SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Oxycodone Hydrochloride G.L. Pharma 10 mg/ml solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 10 mg oxycodone hydrochloride corresponding to 9 mg oxycodone.

Excipients with known effect:
Each ml contains 7.5 mg sodium chloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion

Oxycodone Hydrochloride G.L. Pharma 10 mg/ml solution for injection/infusion is a clear, colourless to slightly yellowish solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Oxycodone Hydrochloride G.L. Pharma 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.

The following general dosage recommendations apply:

The following starting doses are recommended. A gradual increase in dose may be required if analgesia is inadequate or if pain severity increases.

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.

Adults and adolescents (from 12 years and older)

i.v. (Bolus):

Administer a bolus dose of 1 to 10 mg slowly over 1-2 minutes to opioid-naïve patients.

Doses should not be administered more frequently than every 4 hours.

A maximum bolus dose of 5 mg is recommended in adolescents (from 12 years and older).

i.v. (Infusion):

A starting dose of 2 mg/hour is recommended in opioid-naïve patients.

i.v. (PCA):

Bolus doses of 0.03 mg/kg should be administered with a minimum lock-out time of 5 minutes to opioid-naïve patients.

s.c. (Bolus): Use as 10 mg/ml concentration. A starting dose of 5 mg is recommended, repeated at 4-hourly intervals in opioid-naïve patients as required.

s.c. (Infusion):

A starting dose of 7.5 mg/day is recommended in opioid naïve patients, titrating gradually according to symptom control. A starting dose of 5 mg/day is recommended in adolescents (from 12 years and older), titrating gradually according to symptom control. Cancer patients transferring from oral oxycodone may require much higher doses (see below).

Transferring patients between oral and parenteral oxycodone

The dose should be based on the following ratio: 2 mg of oral oxycodone is equivalent to 1 mg of parenteral oxycodone, if only a few doses have been given. In case of shift in choice of opioid to a patient, who has been in long-term opioid-treatment (opioidrotation), it should be emphasised that the above mentioned equipotent doses are guidance only. Often it is necessary to administer less a decreased dose as equipotency recommend. Based on this and the patients

interindividual variability a shift requires that the dosing is titrated carefully for every single patient.

Use in non-malignant pain

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

Special populations

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.

Paediatric population

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

Subcutaneous injection or infusion.

Intravenous injection or infusion.

For instructions on dilution of the product before administration, see section 6.6.

Treatment goals and discontinuation

Before initiating treatment with Oxycodone Hydrochloride G.L. Pharma, 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 Hydrochloride G.L. Pharma should not be used longer than necessary.

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

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
- pancreatitis
- diseases of the biliary tract, biliary or ureteric colic

- 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, Oxycodone Hydrochloride G.L. Pharma 10 mg/ml solution for injection/infusion should be discontinued immediately.

Perioperative use, abdominal surgery

Oxycodone Hydrochloride G.L. Pharma 10 mg/ml solution for injection/infusion should be used with caution pre- or intra-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.

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.

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 Oxycodone Hydrochloride G.L. Pharma 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 Hydrochloride G.L. Pharma 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 Oxycodone Hydrochloride G.L. Pharma 10 mg/ml solution for injection/infusion 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 Hydrochloride G.L. Pharma 10 mg/ml solution for injection/infusion 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 Hydrochloride G.L. Pharma 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 (see section 4.6).

Hepatobiliary disorders

Oxycodone may cause dysfunction and spasm of the sphincter of Oddi, thus raising intrabiliary pressure and 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.

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 enhace the frequency of adverse reactions. Oxycodone hydrochloride should be used with particular care in patients with a history of alcohol and drug abuse.

Sodium chloride

This medicinal product contains less than 1 mmol sodium (23 mg) per ampoule, i.e. essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Alcohol
Alcohol may enhance the pharmacodynamic effects of Oxycodone hydrochloride G.L., concomitant use should be avoided.

Centrally depressant drugs
There can be an enhanced CNS depressant effect during concomitant therapy with drugs which affect the CNS such as sedatives, hypnotics, phenothiazines, neuroleptic drugs, antidepressants, antihistamines, antiemetics and other opioids which may enhance the adverse drug reactions, especially 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).

Anticholinergics (e.g. antipsychotics, tricyclic antidepressants, 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 oxycodone should in patients who are pregnant or lactating be restricted to individual cases where the benefits clearly outweigh the risks.

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

System organ class	Frequency	Adverse event
		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

System organ class	Frequency	Adverse event
		Physical dependence with withdrawal symptoms Drug tolerance Thirst
	rare	Weight changes (increase or decrease) Cellulitis
	not known	Drug withdrawal syndrome neonatal

Description of selected adverse reactions

Drug dependence

Repeated use of Oxycodone Hydrochloride G.L. Pharma 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 Yellow Card Scheme,

Website: www.mhra.gov.uk/yellowcard,

or search for MHRA Yellow Card in the Google Play or Apple App Store.

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

Pharmacokinetic studies in healthy subjects have demonstrated an equivalent availability of oxycodone from oxycodone injection/infusion when administered by the intravenous or subcutaneous routes, as a single bolus dose or a continuous infusion over 8 hours.

Maximum oxycodone plasma concentrations are achieved after 0.5 hours after a subcutaneous injection.

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 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 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

Sodium chloride
Citric acid monohydrate
Sodium hydroxide (for pH-adjustment)
Hydrochloric acid (for pH-adjustment)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

5 years

Chemical and physical in-use stability has been demonstrated for 48 hours/days at room temperature.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution, dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not freeze.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Clear, colourless glass ampoules with OPC (one point cut) breaking system containig 1 ml or 2 ml solution, packed in card board fold boxes containing 1, 3, 5 or 10 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This medicinal product is for single use only, any unused solution should be discarded.

For intravenous use Oxycodone Hydrochloride G.L. Pharma concentrate for solution for infusion should be diluted to a concentration of 1 mg/ml oxycodone hydrochloride.

Oxycodone Hydrochloride G.L. Pharma 10 mg/ml solution for injection/infusion and Oxycodone Hydrochloride G.L. Pharma 20 mg/2 ml solution for injection/infusion may be diluted with

- Water for injections
- Sodium chloride 9 mg/mL (0.9%) solution for injection
- Glucose 50 mg/mL (5%) solution for injection
- Ringer's solution for injection
- Sodium chloride and Glucose solution for injection
  (Sodium chloride 0.18% w/v and Glucose 4% w/v)
- Lactated Ringer's solution for injection
  (Ringer Lactate solution and 5% Glucose solution).

Oxycodone hydrochloride, that was used undiluted or diluted to 1 mg/ml in various studies with different infusion solutions and under the use of representative brands of polypropylene or polycarbonate syringes, polyethylene or PVC tubing and PVC or EVA infusion bags, does not have to be protected against light.

7 MARKETING AUTHORISATION HOLDER

G.L. Pharma GmbH, Schlossplatz 1, 8502 Lannach, Austria

8 MARKETING AUTHORISATION NUMBER(S)

PL 21597/0044

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/05/2018

10 DATE OF REVISION OF THE TEXT

20/06/2024