SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Oxycodone G.L. 1 mg/ml oral solution
Oxycodone G.L. 10 mg/ml oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mg/ml: Each ml contains 1 mg oxycodone hydrochloride, corresponding to 0.9 mg oxycodone.

Excipients with known effect:
1 mg/ml: Each ml contains approx. 4.1 mg sodium and 1 mg sodium benzoate.

10 mg/ml: Each ml contains 10 mg oxycodone hydrochloride, corresponding to 9 mg oxycodone.

Excipients with known effect:
10 mg/ml: Each ml contains approx. 4.5 mg sodium, 1mg sodium benzoate and 0.15 mg Sunset yellow FCF (E 110).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution

<Product name> 1 mg/ml oral solution is a clear colourless to slightly yellowish solution.

<Product name> 10 mg/ml oral solution is a clear orange-red-coloured solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

<Product name> 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 pain intensity, the total condition of the patient, previous or concurrent medication, and the patient's individual susceptibility to the treatment.

For doses not realisable/practicable with this strength other pharmaceutical forms and strenghts of <Product name> are available.

The following general dosage recommendations apply:

Adults and adolescents (from 12 years and older)

The initial dose for opioid-naïve patients is usually 5 mg oxycodone hydrochloride given at intervals of every 6 hours. The dose may be increased in steps of 25% to 50% of the respective dose. The aim is a patient-specific dosage which allows for adequate analgesia with tolerable undesirable effects. Therefore, the dosing interval may be shortened to 4 hours if needed. However, <Product name> should not be taken more often than 6 times a day.

Some patients receiving modified-release oxycodone medication according to a fixed time schedule may require immediate-release analgesics as rescue medication for the management of breakthrough pain. <Product name> is appropriate for the management of breakthrough pain. Single doses of the rescue medication should be adjusted based on the patients' individual requirements. In general, 1/8 to 1/6 of the daily modified-release oxycodone dose is appropriate.

The requirement of rescue medication more than twice daily may indicate that higher doses of modified-release oxycodone are necessary. The aim is to establish a patient-specific dosage which ensures adequate analgesia with tolerable undesirable effects and as low rescue medication as possible for as long as pain medication is necessary in patients receiving modified-release oxycodone treatment twice daily.

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

Conversion from oral morphine
Patients receiving oral morphine before oxycodone therapy should have their daily dose based on the following ratio: 10 mg oxycodone hydrochloride correspond to approximately 20 mg of oral morphine. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

Because of individual differences in sensitivity for different opioids, it is recommended that patients should start conservatively with oxycodone hydrochloride after conversion from other opioids, with 50-75% of the calculated oxycodone dose.
In general, patients should be titrated individually until pain relief is achieved, provided that undesirable adverse events can be adequately managed.

Use in non-malignant pain
Opioids are not first-line therapy for chronic non-malignant pain, nor are they recommended as the only treatment.

<u>Special populations</u>
Elderly
Elderly patients should be treated with caution. The lowest dose should be administered with careful titration to pain control.

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%, and each patient should be titrated to adequate pain control according to his/her clinical situation.

Other risk patients
In patients with low body weight or slow metabolism of drugs who are also opioid-naive, the recommended starting dose should be reduced to half the normally recommended starting dose for adults.

<u>Paediatric population</u>
Opioids must only be used for appropriate indications and prescribed by a specialist experienced in managing severe pain in children, with careful assessments 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.

<Product name> oral solution should be taken every 4-6 hours based on a fixed schedule at the dosage determined.
The oral solution may be taken with or independent of meals with or without an amount of liquid.
<Product name> oral solution should not be used with alcoholic bevarages.

<Product name> 1 mg/ml oral solution is provided with a graduated measuring cup. Each graduation mark (5 ml) of the measuring cup corresponds to 5 mg oxycodone hydrochloride.

<Product name> 10 mg/ml oral solution is provided with a graduate oral syringe for conventional withdrawal or together with an adapter for over-head withdrawal. Each 1 ml graduation mark of the oral syringe corresponds to 10 mg oxycodone hydrochloride (see section 6.5).

Treatment goals and discontinuation
Before initiating treatment with <Product name>, 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
<Product name> should not be taken longer than necessary.

Instructions for use are provided in the package leaflet.

4.3 Contraindications

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

Oxycodone must not be used in any situation where opioids are contraindicated:
- severe respiratory depression with hypoxia and/or hypercapnia
- elevated carbon dioxide levels in the blood
- severe chronic obstructive pulmonary disease
- cor pulmonale
- severe bronchial asthma
- paralytic ileus
- acute abdomen, delayed gastric emptying

4.4 Special warnings and precautions for use

Caution should be exercised in
- elderly or debilitated patients
- patients with severe impairment of lung, liver or kidney function
- central sleep apnoea
- myxoedema, hypothyroidism

- concomitant use of centrally depressant substances
- Addison's disease (adrenal insufficiency)
- intoxication psychosis (e.g. alcohol)
- prostatic hypertrophy
- alcoholism
- known opioid dependence
- drug addiction, substance or alcohol abuse
- delirium tremens
- head injury, increased intracranial pressure,
- impaired consciousness of unknown cause,
- hypotension,
- hypovolaemia,
- epileptic disorder or predisposition to convulsions
- pancreatitis
- diseases of the biliary tract, biliary or ureteric colic
- inflammatory bowel disorders
- obstructive or inflammatory intestinal diseases,
- conditions with increased brain pressure (including head injuries)
- disturbances of circulatory regulation (including hypotension, hypovolaemia)
- in patients taking MAO inhibitors

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.

Oxycodone should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, <Product name> oral solution should be discontinued immediately.

For appropriate patients who suffer with chronic non-malignant pain, opioids should be used as part of a comprehensive treatment programme involving other medications and treatment modalities. A crucial part of the assessment of a patient with chronic non-malignant pain is the patient's addiction and substance abuse history.

If opioid treatment is considered appropriate for the patient, then the main aim of treatment is not to minimise the dose of opioid but rather to achieve a dose which provides adequate pain relief with a minimum of side effects.

Respiratory depression

The major risk of opioid excess is respiratory depression. Caution must be exercised when administering oxycodone to the debilitated elderly; patients with severely impaired pulmonary function, impaired hepatic or renal function; patients with myxoedema, hypothyroidism, Addison's disease, toxic psychosis, prostate hypertrophy, adrenocortical insufficiency, alcoholism, delirium tremens, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, hypotension, hypovolaemia, head injury (due to risk of increased intracranial pressure) or patients taking MAO inhibitors.

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 <Product name> 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 <Product name> 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).

Adrenal insufficiency
Opioids, such as oxycodone hydrochloride, may occasionally cause reversible adrenal insufficiency, with some hormonal changes including increases in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical symptoms may include e.g., severe abdominal pain, nausea and vomiting, low blood pressure, extreme fatigue, decreased appetite, and weight loss. Adrenal insufficiency may require monitoring and glucocorticoid replacement therapy.

MAO-inhibitors
Oxycodone should be used with caution in patients administered MAO-inhibitors or who have received MAO-inhibitors during the last two weeks (see section 4.5).

Tolerance, physical dependence and tapering off
The patient may develop tolerance to the medicinal product 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 withdrawal symptoms. The opioid abstinence or withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, or increased blood pressure, respiratory rate or heart rate.

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.

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 <Product name> 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 <Product name> 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 <Product name> 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.
As with other opioids, infants who are born to dependent mothers may exhibit withdrawal symptoms and may have respiratory depression at birth (please see section 4.6).

Parenteral abuse

Abuse of oral dosage forms by parenteral administration can result in serious adverse events, which may be fatal.

Alcohol
The intake of oxycodone hydrochloride with alcoholic beverages has to be avoided as alcohol may enhance the frequency of adverse reactions. Oxycodone hydrochloride should be used with particular care in patients with a history of alcohol and drug abuse.

Perioperative use, abdominal surgery
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.
Oxycodone should be used with caution pre-operatively and 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 post-operative treatment with oxycodone depends on a careful risk-benefit assessment for each individual patient.Patients about to undergo additional pain relieving procedures (e.g. surgery, plexus blockade) should not receive <Product name> 1 mg/ml oral solution for 6 hours prior to the intervention. If further treatment with oxycodone is indicated the dosage should be adjusted to the new post-operative requirement.

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.

1 mg/ml:
Sodium
This medical product contains approx. 4.1 mg sodium per ml, equivalent to 0.2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

10 mg/ml:
Sunset yellow (FCF)
This medical product contains the coloring agent sunset yellow (FCF) which may cause allergic reactions.

Sodium
This medical product contains approx. 4.5 mg sodium per ml, equivalent to 0.2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Alcohol
Alcohol may enhance the pharmacodynamic effects of <Product name>, concomitant use should be avoided.

Central nervous system depressants (e.g. sedatives, hypnotics, phenothiazines, neuroleptics, anaesthetics, antidepressants, muscle relaxants, antihistamines, antiemetics) and other opioids or alcohol can enhance the CNS depressant effect of oxycodone, in particular respiratory depression.

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).

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 serotoin 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.

Anticholinergics (e.g. antipsychotics, tricyclic anti-depressants, antihistamines, antiemetics, muscle relaxants, antiparkinson medicines) can enhance the anticholinergic undesirable effects of oxycodone (such as constipation, dry mouth or micturition disorders).

Monoaminoxidase (MAO) inhibitors are known to interact with narcotic analgesics, producing CNS excitation or depression with hyper- or hypotensive crisis. 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).

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

Interactions via the CYP system
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), azole-type antifungals (e.g. ketoconazole, voriconazole, itraconazole, and posaconazole), protease inhibitors (e.g. boceprevir, ritonavir, indinavir, nelfinavir and saquinavir), cimetidine and grapefruit juice may reduce the clearance of oxycodone which could result in an increase of oxycodone plasma concentrations. Therefore the oxycodone dose may need to be adjusted accordingly.

Some specific examples are provided below:

- Itraconazole, a potent CYP3A4 inhibitor, administered as 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 as 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 as 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 which could result in a reduction of oxycodone plasma concentrations. 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 and quinidine, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations.

4.6 Fertility, pregnancy and lactation

Use of this medicinal product should be avoided to the extent possible in patients who are pregnant or 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 newborns of mothers undergoing treatment with oxycodone.

Breast-feeding
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 hydrochloride may impair the ability to drive and use machines.
This is particularly likely at the initiation of treatment with oxycodone, after dose increase or changes in therapy, and if oxycodone is combined with alcohol or other CNS depressants.
With stable therapy, a general ban on driving a vehicle is not necessary Therefore, the physician should decide for each individual patient whether the patient is allowed to drive or use machinery.

4.8 Undesirable effects

Oxycodone can cause respiratory depression, miosis, bronchial spasms and spasms of the smooth muscles and can 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 predominantly in elderly or debilitated patients.

The adverse reactions considered at least possibly related to treatment are listed below by system organ class and absolute frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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

System organ class	Frequency	Adverse event
Blood and lymphatic system disorders	rare	Lymphadenopathy
Immune system disorders	uncommon	Hypersensitivity
	not known	Anaphylactic responses
Endocrine disorders	uncommon	Syndrome of inappropriate antidiuretic hormone secretion
Metabolism and nutrition disorders	common	Decreased appetite
	uncommon	Dehydration
Psychiatric disorders	common	Anxiety Confusional state Depression Insomnia Nervousness Abnormal thinking
	uncommon	Agitation Affect lability Euphoric mood Hallucinations Decreased libido Drug dependence (see section 4.4)
	not known	Aggression
Nervous system disorders	very common	Somnolence Dizziness Headache
	common	Tremor
	uncommon	Amnesia Convulsion Hypertonia Hypoaesthesia Involuntary muscle contractions Speech disorder Syncope Paraesthesia Dysgeusia
	rare	Seizures, particularly in epileptic patients or patients with tendency to convulsions Muscle spasm
	not known	Hyperalgesia
Eye disorders	uncommon	Visual impairment Miosis
Cardiac disorders	common	Lowering of blood pressure, rarely accompanied by secondary symptoms such as palpitations, syncope, bronchospasm
	uncommon	Palpitation (in the context of withdrawal syndrome) Supraventricular tachycardia
Vascular disorders	uncommon	Vasodilatation
	rare	Hypotension Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	common	Dyspnoea
	uncommon	Respiratory depression Increased coughing Pharyngitis

System organ class	Frequency	Adverse event
		Rhinitis Voice changes
	not known	Central sleep apnoea syndrome
Gastrointestinal disorders	very common	Constipation Nausea Vomiting
	common	Dry mouth, rarely accompanied by thirst and difficulty swallowing Abdominal pain Diarrhoea Dyspepsia
	uncommon	Dysphagia Oral ulcers Gingivitis Stomatitis Flatulence Eructation Ileus
	rare	Gingival bleeding Increased appetite Tarry stool
	not known	Dental caries
Hepatobiliary disorders	uncommon	Increase hepatic enzymes
	not known	Cholestasis Biliary colic Sphincter of Oddi dysfunction
Skin and subcutaneous tissue disorders	very common	Pruritus
	common	Rash Hyperhidrosis
	uncommon	Dry skin
	rare	Urticaria Manifestations of herpes simplex Increased photosensitivity
	very rare	Exfoliative dermatitis
Renal and urinary disorders	uncommon	Micturition disturbances (urinary retention, but also increased urge to urinate)
	rare	Haematuria
Reproductive system and breast disorders	uncommon	Reduced libido Erectile dysfunction
	not known	Amenorrhoea
General disorders and administration site conditions	common	Sweating Asthenic conditions
	uncommon	Chills Malaise Accidental injuries Pain (e.g. chest pain) Oedema, peripheral oedema Migraine Physical dependence with withdrawal symptoms Drug tolerance Thirst
	rare	Weight changes (increase or decrease)

System organ class	Frequency	Adverse event
		Cellulitis
	not known	Drug withdrawal syndrome neonatal

Description of selected adverse reactions

Drug dependence
Repeated use of <Product name> can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

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
Acute overdose with oxycodone can be manifested by miosis, respiratory depression, somnolence progressing to stupor or coma, reduced skeletal muscle tone and drop in blood pressure. In severe cases circulatory collapse, bradycardia and non-cardiogenic lung oedema may occur; abuse of high doses of strong opioids such as oxycodone can be fatal. Toxic leukoencephalopathy has been observed with oxycodone overdose.

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

In case of severe overdose, intravenous administration of an opioid 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.

For less severe overdosage, administer naloxone 0.2 mg intravenously followed by increments of 0.1 mg every 2 minutes, if required.

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: Analgesics; Opioids; Natural opium alkaloids
ATC code: N02AA05

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, anxiolytic and sedative.

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 Undesirable effects).
There are no clinical trial data on longer term use in children aged 12 to 18 years.

5.2 Pharmacokinetic properties

Absorption
The mean absolute bioavailability of oxycodone is approximately 50%. A pharmacokinetic study in healthy volunteers has demonstrated that, following administration of a single 10 mg dose, oxycodone liquid 1 mg/ml and oxycodone concentrate 10 mg/ml provided an equivalent rate and extent of absorption of oxycodone. Mean peak plasma concentrations of approximately 20 ng/ml were achieved within 1.5 hours of administration, median t_{max} values from both strengths of liquid being less than 1 hour. Plasma concentrations are linear within a dose range of 5 to 20 mg.

Distribution
Approximately 45% is bound to plasma protein.
The volume of distribution at steady-state is 2.6 l/kg.

Biotransformation
Oxycodone is metabolised in the liver via CYP3A4 and CYP2D6 to noroxycodone**,** oxymorphone and noroxymorphone as well as to several glucuronide conjugates. The analgesic effect of the metabolites is considered clinically insignificant.

Elimination
Oxycodone and its metabolites are excreted via urine and faeces. Oxycodone has an elimination half-life of about 3 hours.

Special populations
The plasma concentrations of oxycodone are only minimally affected by age, being 15% greater in elderly as compared to young subjects.

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

When compared to normal subjects, patients with mild to severe hepatic dysfunction may have higher plasma concentrations of oxycodone and noroxycodone and lower plasma concentrations of oxymorphone. There may be an increase in the elimination half-life of oxycodone and this may be accompanied by an increase in drug effects.

When compared to normal subjects, patients with mild to severe renal dysfunction may have higher plasma concentrations of oxycodone and its metabolites. There may be an increase in the elimination half-life of oxycodone and this may be accompanied by an increase in drug effects.

5.3 Preclinical safety data

Studies showed that oxycodone 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 and in rabbits in doses of 125 mg/kg bodyweight. However, in rabbits, when individual

fetuses 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 with oxycodone have not been conducted owing to the length of clinical experience with the drug substance.

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 hydrochloride to humans at therapeutic concentrations may be ruled out with adequate certainty.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

1 mg/ml: Sodium benzoate (E 211)
Hypromellose
Saccharin sodium
Citric acid monohydrate
Sodium hydroxide (for pH-adjustment)
Orange flavour
Water

10 mg/ml: Sodium benzoate (E 211)
Saccharin sodium
Citric acid monohydrate
Sodium hydroxide (for pH-adjustment)
Sunset yellow FCF (E 110)
Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

1 mg/ml: 3 years
10 mg/ml: 5 years

After first opening: 3 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

1 mg/ml: Amber glass bottle with a child-resistant white polypropylene screw cap and a graduated measuring cup made of polypropylene. Each graduation mark (5 ml) of the measuring cup corresponds to 5 mg oxycodone hydrochloride.

100 ml bottle with a 30 ml measuring cup
250 ml bottle with a 30 ml measuring cup
300 ml bottle with a 30 ml measuring cup

10 mg/ml: Amber glass bottle with child-resistant white polypropylene screw cap and a graduate oral syringe made of polyethylene together with an adapter. The syringes are graduated with marks of 0.5 ml and 1.0 ml. Each 1 ml graduation mark of the oral syringe corresponds to 10 mg oxycodone hydrochloride.

30 ml bottle with a 3 ml oral syringe and an adapter.
100 ml bottle with a 5 ml oral syringe and an adapter.
120 ml bottle with a 5 ml oral syringe and an adapter.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Instructions for use are provided in the package leaflet.

7. MARKETING AUTHORISATION HOLDER

<to be completed nationally>

8. MARKETING AUTHORISATION NUMBERS

<to be completed nationally>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<to be completed nationally>

10. DATE OF REVISION OF THE TEXT

2025-03-07