not be used in breastfeeding mothers.

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).

4.7 Effects on ability to drive and use machines

Oxycodone may impair the ability to drive and use machines (see section 4.8).

This is particularly likely at the initiation of treatment with oxycodone, after dose increase or product rotation and if oxycodone is combined with other CNS depressant agents. During the long-term therapy, a general ban on driving a vehicle is not necessary. The treating physician must assess the

individual situation.

4.8 Undesirable effects

Summary of the safety profile
Due to its pharmacological properties oxycodone may cause respiratory depression, miosis, bronchial spasm and spasm of unstriated 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.

Tolerance development may occur in patients treated with oxycodone but has not been a significant problem in the clinical trial program.

Tabulated list of adverse events
The adverse events are listed below by system organ class and frequency.

System organ class	**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** (frequency cannot be estimated from the available data**)**
Infections and infestations				Herpes simplex		
Blood and lymphatic system disorders				Lymphadenopathy		
Immune system disorders			Hypersensitivity			Anaphylactic reaction, anaphylactoid reaction
Endocrine disorders			Syndrome of inappropriate antidiuretic hormone secretion			
Metabolism and nutrition disorders		Decreased appetite	Dehydration	Increased appetite		
Psychiatric disorders		Anxiety, confusional state, depression, nervousness, insomnia,	Agitation, affect lability, euphoric mood, perception disturbances (e.g.			Aggression

		abnormal thinking	hallucination, derealisation), decreased libido, drug dependence (see section 4.4)			
Nervous system disorders	Somnolence, dizziness, headache	Tremor, lethargy	Amnesia, convulsion (especially in persons with epileptic disorder or predisposition to convulsions), migraine, hypertonia, hypotonia, involuntary muscle contractions, hypoesthesia, abnormal coordination, speech disorder, syncope, paraesthesia, dysgeusia			Hyperalgesia
Eye disorders			Visual impairment, miosis, lacrimation disorder			
Ear and labyrinth disorders			Hyperacousis, vertigo			
Cardiac disorders			Tachycardia, palpitations (in the context of withdrawal syndrome)			
Vascular disorders			Vasodilatation	Hypotension, orthostatic hypotension		
Respiratory, thoracic and mediastinal disorders		Dyspnoea, bronchospasm	Respiratory depression, dysphonia, cough, pharyngitis, rhinitis			Central sleep apnoea syndrome
Gastrointestinal disorders	Constipation,	Abdominal pain, diarrhoea,	Mouth ulceration, gingivitis,	Melaena, tooth discolouration,		Dental caries

	vomiting, nausea	dry mouth, dyspepsia	stomatitis, dysphagia, flatulence, eructation, ileus	gingival bleeding		
Hepatobiliary disorders			Increased hepatic enzymes, ureteral spasm			Cholestasis, biliary colic, sphincter of Oddi dysfunction
Skin and subcutaneous tissue disorders	Pruritus	Skin reactions/rash, hyperhidrosis	Dry skin	Urticaria, photosensitivity reaction	Exfoliative dermatitis	
Renal and urinary disorders		Micturition urgency	Urinary retention	Haematuria		
Reproductive system and breast disorders			Erectile dysfunction, hypogonadism			Amenorrhoea
General disorders and administration site conditions		Asthenia, fatigue	Chills, drug withdrawal syndrome, pain (e.g. chest pain), malaise, oedema, peripheral oedema, drug tolerance, thirst	Weight increase, weight decrease, cellulitis		Drug withdrawal syndrome neonatal
Injury, poisoning and procedural complications			Injuries from accidents			

Description of selected adverse reactions

Drug dependence
Repeated use of Oxycodone Teva 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).

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).

Counteractive measures

As constipation is a very common side effect it may be helpful to instruct the patient that this may be prevented by a fiber enriched diet and increased intake of fluids.
For nausea and vomiting, prescribing antiemetics may be considered.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
Miosis, respiratory depression, somnolence, reduced skeletal muscle tone, drop in blood pressure and toxic leukoencephalopathy have been observed with oxycodone overdose.

In severe cases circulatory collapse, stupor, coma, bradycardia, non-cardiogenic lung oedema, hypotension and death may occur; abuse of high doses of strong opioids such as oxycodone can be fatal.

The lethal dose for adults (without development of tolerance) is stated to be approximately 60-100 mg orally.

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

In the event of overdosing intravenous administration of an opiate antagonist (e.g. 0.4-2 mg intravenous naloxone) may be indicated. 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. Consider activated charcoal (50 g for adults, 10-15 g for children), if a substantial amount has been ingested within 1 hour, provided the airway can be protected. It may be reasonable to assume that late administration of activated charcoal may be beneficial for prolonged release preparations; however there is no evidence to support this.

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 should be performed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids, ATC-Code: N02AA05

Mechanism of action
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.

Endocrine system
See section 4.4.

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

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

5.2 Pharmacokinetic properties

Absorption
The absolute bioavailability of oxycodone is 60-87% following oral administration and the peak plasma concentration is achieved after approximately 1 to 1.5 hours.

Distribution
At steady state, the volume of distribution of oxycodone amounts to 2.6 l/kg and plasma protein binding to 38-45%.

Biotransformation
Oxycodone is metabolised in the intestine and liver via the P450 cytochrome system to noroxycodone (CYP3A4) and oxymorphone (CYP2D6) as well as to several glucuronide conjugates. The contribution of the metabolites to the overall pharmacodynamic effect is irrelevant.

Elimination
At steady state, the plasma elimination half-life amounts to approximately 3 hours. Oxycodone and its metabolites are excreted via urine. Faecal excretion has not been studied.

Linearity/non-linearity
After administration of the capsule formulation of oxycodone hydrochloride the plasma concentration increases linear over the dose range of 5 to 20 mg.

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

5.3 Preclinical safety data

Teratogenicity
Oyxcodone had 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 malformations 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.

Carcinogenicity

Long-term carcinogenicity studies were not performed.

Mutagenicity
Oxycodone shows a clastogenic potential in in vitro assays. No similar effects were observed, however, under in vivo conditions, even at toxic doses. The results indicate that the mutagenic risk of oxycodone to humans at therapeutic concentrations may be ruled out with adequate certainty.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Microcrystalline cellulose
Magnesium stearate

Capsule shell:
Gelatine
Sodium laurilsulfate
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172)
Indigotine (E132)

Printing ink:
Shellac
Propylene glycol
Ammonia solution (for pH-adjustment)
Iron oxide black (E172)
Potassium hydroxide (for pH-adjustment)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Peel-off blister packs (PVC/PVdC/Alu/PET/paper).
Pack sizes:
5 mg
14, 20, 28, 30, 50, 56, and 100 capsules
10 mg
20, 28, 30, 50, 56, and 100 capsules
20 mg
20, 28, 30, 50, 56, and 100 capsules

Push-through blister packs (PVC/PVdC/Alu).
Pack sizes:

5 mg
14, 20, 28, 30, 50, 56, and 100 capsules
10 mg
20, 28, 30, 50, 56, and 100 capsules
20 mg
20, 28, 30, 50, 56, and 100 capsules

HDPE containers with child resistant PP caps.
Pack sizes: 98, 100 and 250 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

Instructions for use of peel-off blisters:
1. Do not push the capsule directly out of the pocket
2. Separate one blister cell from the strip at the perforations
3. Carefully peel off the backing to open the pocket

Instruction for use of HDPE containers with child resistant PP caps:
Push down and turn to open.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

05-SEP-2025