SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Oxikodon Actavis 5 mg capsules, hard
Oxikodon Actavis 10 mg capsules, hard
Oxikodon Actavis 20 mg capsules, hard

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Oxikodon Actavis 5 mg capsules:
Each capsule contains 5 mg oxycodone hydrochloride corresponding to 4.48 mg oxycodone.
Oxikodon Actavis 10 mg capsules:
Each capsule contains 10.0 mg oxycodone hydrochloride corresponding to 8.96 mg oxycodone.
Oxikodon Actavis 20 mg capsules:
Each capsule contains 20.0 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)

Oxikodon Actavis 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’.
Oxikodon Actavis 10 mg capsules:
Hard capsules, 14.4 mm in length, with a white body marked with ‘10’ and a brown cap marked with ‘OXY’.
Oxikodon Actavis 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

Severe pain, which can only be adequately managed 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 following general dose recommendations apply:

Adults and adolescents over 12 years of age

Dose initiation
In general, the initial dose for opioid naïve patients is 5 mg oxycodone hydrochloride given at intervals of 6 hours. Patients already receiving opioids may start treatment with higher doses taking into account their experience with former opioid therapies.

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
Increasing severity of pain will require an increased dose of Oxikodon Actavis. The dose should be carefully titrated, as frequently as once a day if necessary, to achieve pain relief. In doing so, the dosing interval may be reduced to 4 hours. 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, Oxikodon Actavis 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. The rescue medication should not be used more frequently than every 6 hours.

Duration of administration
Oxycodone should not be taken longer than necessary. If long-term treatment is necessary due to the type and severity of the illness careful and regular monitoring is required to determine whether and to what extent treatment should be continued.

Discontinuation of treatment
If opioid therapy is no longer indicated it may be advisable to reduce the daily dose gradually in order to prevent symptoms of a withdrawal syndrome.

Special populations

Paediatric population
Oxikodon Actavis is not recommended for children under 12 years of age as the safety and efficacy has not been established.

Elderly patients
The lowest dose should be administered with careful titration to pain control.

Patients with renal or hepatic impairment
The dose initiation should follow a conservative approach in these patients. The recommended adult starting dose should be reduced by 50% (for example a total daily dose of 10 mg orally in opioid naïve patients), and each patient should be titrated to adequate pain control according to their clinical situation.

Risk patients
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
For oral use.
Oxikodon Actavis 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

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

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.

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

Respiratory and cardiac depression
Respiratory depression is the most significant risk induced by opioids and 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.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs
Concomitant use of Oxikodon Actavis 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 Oxikodon Actavis 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).

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

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.

Oxycodone hydrochloride capsules have a primary dependence potential. Oxycodone has an abuse profile similar to other strong agonist opioids. Oxycodone may be sought and abused by people with latent or manifest addiction disorders. There is potential for development of psychological dependence (addiction) to opioid analgesics, including oxycodone. However, when used as directed in patients with chronic pain the risk of developing physical or psychological dependence is markedly reduced or needs to be assessed in a differentiated manner. There are no data available on the actual incidence of psychological dependence in chronic pain patients. In patients with a history of alcohol and drug abuse Oxikodon Actavis must be prescribed with special care.

Abuse
In case of abusive parenteral venous injection the capsule content (especially talc) may lead to serious, potentially fatal events.

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

Alcohol
Oxikodon Actavis must not be taken together with alcoholic beverages, since alcoholic drinks enhance the impairment of alertness and reactivity and may increase the incidence of undesirable effects (e.g. somnolence, respiratory depression).

Paediatric population
Oxycodone has not been studied in children younger than 12 years of age. The safety and efficacy of the capsules have not been demonstrated and the use in children younger than 12 years of age is therefore not recommended.

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

There can be an enhanced CNS depressant effect during concomitant therapy with drugs which affect the CNS such as other opioids, sedatives, hypnotics, anti-depressants, phenothiazines and neuroleptic drugs. 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).

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).

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.

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

Anticholinergics (e.g. neuroleptics, antihistamines, antiemetics, antiparkinson medicinal products) can enhance the anticholinergic undesirable effects of oxycodone (such as constipation, dry mouth or micturition disorders).

Oxycodone is metabolised mainly by CYP3A4, with a contribution from CYP2D6. The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs or dietary elements.

CYP3A4 inhibitors, such as macrolide antibiotics (e.g. clarithromycin, erythromycin and telithromycin), azol-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, carbamazepin, 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 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

Drugs that inhibit CYP2D6 activity, such as paroxetine and quinidine, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations.

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 hydrochloride capsules.

4.6 Fertility, pregnancy and lactation

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

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

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

4.7 Effects on ability to drive and use machines

Oxycodone may impair the ability to drive and use machines (see section 4.8). With stable therapy, a general ban on driving a vehicle is not necessary. The treating physician must assess the individual situation.

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse reactions

The displayed frequency categories use the following convention: 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 clinical clinical data).

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** (Cannot be estimated from the available data**)**
Infections and infestations				Herpes simplex		

Blood and lymphatic system disorders				Lymphadeno pathy		
Immune system disorders			Hypersensitivity reactions			Anaphylactic responses
Endocrine disorders			Syndrome of inappropriate antidiuretic hormone secretion			
Metabolism and nutrition disorders		Anorexia; loss of appetite	Dehydration	Increased appetite		
Psychiatric disorders		Various psychologi-cal adverse reactions including changes in mood (e.g. anxiety, depression), changes in activity (mostly suppression sometimes associated with lethargy, occasionally increase with nervousness and insomnia) and changes in cognitive performance (abnormal thinking, confusional state)	Change in perception such as depersonali-sation, hallucinations; decreased libido; agitation; affect lability; euphoric mood; drug dependence (see section 4.4)			Aggression

Nervous system disorders	Somnolence; dizziness; headache	Tremor	Both increased and decreased muscle tone; involuntary muscle contractions; convulsions, in particular in epileptic patients or patients with tendency to convulsions; hypertonia; hypoaesthesia; speech disorder; syncope; paraesthesia; coordination disturbances; change in taste; migraine; vertigo; amnesia			Hyperalgesia
Eye disorders			Lacrimation disorder; miosis; visual impairment			
Ear and labyrinth disorders			Hyperacousis; vertigo			
Cardiac disorders			Supraventricular tachycardia; palpitations (in the context of withdrawal syndrome)			
Vascular disorders			Vasodilatation	Hypotension; orthostatic hypotension		
Respiratory, thoracic and mediastinal disorders		Bronchospasm; dyspnoea; hiccups	Respiratory depression; cough; pharyngitis; rhinitis; voice changes			
Gastrointestinal disorders	Constipation; nausea; vomiting	Dry mouth; abdominal pain; diarrhoea; dyspepsia	Dysphagia; oral ulcers; gingivitis; stomatitis;	Gum bleeding; tarry stools; tooth		Dental caries

			flatulence; eructation; ileus	staining and damage		
Hepato-biliary disorders			Increased hepatic enzymes			Cholestasis; biliary colic
Skin and subcutaneous tissue disorders	Pruritus	Skin eruptions including rash; hyper-hidrosis	Dry skin	Urticaria; photosensi-tivity	Exfoliative dermatitis	
Musculoskeletal and connective tissue disorders				Muscle spasm		
Renal urinary disorders		Increased urge to urinate	Urinary retention	Haematuria		
Reproductive system and breast disorders			Erectile dysfunction			Amenorrhoea
General disorders and administration site conditions		Asthenic conditions	Pain (e.g. chest pain); chills; oedema; peripheral oedema; malaise; physical dependence with withdrawal syndrome; drug tolerance; thirst	Weight changes (increase or decrease); cellulitis		Drug withdrawal syndrome neonatal
Injury, poisoning and procedural complications			Accidental injuries			

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 of overdose
Miosis, respiratory depression, somnolence, reduced skeletal muscle tone and drop in blood pressure. In severe cases circulatory collapse, stupor, coma, bradycardia and non-cardiogenic lung oedema, hypotension and death may occur; abuse of high doses of strong opioids such as oxycodone can be fatal.

Therapy of overdose
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.

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.

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.

5.3 Preclinical safety data

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.

Long-term carcinogenicity studies were not performed.
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
Iron oxide black (E172)
Potassium hydroxide (for pH-adjustment)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

<[For HDPE container only:]>
After opening: 6 months

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Blister packs (PVC/PVdC/Al).
Pack sizes: 10, 14, 20, 28, 30, 50, 56, 90, 98 and 100 capsules

Child resistant blister packs (PVC/PVdC/Al/PET/paper).
Pack sizes: 10, 14, 20, 28, 30, 50, 56, 90, 98 and 100 capsules

Child resistant HDPE containers with threaded neck with PP Cap (Twist off Cap).
Pack sizes: 56, 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 child resistant 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

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

2019-11-21