SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Oxikodon Depot Actavis 5 mg prolonged-release tablets
Oxikodon Depot Actavis 10 mg prolonged-release tablets
Oxikodon Depot Actavis 15 mg prolonged-release tablets
Oxikodon Depot Actavis 20 mg prolonged-release tablets
Oxikodon Depot Actavis 30 mg prolonged-release tablets
Oxikodon Depot Actavis 40 mg prolonged-release tablets
Oxikodon Depot Actavis 60 mg prolonged-release tablets
Oxikodon Depot Actavis 80 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Oxikodon Depot Actavis 5 mg:
Each prolonged-release tablet contains 5 mg oxycodone hydrochloride corresponding to 4.5 mg oxycodone.

Oxikodon Depot Actavis 10 mg:
Each prolonged-release tablet contains 10 mg oxycodone hydrochloride corresponding to 9 mg oxycodone.

Oxikodon Depot Actavis 15 mg:
Each prolonged-release tablet contains 15 mg oxycodone hydrochloride corresponding to 13.5 mg oxycodone.

Oxikodon Depot Actavis 20 mg:
Each prolonged-release tablet contains 20 mg oxycodone hydrochloride corresponding to 18 mg oxycodone.

Oxikodon Depot Actavis 30 mg:
Each prolonged-release tablet contains 30 mg oxycodone hydrochloride corresponding to 27 mg oxycodone.

Oxikodon Depot Actavis 40 mg:
Each prolonged-release tablet contains 40 mg oxycodone hydrochloride corresponding to 36 mg oxycodone.

Oxikodon Depot Actavis 60 mg:
Each prolonged-release tablet contains 60 mg oxycodone hydrochloride corresponding to 54 mg oxycodone.

Oxikodon Depot Actavis 80 mg:
Each prolonged-release tablet contains 80 mg oxycodone hydrochloride corresponding to 72 mg oxycodone.

Excipient with known effect:

Oxikodon Depot Actavis 5 mg:
Each prolonged-release tablet contains 31.6 mg lactose monohydrate

Oxikodon Depot Actavis 10 mg:
Each prolonged-release tablet contains 63.2 mg lactose monohydrate

Oxikodon Depot Actavis 15 mg:
Each prolonged-release tablet contains 63.2 mg lactose monohydrate

Oxikodon Depot Actavis 20 mg:
Each prolonged-release tablet contains 31.6 mg lactose monohydrate

Oxikodon Depot Actavis 30 mg:
Each prolonged-release tablet contains 63.2 mg lactose monohydrate

Oxikodon Depot Actavis 40 mg:
Each prolonged-release tablet contains 31.6 mg lactose monohydrate

Oxikodon Depot Actavis 60 mg:
Each prolonged-release tablet contains 63.2 mg lactose monohydrate

Oxikodon Depot Actavis 80 mg:
Each prolonged-release tablet contains 63.2 mg lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet.

Oxikodon Depot Actavis 5 mg:
Blue, round, biconvex tablets, 7 mm in diameter, with ‘OX 5’ debossed on one side.

Oxikodon Depot Actavis 10 mg:
White, round, biconvex tablets, 9 mm in diameter, with ‘OX 10’ debossed on one side.

Oxikodon Depot Actavis 15 mg:
Grey, round, biconvex tablets, 9 mm in diameter, with ‘OX 15’ debossed on one side.

Oxikodon Depot Actavis 20 mg:
Pink, round, biconvex tablets, 7 mm in diameter, with ‘OX 20’ debossed on one side.

Oxikodon Depot Actavis 30 mg:
Brown, round, biconvex tablets, 9 mm in diameter, with ‘OX 30’ debossed on one side.

Oxikodon Depot Actavis 40 mg:
Yellow, round, biconvex tablets, 7 mm in diameter, with ‘OX 40’ debossed on one side.

Oxikodon Depot Actavis 60 mg:
Red, round, biconvex tablets, 9 mm in diameter, with ‘OX 60’ debossed on one side.

Oxikodon Depot Actavis 80 mg:
Green, round, biconvex tablets, 9 mm in diameter, with ‘OX 80’ debossed on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oxikodon Depot Actavis 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 dosage recommendations apply:

Adults and adolescents (from 12 years and older)

Starting dose
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 side effects.

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

For doses not realisable/practicable with these strengths, other strengths are available.

Because of individual differences in sensitivity for different opioids, it is recommended that patients should start conservatively with Oxikodon Depot Actavis after conversion from other opioids, with 50-75% of the calculated oxycodone dose.

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. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose. Initially, a lower-than-equivalent dose may be advisable.

Dose adjustment
Some patients who take Oxikodon Depot Actavis following a fixed schedule need rapid release analgesics as rescue medication in order to control breakthrough pain. Oxikodon Depot Actavis is 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 Oxikodon Depot Actavis. Use of the rescue medication more than twice daily indicates that the dose of Oxikodon Depot Actavis 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 mornings and evenings) following a fixed schedule (every 12 hours) is appropriate for the majority of the patients. For some patients it may be advantageous to distribute the doses unevenly. In general, the lowest effective analgesic dose should be chosen. For the treatment of non- malignant pain a daily dose of 40 mg is generally sufficient; but higher dosages may be necessary. Patients with cancer- related pain may require dosages of 80 to 120 mg, which in individual cases can be increased to up to 400 mg. If even higher doses are required, the dose should be decided individually balancing efficacy with the tolerance and risk of undesirable effects.

Treatment goals and discontinuation
Before initiating treatment with Oxikodon Depot Actavis, 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.

Elderly patients
A dose adjustment is usually not necessary in elderly without clinical manifestation of impaired liver and/or kidney 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.

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 dose if they are opioid naïve. Dose titration should be performed in accordance with the individual clinical situation.

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.

Method of administration
Oral use.
Oxikodon Depot Actavis 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. Oxikodon Depot Actavis prolonged release tablets must be swallowed whole, not chewed.

For instructions how to open the child resistant blisters, see section 6.6.

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 and dose may need to be reduced in patients with the following conditions:
- severely impaired respiratory function,
- 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),
- signs of Opioid Use Disorder (see below),
- tolerance and withdrawal (see below),
- debilitated or elderly,
- head injury (due to risk of increased intracranial pressure),
- hypotension,
- hypovolaemia,
- epileptic disorder or predisposition to convulsions,
- pancreatitis,
- obstructive and inflammatory intestinal disease,
- impaired hepatic function,
- impaired renal function,
- myxoedema,
- hypothyroidism,
- Addison's disease (adrenal insufficiency),
- prostatic hypertrophy,
- alcoholism,
- toxic psychosis,
- delirium tremens,
- constipation,
- diseases of the biliary tract, biliary or ureteric colic.

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

Respiratory depression
The primary risk of opioid excess is respiratory depression and is most likely to occur in elderly or debilitated patients.

Sleep-related breathing disorders
Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs
Concomitant use of 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 Oxikodon Depot Actavis 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 Oxikodon Depot Actavis 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 Oxikodon Depot Actavis 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 behaviour (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, insomnia, and myalgia.

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 tablet excipients may lead to necrosis of the local tissue, infection, increased risk of endocarditis, and valvular heart injury which may be fatal, granulomas of the lung or other serious, potentially fatal events.

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

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 is 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 Oxikodon Depot Actavis depends on a careful risk-benefit assessment for each individual patient.

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.

Paediatric population
Oxikodon Depot Actavis is not recommended for use in children below the age of 12 years due to insufficient data on safety and efficacy.

Excipients
Lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 causes 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.

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

There are no studies investigating the effect of oxycodone on CYP catalysed metabolism of other drugs.

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.

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.
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.

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.

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. Opioids may cause severe hypotension in susceptible individuals.

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, abnormal thinking	Agitation, affect lability, euphoric mood, perception disturbances (e.g. hallucination, derealisation), decreased libido, drug dependence (see section 4.4)			Aggression
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, vomiting, nausea	Abdominal pain, diarrhoea, dry mouth, dyspepsia	Mouth ulceration, gingivitis, stomatitis, dysphagia, flatulence, eructation, ileus	Melaena, tooth discolouration, gingival bleeding		Dental caries
Hepatobiliary disorders			Increased hepatic enzymes			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	Weight increase, weight decrease, cellulitis		Drug withdrawal syndrome neonatal

			tolerance, thirst			
Injury, poisoning and procedural complications			Injuries from accidents			

Description of selected adverse reactions

Drug dependence
Repeated use of Oxikodon Depot Actavis 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).

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 should not be routinely used. In specific cases of potentially life-threatening co-ingestions, it might 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.

A suitable laxative may be used when appropriate.

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: N02A A05

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. 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.

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.

Other pharmacological effects
In-vitro and animal studies indicate various effects of natural opioids, such as morphine, on components of the immune system; the clinical significance of these findings is unknown. Whether oxycodone, a semisynthetic opioid, has immunological effects similar to morphine is unknown.

5.2 Pharmacokinetic properties

Absorption
The relative bioavailability of Oxikodon Depot Actavis prolonged-release tablets is comparable to that of rapid release oxycodone with maximum plasma concentrations being achieved 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 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 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.

Biotransformation
Oxycodone is metabolised in the intestine and liver to noroxycodone and oxymorphone as well as to several glucuronide conjugates. CYP3A4 and CYP2D6 are probably involved in the formation of noroxycodone and oxymorphone respectively. Oxymorphone has analgesic activity but is present in the plasma in low concentrations and is not considered to contribute to oxycodone's pharmacological effect.

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 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.

Elderly
The plasma concentration of oxycodone in elderly subjects is 15% greater when compared with young subjects.

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.

Patients with renal impairment
Patients with mild, moderate and severe renal impairment showed 1.1-, 1.4- and 1.7- fold increased plasma concentrations respectively compared to patients with normal renal function. AUC increased on average 1.5-, 1.7- and 2.3-fold respectively compared to patients with normal renal function. The elimination half-life for oxycodone increased 1.5-, 1.2- and 1.4- fold respectively compared to patients with normal renal function.

Patients with hepatic impairment
Patients with mild, moderate and severe hepatic impairment showed 1.2-, 2.0- and 1.9- fold increased plasma concentrations respectively compared to patient with normal hepatic function. AUC increased on average 1.4-, 3.2- and 3.2- fold respectively compared to patients with normal hepatic function. The elimination half-life of oxycodone increased 1.1-, 1.8- and 1.8- fold respectively compared to patients with normal hepatic function.

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 of peri- and postnatal development in rats, maternal body weight and food intake parameters were reduced for doses $\geq$ 2 mg/kg/d compared to the control group. Body weights were lower in the F1 generation from maternal rats in the 6 mg/kg/d 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/d based on body weight effects seen at 6 mg/kg/d). There were no effects on the F2 generation at any dose in the study.

Carcinogenicity
Long-term carcinogenicity studies were not performed.

Mutagenicity
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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Hypromellose
Povidone K30
Stearic acid
Magnesium stearate
Colloidal anhydrous silica

Tablet coating
5 mg:
Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol 3350
Talc
Blue Indigo Carmine Aluminium Lake (E132)
Iron oxide, yellow (E172)

10 mg:
Titanium dioxide (E171)
Hypromellose
Macrogol 400
Polysorbate 80

15 mg:
Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol 3350
Talc
Iron oxide, black (E172)
Iron oxide, yellow (E172)

20 mg:
Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol 3350
Talc
Iron oxide, red (E172)

30 mg:
Polyvinyl alcohol
Macrogol 3350
Talc

Iron oxide, red (E172)
Iron oxide, black (E172)
Blue Indigo Carmine Aluminium Lake (E132)

40 mg:
Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol 3350
Talc
Iron oxide, yellow (E172)

60 mg:
Polyvinyl alcohol
Macrogol 3350
Talc
Iron oxide, red (E172)
Carmine (E120)
Iron oxide, black (E172)

80 mg:
Polyvinyl alcohol
Macrogol 3350
Talc
Titanium dioxide (E171)
Blue Indigo Carmine Aluminium Lake (E132)
Iron oxide, yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Blister packs:
Do not store above 25°C.

HDPE container:
5 mg, 10 mg, 15 mg: Do not store above 30°C.
20 mg, 30 mg, 40 mg, 60 mg, 80 mg: This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Child resistant blister packs (PVC/Al/PET/paper).
Pack sizes:
5 mg: 1, 20, 28, 30, 50, 56, 60 and 100 prolonged-release tablets
10 mg, 20 mg, 40 mg, 80 mg: 1, 20, 28, 30, 50, 56, 60, 98 and 100 prolonged-release tablets
15 mg: 1, 20, 28, 30, 50, 56, 98 and 100 prolonged-release tablets
30 mg, 60 mg: 1, 20, 28, 30, 50, 56, 98 and 100 prolonged-release tablets

Blister packs (PVC/Al) in cartons.
Pack sizes:
5 mg: 1, 20, 28, 30, 50, 56, 60 and 100 prolonged-release tablets

10 mg, 20 mg, 40 mg, 80 mg: 1, 20, 28, 30, 50, 56, 60, 98 and 100 prolonged-release tablets
15 mg: 1, 20, 28, 30, 50, 56, 98 and 100 prolonged-release tablets
30 mg, 60 mg: 1, 20, 28, 30, 50, 56, 98 and 100 prolonged-release tablets

White, round, child-resistant, HDPE tablet containers with PP caps.
Pack size: 98 and 100 prolonged-release tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

Instructions for use of child resistant blisters:
1. Do not push the tablet 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

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

2025-06-11
[To be completed nationally]