SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Oxycodone Depot Orion 5 mg prolonged-release tablets
Oxycodone Depot Orion 10 mg prolonged-release tablets
Oxycodone Depot Orion 15 mg prolonged-release tablets
Oxycodone Depot Orion 20 mg prolonged-release tablets
Oxycodone Depot Orion 30 mg prolonged-release tablets
Oxycodone Depot Orion 40 mg prolonged-release tablets
Oxycodone Depot Orion 60 mg prolonged-release tablets
Oxycodone Depot Orion 80 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Oxycodone Depot Orion 5 mg prolonged-release tablets:
Each prolonged-release tablet contains 5 mg oxycodone hydrochloride corresponding to 4.5 mg oxycodone.

Excipients with known effect:
Each prolonged-release tablet contains 64 mg lactose (as monohydrate)

Oxycodone Depot Orion 10 mg prolonged-release tablets:
Each prolonged-release tablet contains 10 mg oxycodone hydrochloride corresponding to 9 mg oxycodone.

Excipients with known effect:
Each prolonged-release tablet contains 56 mg lactose (as monohydrate)

Oxycodone Depot Orion 15 mg prolonged-release tablets:
Each prolonged-release tablet contains 15 mg oxycodone hydrochloride corresponding to 13.5 mg oxycodone.

Excipients with known effect:
Each prolonged-release tablet contains 51 mg lactose (as monohydrate)

Oxycodone Depot Orion 20 mg prolonged-release tablets:
Each prolonged-release tablet contains 20 mg oxycodone hydrochloride corresponding to 17.9 mg oxycodone.

Excipients with known effect:
Each prolonged-release tablet contains 46 mg lactose (as monohydrate)

Oxycodone Depot Orion 30 mg prolonged-release tablets:
Each prolonged-release tablet contains 30 mg oxycodone hydrochloride corresponding to 26.9 mg oxycodone.

Excipients with known effect:
Each prolonged-release tablet contains 36 mg lactose (as monohydrate)

Oxycodone Depot Orion 40 mg prolonged-release tablets:
Each prolonged-release tablet contains 40 mg oxycodone hydrochloride corresponding to 35.9 mg oxycodone.

Excipients with known effect:
Each prolonged-release tablet contains 25 mg lactose (as monohydrate)

Oxycodone Depot Orion 60 mg prolonged-release tablets:
Each prolonged-release tablet contains 60 mg oxycodone hydrochloride corresponding to 53.8 mg oxycodone.

Excipients with known effect:
Each prolonged-release tablet contains 86 mg lactose (as monohydrate)

Oxycodone Depot Orion 80 mg prolonged-release tablets:
Each prolonged-release tablet contains 80 mg oxycodone hydrochloride corresponding to 71.7 mg oxycodone.

Excipients with known effect:
Each prolonged-release tablet contains 60 mg lactose (as monohydrate)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet.

Oxycodone Depot Orion 5 mg prolonged-release tablets:
Light blue, round, biconvex, prolonged-release tablets with a diameter of 6.9 – 7.3 mm and a height of 3.2 – 3.9 mm.

Oxycodone Depot Orion 10 mg prolonged-release tablets:
White, round, biconvex, prolonged-release tablets with a diameter of 6.9 – 7.3 mm and a height of 3.2 – 3.9 mm.

Oxycodone Depot Orion 15 mg prolonged-release tablets:
Grey, round, biconvex, prolonged-release tablets with a diameter of 6.9 – 7.3 mm and a height of 3.2 – 3.9 mm.

Oxycodone Depot Orion 20 mg prolonged-release tablets:
Light pink, round, biconvex, prolonged-release tablets with a diameter of 6.9 – 7.3 mm and a height of 3.2 – 3.9 mm.

Oxycodone Depot Orion 30 mg prolonged-release tablets:
Brown, round, biconvex, prolonged-release tablets with a diameter of 6.9 – 7.3 mm and a height of 3.2 – 3.9 mm.

Oxycodone Depot Orion 40 mg prolonged-release tablets:
Light orange to ochre, round, biconvex, prolonged-release tablets with a diameter of 6.9 – 7.3 mm and a height of 3.2 – 3.9 mm.

Oxycodone Depot Orion 60 mg prolonged-release tablets:
Pink-red, round, biconvex, prolonged-release tablets with a diameter of 8.6 – 9.0 mm and a height of 4.6 – 5.3 mm.

Oxycodone Depot Orion 80 mg prolonged-release tablets:
Green, round, biconvex, prolonged-release tablets with a diameter of 8.6 – 9.0 mm and a height of 5.0 – 5.6 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oxycodone Depot Orion is indicated in adults and adolescents (from 12 years to 18 years) for the treatment of severe pain, which can be adequately managed only with opioid analgesics.

4.2 Posology and method of administration

Posology
The dose should be adjusted to the intensity of the pain and the sensitivity of the individual patient. 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 to 18 years)
If a prolonged-release formulation is required as initial treatment for opioid naïve patients, the usual starting dose is 10 mg oxycodone hydrochloride per dose at 12-hour intervals. Some patients may benefit from a starting dose of 5 mg oxycodone hydrochloride to minimize the incidence of adverse reactions.

Patients already receiving opioids may be initiated on higher doses depending on their previous opioid experience.

For doses not realizable/practicable with this strength other strengths of this medicinal product are available.

According to well-controlled clinical studies 10–13 mg oxycodone hydrochloride corresponds to approximately 20 mg morphine sulphate, both in the prolonged-release formulation.

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

Some patients who take Oxycodone Depot Orion following a fixed schedule need rapid release analgesics as rescue medication in order to control breakthrough pain. Oxycodone Depot Orion 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 Oxycodone Depot Orion. If an immediate release opioid formulation is used as rescue medication in addition to prolonged-release, the need for more than two ”rescues” per day could be an indication that the prolonged-release dosage requires upward titration. 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. 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.

Elderly
Caution should be exercised when administering oxycodone to elderly patients. The plasma concentration of oxycodone appears to be higher in older people compared to younger people. The lowest dose should be given with careful titration to pain control.

Risk patients
Risk patients, for example patients with low body weight or slow metabolism of medicinal products, should initially half the recommended adult dose if they are opioid naïve.

Therefore the lowest recommended dosage, i.e. 10 mg, may not be suitable as a starting dose. Dose titration should be performed in accordance with the individual clinical situation.

Renal impairment
The plasma concentration of oxycodone is higher in patients with renal impairment compared to patients with normal renal function.
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 sections 4.4 and 5.2).

Hepatic impairment
The plasma concentration of oxycodone is higher in patients with hepatic impairment compared to patients with normal liver function.
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 sections 4.4 and 5.2).

Paediatric population
Opioids must only be used for management of severe pain in children with careful assessments of the benefits and risks.

Children under 12 years of age
The safety and efficacy of oxycodone in children below 12 years of age has not yet been established. Currently available data are described in section 4.8, but no recommendation on posology can be made.

Method of administration
For oral use.

The prolonged-release tablets may be taken with or independent of meals with a sufficient amount of liquid. Oxycodone Depot Orion must be swallowed whole, not chewed, divided or crushed. Taking chewed, divided or crushed Oxycodone Depot Orion tablets may lead to a rapid release and absorption of a potentially fatal dose of oxycodone.

Oxycodone Depot Orion should not be taken with alcoholic beverages.

Treatment goals and discontinuation
Before initiating treatment with Oxycodone Depot Orion, 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 used for longer than necessary. See section 4.4 Special warnings and precautions for use regarding the need for close monitoring for development of dependence and abuse.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- any situation where opioids are contraindicated
- severe chronic obstructive pulmonary disease
- cor pulmonale
- severe bronchial asthma
- paralytic ileus
- severe respiratory depression with hypoxia and/or elevated carbon dioxide levels in the blood (hypercapnia)
- acute abdomen, delayed gastric emptying.

4.4 Special warnings and precautions for use

Respiratory depression is the most significant risk induced by excessive opioid intake. Oxycodone must be used with particular caution in debilitated patients, in patients with severe impairment of lung, renal or hepatic function, sleep apnea, intoxication psychosis, myxedema, hypothyroidism, prostatic hypertrophy, Addison's disease (adrenal insufficiency), alcoholism, delirium tremens, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, constipation, hypotension, hypovolemia, head injuries (due to increased risk of intracranial pressure) and in patients taking MAO inhibitors, benzodiazepines or other CNS depressants (including alcohol) and in patients treated with MAO inhibitors within the last two weeks (see section 4.5). The dose may need to be reduced.

Sleep-related breathing disorders
Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent manner. In patients who present with CSA, consider decreasing the total opioid dosage. Opioids may also cause worsening of pre-existing sleep apnea (see section 4.8).

Hepatobiliary disorders
Oxycodone may cause dysfunction and spasm of the sphincter of Oddi, thus increasing the risk of biliary tract symptoms and pancreatitis. Therefore, oxycodone has to be administered with caution in patients with pancreatitis and diseases of the biliary tract.

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

Surgical procedures
Oxycodone Depot Orion is not recommended for pre-operative use or within the first 12–24 hours postoperatively. Depending on the type and extent of surgery, the anesthetic procedure selected, other co-medication and the individual condition of the patient, the exact timing for initiating postoperative treatment with Oxycodone Depot Orion depends on a careful risk-benefit assessment for each individual patient.

As with all opioids, special care should be taken when oxycodone is administered to patients undergoing bowel-surgery, because opiates are known to impair intestinal motility and must not be used until the physician is certain that bowel function is normal. If volvulus is suspected while using Oxycodone Depot Orion, the treatment should be stopped immediately.

Cough reflex
This medicinal product can inhibit the cough reflex.

Withdrawal
Like all opioids, long-term use of oxycodone can create dependence. Withdrawal symptoms may occur upon abrupt discontinuation of treatment. If therapy with oxycodone is no longer required it may be advisable to reduce the daily dose gradually in order to avoid the occurrence of withdrawal symptoms. Withdrawal symptoms may include yawning, mydriasis, lacrimation, rhinorrhea, tremor, hyperhidrosis, anxiety, agitation, convulsions and insomnia.

Abrupt discontinuation of treatment may cause the following withdrawal symptoms within 24 hours: restlessness, lacrimation, runny nose, sweating and restless sleep. These symptoms may intensify over the following three days.

Tolerance
Like all opioids, long-term use of Oxycodone Depot Orion can cause the development of tolerance which leads to the use of higher doses in order to achieve the desired analgesic effect.

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

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.

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.

Oxycodone should not be used in idiopathic or psychopathological pain conditions.

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 Depot Orion 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 Depot Orion 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 Depot Orion and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician.

Patients will require monitoring for signs of drug-seeking behavior (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For

patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

Abuse
Abuse of oral dosage forms for parenteral administration may lead to serious, potentially fatal events (see section 4.9).

Swallowing the prolonged-release tablets
Oxycodone Depot Orion prolonged-release tablets must be swallowed whole, not chewed, divided or crushed. The administration of chewed, divided or crushed prolonged-release tablets leads to rapid release of oxycodone and absorption of a potentially fatal dose (see section 4.9).

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Sedative medicines such as benzodiazepines or related drugs
The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4). Central nervous system depressants include but are not limited to: other opioids, gabapentinoids such as pregabalin, anxiolytics, hypnotics and sedatives (including benzodiazepines), antipsychotics, antidepressants, phenothiazines, neuroleptics, anesthetics, muscle relaxants, antihistamines, antiemetics and alcohol.

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

Concomitant use of oxycodone and medicines with anticholinergic effects (e.g. tricyclic antidepressants, neuroleptics, antihistamines, antiemetics, antipsychotics, muscle relaxants, antiparkinsonian drugs) may intensify the anticholinergic side effects of oxycodone (such as constipation, dry mouth or dysfunction of urinary excretion).

Concomitant administration of oxycodone with serotonin agents, such as Selective Serotonin Reuptake Inhibitors (SSRIs) or Serotonin Norepinephrine Re-uptake Inhibitors (SNRIs) 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, diarrhea). Oxycodone should be used with caution and the dosage may need to be reduced in patients using these medications.

MAO inhibitors are known to interact with narcotic analgesics, producing CNS excitation or depression with hyper- or hypotensive crisis (see section 4.4). Oxycodone should be used with caution in patients administered MAO-inhibitors or who have received MAO-inhibitors during the last two weeks (see section 4.4).

Oxycodone is metabolised mainly by CYP3A4, with a contribution from CYP2D6. The activities of these enzymes 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 reduced and titrated accordingly.

Some specific examples are provided below:

- Itraconazole, a potent CYP3A4 inhibitor, administered 200 mg orally for five days, increased the AUC of 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 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 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 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. Therefore, caution should be exercised and further titration may be needed to achieve pain control.

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, fluoxetine and quinidine, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentration. 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.

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 lactating.

Pregnancy

There are limited data from the use of oxycodone in pregnant women. During pregnancy, oxycodone must only be given on strict indication and after the mother's needs have been weighed against the risks to the baby.

Infants born to mothers who have received opioids during the last 3 to 4 weeks before giving birth should be monitored for respiratory depression. Long-term use of oxycodone during pregnancy may result in neonatal opioid withdrawal syndrome.

Oxycodone crosses the placenta. Animal studies with oxycodone have not shown any teratogenic or embryotoxic effects. Oxycodone Depot Orion should only be used during pregnancy if the benefit outweighs the possible risks to the fetus/newborn child.

Breastfeeding
Oxycodone is excreted in human milk and can cause respiratory depression in the newborn. The concentration ratio between milk and plasma was 3.4:1. Oxycodone Depot Orion should therefore not be used during breastfeeding.

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

4.7 Effects on ability to drive and use machines

Treatment with Oxycodone Depot Orion may impair the ability to react. Sedation is a common side effect. Especially at the beginning of therapy and after dose increase, opioids impair the ability to react and consequently impair the ability to drive and use machines. This should be taken into account when increased attention is required, e.g. when driving and using machines.

4.8 Undesirable effects

The most common adverse reactions are constipation and nausea, both of which occur in 25–30% of patients in connection with oral administration. If nausea or vomiting becomes troublesome, Oxycodone Depot Orion can be combined with antiemetics. As with other strong opioids, constipation may occur and should be treated appropriately with laxatives. If the opioid-related undesirable effects persist, they should be investigated for alternative causes.

With the exception of constipation, undesirable effects from pure opioid agonists tend to decrease with continued treatment. As with other opioids, the most serious adverse reaction is respiratory depression (see also section 4.9) and it usually occurs in elderly, frail and opioid-intolerant patients.

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

The following frequencies form the basis for the assessment of undesirable effects:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1 000 to <1/100)
Rare (≥1/10 000 to <1/1 000)
Very rare (<1/10 000)
Not known (cannot be estimated from the available data)
The following undesirable effects may occur:

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)**
Blood and lymphatic system disorders				Lymphadeno-pathy		

Immune system disorders			Hypersen-sitivity			Anaphylactic reactions, anaphylactoid reaction
Endocrine disorders			Syndrome of inappropriate antidiuretic hormone secretion, increased ADH release			
Metabolism and nutrition disorders		Anorexia; decreased appetite	Dehydration			
Psychiatric disorders		Various psychological 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, confusion, isolated cases of speech disorders)	Change in perception such as depersonali-sation; hallucinations ; affected lability; hyperacousis; euphoria; dysphoria; agitation; decreased libido; drug dependence (see section 4.4)			Aggression
Nervous system disorders	Somnolence; dizziness; headache	Lethargy; tremor	Both increased and decreased muscle tone; amnesia; convulsion; hypertonia; involuntary muscle contractions; hypoaesthesia ; speech disorder; syncope; paraesthesia; dysgeusia; coordination disturbances	Seizures, in particular in epileptic patients or patients with tendency to convulsions; muscle spasm		Hyperalgesia

Eye disorders			Lacrimation disorder; visual impairment; miosis			
Ear and labyrinth disorders			Vertigo, tinnitus			
Cardiac disorders			Supraventri-cular tachycardia, palpitations (in context of withdrawal syndrome)			
Vascular disorders			Vaso-dilatation	Hypotension; orthostatic hypotension		
Respiratory, thoracic and mediastinal disorders		Dyspnoea, bronchospasm	Respiratory depression; increased coughing; pharyngitis; rhinitis; voice changes			Central sleep apnoea syndrome
Gastro-intestinal disorders	Constipation; nausea; vomiting	Dry mouth, rarely accompanied by thirst and difficulty swallowing; gastrointesti-nal disorders such as abdominal pain; diarrhoea; dyspepsia	Oral ulcers; gingivitis; stomatitis; flatulence; eructation; dysphagia; ileus	Gum bleeding; increased appetite; tarry stool; tooth staining and damage		Dental caries, dental problems
Hepatobiliary disorders			Increased hepatic enzymes, ureteral spasm			Cholestasis; biliary colic, sphincter of Oddi dysfunction
Skin and subcutaneous tissue disorders	Pruritus	Skin eruptions including rash; hyperhidrosis; in rare cases increased photosensi-tivety; in isolated cases urticaria or exfoliative dermatitis	Dry skin	Herpes simplex, urticaria		
Renal and urinary disorders		Micturition disturbances (increased urge to urinate)	Urinary retention			

Reproductive system and breast disorders			Erectil dysfunction, impotence, hypogonadism			Amenorrhoea
General disorders and administration site conditions		Asthenia, fatigue	Accidental injuries; pain (e.g. chest pain); malaise; oedema; peripheral oedema; migraine; physical dependence with withdrawal syndrome; drug tolerance; allergic reactions; chills; thirst	Weight changes (increase or decrease); cellulitis		Drug withdrawal syndrome neonatal

Description of selected adverse reactions
Drug dependence
Repeated use of Oxycodone Depot Orion 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 of overdose
Acute oxycodone overdose may manifest as pinhead-size pupils, respiratory depression, drowsiness progressing to lethargy or coma, reduced skeletal muscle tone, bradycardia, hypotoni and lung oedema. Death may occur in severe cases.
Toxic leukoencephalopathy has been observed with oxycodone overdose.

Treatment of overdose
If justified gastric emptying, coal, laxative.

The most important thing is to ensure that the airways are open and to institute assisted or controlled ventilation. Maintain and facilitate breathing and circulation.

In severe cases, intravenous administration of naloxone 0.8 mg may be considered. Repeat depending on the needs at intervals of 2 to 3 minutes or infuse 2 mg of naloxone in 500 ml isotonic saline or 5 % dextrose solution (0.004 mg/ml).

The rate of infusion should be adjusted to the previous bolus injections and the response of the patient. Because naloxone has a relatively short duration of action, the patient must be closely monitored until spontaneous breathing has reliably started. Monitoring for a further 24–48 hours is recommended if there is a risk of recurring symptoms.

For less serious cases of overdose, 0.2 mg of naloxone should be given intravenously and, if necessary, followed up with supplementary injections of 0.1 mg every two minutes.

Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose.

Naloxone should be administered cautiously to patients who are known, or suspected, to be dependent on oxycodone. In such cases, an abrupt or complete reversal of opioid effects may precipitate pain and an acute withdrawal syndrome.

Toxicity
The lethal dose for adults (without development of tolerance) is stated to be approximately 60–100 mg orally. Scopolamine, hypnotics and alcohol potentiate toxic effects.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics; Opioids; Natural opium alkaloids, ATC code: N02AA05

Oxycodone is an opioid analgesic with a strong analgesic effect. Oxycodone is a pure opioid agonist with no antagonistic action. Its main action appears to be through the myopioid receptors but affinity for delta or kappa opioid receptors has also been demonstrated. Its action resembles that of morphine. Oral oxycodone is equipotent to oral morphine in a 1:2 ratio. The analgesic effect depends partly on a changed pain experience and partly on an increase in the pain threshold. The mechanism of action involves CNS opioid receptors for the body's own compounds with opioid-like activity. Oxycodone exerts its analgesic effect at different levels within the CNS.

Central nervous system effects of oxycodone also include respiratory depression, psychological symptoms, nausea and vomiting, miosis, release of antidiuretic hormone as well as anxiolytic, antitussive and sedative effects.

Compared to rapid-release oxycodone, the prolonged-release tablets provide pain relief for a longer period without increased occurrence of undesirable effects.

The respiratory depressant effect of oxycodone is due to an inhibition of the stimulatory action of carbon dioxide on the respiratory center in the medulla oblongata. This effect can lead to respiratory insufficiency in patients with impaired ventilation due to lung disease or the influence of other medicines.

After encephalitis, the effects of oxycodone may be enhanced. Intoxication with oxycodone requires respiratory support treatment and administration of antidote.

Psychological symptoms include euphoria, but also depression as well as sleep, concentration and memory disorders.

Nausea and vomiting can occur through stimulation of dopamine receptors in the ”trigger zone” in the medulla oblongata. The increased release of antidiuretic hormone contributes to decreased urine volumes during oxycodone therapy. Oxycodone increases tone in the smooth muscle of the gastrointestinal tract. This leads to constipation through slowed passage of food through the gastrointestinal tract. Furthermore, the pressure in the biliary and urinary tracts increases, which is

why oxycodone is less suitable for biliary or ureteric spasms.

Oxycodone has addictive properties and tolerance can develop to the oxycodone effects.

Endocrine system
See section 4.4.

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

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 semi-synthetic opioid, has immunological effects similar to morphinie is unkown.

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

5.2 Pharmacokinetic properties

Relationships between dose and plasma concentration of oxycodone, as well as between concentration and certain expected opioid effects, have been shown.

Absorption
The relative bioavailability of Oxycodone Depot Orion is comparable to that of rapid release oxycodone with maximum plasma concentrations being achieved after approximately 3 hours after intake of the prolonged-release tablets compared to 1 to 1.5 hours. Peak plasma concentrations and oscillations of the concentrations of oxycodone from the prolonged-release and rapid-release formulations are comparable when given at the same daily dose at intervals of 12 and 6 hours, respectively.

The tablets must not be crushed, divided, or chewed as this leads to rapid oxycodone release and absorption of a potentially fatal dose of oxycodone due to the damage of the prolonged release properties.

Distribution
After absorption, the active substance is distributed throughout the body. About 45% is bound to plasma protein and the volume of distribution at steady-state is 2.6 l/kg.

Biotransformation
Oxycodone is metabolized in the liver via CYP3A4 and CYP2D6 to noroxycodone, oxymorphone and noroxymorphone which are thereafter glucuronidated. The contribution of the metabolites to the overall pharmacodynamic effect is not considered to be clinically significant.

Elimination
Clearance is 0.8 l/min and the half-life of oxycodone prolonged-release tablets is approximately 4.5 hours. In urine, 45 + 21% are excreted as N-demethylated metabolites (including noroxycodone and noroxymorphone) and 11 + 6% of the dose as O-demethylated metabolites (including oxymorphone).

Special populations
Plasma concentrations of oxycodone are only nominally affected by age and are 15% higher in

elderly compared to younger patients.

Female patients have, on average, up to 25% higher oxycodone plasma concentrations than males on a body weight adjusted basis.

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

Patients with mild, moderate and severe renal impairment show an increase in plasma concentrations of 1.1-, 1.4- and 1.7-fold, respectively, compared to patients with normal renal function. AUC values increased on average by 1.5-, 1.7-, and 2.3-fold, respectively, compared to patients with normal renal function. The elimination half-life of oxycodone was increased by only 1.5-, 1.2-, and 1.4-fold, respectively, compared to patients with normal renal function.

5.3 Preclinical safety data

Teratogenicity
Oxycodone was not teratogenic even at maternally toxic doses in rats and rabbits. Oxycodone did not affect fertility or reproduction, or adversely affect long-term development in pups (F1 generation) of rats treated with oxycodone during late pregnancy and lactation. Furthermore, oxycodone had no developmental effects on pups of F1 generation females.

Carcinogenicity
Long-term carcinogenicity studies have not been performed.

Mutagenicity
Like other opioids, oxycodone was genotoxic in some *in vitro* assays (e.g. mouse lymphoma test). No genotoxicity was observed in the bacterial mutagenicity test or in the mouse micronucleus assay *in vivo* at doses up to the toxic level.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Ammonio Methacrylate Copolymer, Type B
Povidone (K29/32)
Talc
Triacetin
Stearyl alcohol
Magnesium stearate

Film- coating
[Oxycodone Depot Orion 5 mg prolonged-release tablets]
Hypromellose
Talc
Macrogol 400
Titanium dioxide
Brilliant Blue FCF

[Oxycodone Depot Orion 10 mg prolonged-release tablets]
Hypromellose

Talc
Macrogol 400
Titanium dioxide

[Oxycodone Depot Orion 15 mg prolonged-release tablets]
Hypromellose
Talc
Macrogol 400
Titanium dioxide
Iron oxide black

[Oxycodone Depot Orion 20 mg prolonged-release tablets]
Hypromellose
Talc
Macrogol 400
Titanium dioxide
Iron oxide red

[Oxycodone Depot Orion 30 mg prolonged-release tablets]
Hypromellose
Talc
Macrogol 400
Titanium dioxide
Iron oxide brown
Iron oxide black

[Oxycodone Depot Orion 40 mg prolonged-release tablets]
Hypromellose
Talc
Macrogol 400
Titanium dioxide
Iron oxide red
Iron oxide yellow

[Oxycodone Depot Orion 60 mg prolonged-release tablets]
Hypromellose
Talc
Macrogol 400
Titanium dioxide
Iron oxide red
Erythrosine

[Oxycodone Depot Orion 80 mg prolonged-release tablets]
Hypromellose
Macrogol 400
Titanium dioxide
Indigo carmine aluminum lake
Iron oxide yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

[Oxycodone Depot Orion 5 mg]
2 years.

[Oxycodone Depot Orion 10 mg]
3 years.

[Oxycodone Depot Orion 15 mg/20 mg/30 mg/40 mg/60 mg/80 mg]
3 years.

6.4 Special precautions for storage

[Oxycodone Depot Orion 5 mg]
Do not store above 25°C.

[Oxycodone Depot Orion 10 mg]
Do not store above 25°C.

[Oxycodone Depot Orion 15 mg/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 PVC/PVdC-Aluminium perforated unit dose blisters with 10x1, 14x1, 20x1, 25x1, 28x1, 30x1, 40x1, 50x1, 56x1, 60x1, 98x1 and 100x1 prolonged-release tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Orion Corporation
Orionintie 1
FI-02200 Espoo
Finland

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

18/02/2025