Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

OxyNorm 10 mg/ml, solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of ***OxyNorm*** injection contains 10 mg oxycodone hydrochloride (equivalent to 9 mg of oxycodone base).
Each 1 ml ampoule contains 10 mg of oxycodone hydrochloride.
Each 2 ml ampoule contains 20 mg of oxycodone hydrochloride (10 mg/ml).
Each 20 ml ampoule contains 200 mg of oxycodone hydrochloride (10 mg/ml).

Excipient(s) with known effect:
Each ml contains 2.78 mg of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion.

A clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Oxynorm injection 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:
Prescribers should consider concomitant treatment with antiemetics and laxatives for the prevention of nausea, vomiting and constipation. The dose should be adjusted according to the intensity of pain and the sensitivity of the individual patient. The correct dosage per individual patient is that which controls the pain with no tolerable side effects. The patient's previous history of analgesic requirements should also be taken into account when determining the dose.

Generally, the lowest effective dose for analgesia should be selected. If higher doses are necessary, increases should be made in 25% - 50% increments where possible.

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):
The following starting doses are recommended for opioid-naïve patients. The initial dose should be adjusted to previous or concurrent medication (especially if the patient has been treated with other opioids before), the total condition of the patient, and the severity of pain. A gradual increase in dose may be required if analgesia is inadequate or if pain severity increases.

- **Intravenous bolus:** Slow administration of a bolus dose of 1 to 10 mg slowly over 1-2 minutes is recommended. With acute pain the dose should be titrated gradually until optimum analgesic effect is achieved. Bolus doses can be repeated, usually every 4 hours. In adolescents, a maximum bolus dose of 5mg oxycodone hydrochloride is recommended.
- **Intravenous infusion:** A starting dose of 2 mg/hour is recommended.
- **Intravenous patient-controlled analgesia:** Administration of a bolus doses of 0.03 mg/kg should be administered with a minimum lock-out time of 5 minutes.

- **Subcutaneous bolus:** Use as 10 mg/ml strength. A starting dose of 5 mg is recommended. With acute pain the dose should be titrated gradually until optimum analgesic effect is achieved. Bolus doses can be repeated, usually every 4 hours, if pain relief decreases.
- **Subcutaneous infusion:** A starting dose of 7.5 mg/day is recommended in opioid naïve patients, titrating gradually according to symptom control. In adolescents, a starting dose of 5mg oxycodone hydrochloride per day is recommended.

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. It must be emphasised that this is a guide to the dose required. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

Conversion from morphine:

Patients switching from parenteral morphine to parenteral oxycodone therapy should do so on the basis of a one to one dose ratio.

Elderly:
The lowest dose should be administered with careful titration to pain control.
Controlled pharmacokinetic studies in elderly patients (aged over 65 years) have shown that compared with younger adults the clearance of oxycodone is only slightly reduced. No untoward adverse drug reactions were seen based on age, therefore adult doses and dosage intervals are appropriate.

Patients with renal or hepatic impairment:
The dose initiation should follow a conservative approach in these patients. The recommended adult starting dose should be reduced by 50% (for example a total daily dose of 10 mg orally in opioid naïve patients), and each patient should be titrated to adequate pain control according to their clinical situation.
Unlike morphine preparations, the administration of oxycodone does not result in significant levels of active metabolites. However, the plasma concentration of oxycodone in this patient population may be increased compared with patients having normal renal or hepatic function.
Studies involving other intravenous oxycodone preparations, administered by bolus injection to six patients with end-stage liver cirrhosis and ten patients with end-stage renal failure have been reported in the literature. In each case, the elimination of oxycodone was impaired.

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:
Oxynorm injection is intended for subcutaneous or intravenous injection or infusion after dilution.
For instructions on dilution of the product before administration, see section 6.6.

Treatment goals and discontinuation
Before initiating treatment with ***Oxynorm*** injection, 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 oxycodone 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, elevated carbon dioxide levels in the blood (hypercarbia), head injury, paralytic ileus, acute abdomen, delayed gastric emptying, severe chronic obstructive lung disease, severe bronchial asthma, cor pulmonale, known sensitivity to morphine or other opioids.

4.4 Special warnings and precautions for use

Oxycodone has to be administered with caution in patients with:

- Severely impaired respiratory function
- Chronic obstructive airways disease
- Reduced respiratory reserve
- Sleep apnoea
- CNS depressants co-administration (see below and section 4.5)
- Monoamine oxidase inhibitors (MAOIs, see below and section 4.5)
- Tolerance, physical dependence and withdrawal (see below)
- Psychological dependence [addiction], abuse profile and history of substance and/or alcohol abuse (see below)
- Debilitated elderly
- Intracranial lesions or increased intracranial pressure, disorders of consciousness
- Hypotension
- Hypovolaemia
- Pancreatitis
- Obstructive and inflammatory bowel disorders
- Impaired hepatic function
- Impaired renal function,
- Myxedema,
- Hypothyroidism,
- Addison's disease
- Adrenocortical insufficiency
- Prostate hypertrophy
- Alcoholism
- Toxic psychosis
- Convulsive disorders
- Delirium tremens
- Constipation
- Diseases of the biliary tract
- Biliary or ureteric colic

In patients in whom caution is required, a reduction in dosage may be advisable.

<u>Respiratory depression</u>
The primary risk of opioid excess is respiratory depression.

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

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:
Concomitant use of opioids, including oxycodone and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma, and death. Because of these risks, concomitant prescribing with these sedative

medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe oxycodone concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

OxyNorminjection should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, ***OxyNorm***injection should be discontinued immediately (see section 4.3). Due to an increased perioperative risk of ileus and respiratory depression ***OxyNorm***injection should be used with caution pre- or intra-operatively and within the first 24 hours post-operatively.

As with all opioid preparations, oxycodone products should be used with caution following abdominal surgery as opioids are known to impair intestinal motility and should not be used until the physician is assured of normal bowel function.

As with all opioid preparations, patients about to undergo additional pain relieving procedures (e.g. surgery, plexus blockade) should not receive ***OxyNorm***injection for six hours prior to the intervention. If further treatment with ***OxyNorm***injection is indicated then the dosage should be adjusted to the new post-operative requirement.

MAOIs
Oxycodone must be administered with caution in patients taking MAOIs or who have received MAOIs within the previous two weeks.

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 ***OxyNorm*** injection can 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 ***OxyNorm*** injection 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 ***OxyNorm*** injection 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.

Tolerance and withdrawal
Patients will require monitoring for signs of drug-seeking behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

The patient may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain control. Prolonged use of this product may lead to physical dependence and a withdrawal syndrome may occur upon abrupt cessation of therapy. When a patient no longer requires therapy with oxycodone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. Withdrawal symptoms may include yawning, mydriasis, lacrimation, rhinorrhoea, tremor, hyperhidrosis, anxiety, agitation, convulsions and insomnia.

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.

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 programme involving other medications and treatment modalities. Patients with chronic non-malignant pain should be assessed and monitored for addiction and substance abuse.

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.

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.

Concomitant use of alcohol and ***OxyNorm*** may increase the undesirable effects of ***OxyNorm***; concomitant use should be avoided.

It should be emphasised that patients, once titrated to an effective dose of a certain opioid, should not be changed to other opioid analgesic preparations without clinical assessment and careful retitration as necessary. Otherwise, a continuous analgesic action is not ensured.

OxyNorm injection contains sodium as saccharin sodium, sodium citrate & sodium hydroxide.

This medicine contains 2.78 mg sodium in each millilitre. This is equivalent to 0.139% of the recommended maximum daily dietary intake of sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4). Drugs which depress the CNS include, but are not limited to: other opioids, gabapentinoids such as pregabalin, anxiolytics, hypnotics, and sedatives (incl. benzodiazepines), antipsychotics, antidepressants, phenothiazines, and alcohol.. Oxycodone should be used with caution and the dosage may need to be reduced in patients using these medications.

Concomitant administration of oxycodone with serotonin agents, such as a Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) may cause serotonin toxicity. The symptoms of serotonin toxicity may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea). Oxycodone should be used with caution and the dosage may need to be reduced in patients using these medications.

Concomitant administration of oxycodone with anticholinergics or medicines with anticholinergic activity (e.g. tricyclic anti-depressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects. Oxycodone should be used with caution and the dosage may need to be reduced in patients using these medications.

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

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

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

CYP3A4 inhibitors, such as macrolide antibiotics (e.g. clarithromycin, erythromycin and telithromycin), azol-antifungals (e.g. ketoconazole, voriconazole, itraconazole, and posaconazole), protease inhibitors (e.g. boceprevir, ritonavir, indinavir, nelfinavir and saquinavir), cimetidine and grapefruit juice may cause a reduced clearance of oxycodone that could cause an increase of the plasma concentrations of oxycodone. Therefore, the oxycodone dose may need to be adjusted accordingly.

Some specific examples are provided below:

- Itraconazole, a potent CYP3A4 inhibitor, administered 200 mg orally for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 2.4 times higher (range 1.5 - 3.4).

- Voriconazole, a CYP3A4 inhibitor, administered 200 mg twice-daily for four days (400 mg given as first two doses), increased the AUC of oral oxycodone. On average, the AUC was approximately 3.6 times higher (range 2.7 - 5.6).
- Telithromycin, a CYP3A4 inhibitor, administered 800 mg orally for four days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.8 times higher (range 1.3 – 2.3).
- Grapefruit Juice, a CYP3A4 inhibitor, administered as 200 ml three times a day for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.7 times higher (range 1.1 – 2.1).

CYP3A4 inducers, such as rifampicin, carbamazepine, phenytoin and St John's Wort may induce the metabolism of oxycodone and cause an increased clearance of oxycodone that could cause a reduction of the plasma concentrations of oxycodone. The oxycodone dose may need to be adjusted accordingly.

Some specific examples are provided below:

- St John's Wort, a CYP3A4 inducer, administered as 300 mg three times a day for fifteen days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 50% lower (range 37-57%).
- Rifampicin, a CYP3A4 inducer, administered as 600 mg once-daily for seven days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 86% lower

Drugs that inhibit CYP2D6 activity, such as paroxetine 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 newborn of mothers undergoing treatment with oxycodone.

Oxycodone penetrates the placenta. Oxycodone should not be used during pregnancy and labour due to impaired uterine contractility and the risk of neonatal respiratory depression. For animal studies see section 5.3.

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

Fertility
Non-clinical toxicology studies in rats have not shown any effects upon fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Oxycodone may impair the ability to drive and use machines. Oxycodone may modify patients' reactions to a varying extent depending on the dosage and individual susceptibility. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

The most commonly reported adverse reactions are nausea and constipation. If nausea or vomiting are troublesome, oxycodone may be combined with an antiemetic. Constipation should be anticipated as with any strong opioid, and treated appropriately with laxatives. Should opioid related adverse events persist, they should be investigated for an alternative cause.

Adverse drug reactions are typical of full opioid agonists, and tend to reduce with time, with the exception of constipation. Anticipation of adverse drug reactions and appropriate patient management can improve acceptability.

The most serious adverse reaction, as with other opioids, is respiratory depression (see section 4.9). This is most likely to occur in elderly, debilitated or opioid-intolerant patients.

The adverse drug reactions seen during clinical trials and from spontaneous reports are listed below.

The following frequency categories form the basis for classification of the undesirable effects:

Term	Frequency
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

	Very Common	Common	Uncommon	Rare	Not known
Immune system disorders			hypersensitivity		anaphylactic responses
Endocrine disorders			syndrome of inappropriate antidiuretic hormone secretion (SIADH)		
Metabolism and nutrition disorders		decreased appetite	dehydration, weight fluctuation		
Psychiatric disorders		abnormal dreams, abnormal thinking, anxiety, confusional state, depression, insomnia, nervousness	agitation, depersonalisation, affect lability, euphoric mood, hallucinations, decreased libido, drug dependence (see section 4.4)		aggression
Nervous system disorders	somnolence, dizziness, headache	tremor, lethargy	amnesia, convulsion, hyperkinesia, hypertonia, hypoaesthesia, hypotonia, involuntary muscle contractions, speech disorder, stupor, paraesthesia, dysgeusia, syncope		hyperalgesia
Eye disorders			lacrimation disorder, miosis, visual impairment		
Ear and labyrinth disorders			tinnitus, vertigo		
Cardiac disorders			palpitations (in the context of withdrawal syndrome)		
Vascular disorders			vasodilatation	hypotension, orthostatic hypotension	
Respiratory, thoracic and mediastinal disorders		dyspnoea, bronchospasm	rhinitis, epistaxis, hiccup, voice alteration, respiratory depression		central sleep apnoea syndrome
Gastrointestinal disorders	constipation, nausea, vomiting	abdominal pain, diarrhoea, dry mouth, dyspepsia	dysphagia, flatulence, gastritis, mouth ulceration, eructation, ileus, stomatitis		dental caries
Hepatobiliary disorders			hepatic enzyme increased		biliary colic, cholestasis, sphincter of Oddi

					dysfunction
Skin and subcutaneous tissue disorders	pruritus	rash, hyperhidrosis	dry skin	urticaria	
Renal and urinary disorders		urinary disorders	urinary retention		
Reproductive system and breast disorders			erectile dysfunction, hypogonadism		amenorrhoea
General disorders and administration site conditions		asthenia, fever, fatigue	chills, chest pain, drug withdrawal syndrome, gait disturbance, malaise, oedema, peripheral oedema, drug tolerance, thirst		drug withdrawal syndrome neonatal

Tolerance may occur in patients treated with oxycodone. Patients requiring marked dose escalation should have their pain control regimen carefully reviewed.

Drug dependence
Repeated use of ***OxyNorm*** injection 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 HPRA Pharmacovigilance at www.hpra.ie.

4.9 Overdose

Acute overdose with oxycodone can be manifested by respiratory depression, somnolence progressing to stupor or coma, hypotonia, miosis, bradycardia, hypotension, pulmonary oedema and death.

Toxic leukoencephalopathy has been observed with oxycodone overdose.

Treatment of oxycodone overdose: A patent airway must be maintained. The pure opioid antagonists such as naloxone are specific antidotes against symptoms from opioid overdose. Other supportive measures should be employed as needed.

In the case of massive overdose, administer naloxone 0.8 mg intravenously. Repeat at 2-3 minute intervals as necessary, or by an infusion of 2 mg in 500 ml of normal saline or 5% dextrose (0.004 mg/ml).

The infusion should be run at a rate related to the previous bolus doses administered and should be in accordance with the patient's response. However, because the duration of action of naloxone is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established.

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloid, opioid, analgesics
ATC code: N02AA05

Oxycodone is a full opioid agonist with no antagonist properties and has an affinity for kappa, mu and delta opiate receptors in the brain and spinal cord. Its effects are similar to those of morphine. The therapeutic effect is mainly analgesic, anxiolytic, antitussive and sedative. The mechanism of action involves CNS opioid receptors for endogenous compounds with opioid-like activity.

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

Endocrine system
See section 4.4.

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.

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 morphine is unknown.

5.2 Pharmacokinetic properties

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

Distribution
Oxycodone is distributed throughout the entire body. Approximately 45% is bound to plasma protein.

Biotransformation
Oxycodone is metabolized in the liver via CYP3A4 and CYP2D6 to noroxycodone, oxymorphone and noroxymorphone, which are subsequently glucuronidated. Noroxycodone and noroxymorphone are the major circulating metabolites. Noroxycodone is a weak mu opioid agonist. Noroxymorphone is a potent mu opioid agonist; however, it does not cross the blood-brain barrier to a significant extent. Oxymorphone is a potent mu opioid agonist but is present at very low concentrations following oxycodone administration. None of these metabolites are thought to contribute significantly to the analgesic effect of oxycodone. The in vitro drug-drug interaction studies with noroxymorphone using human liver microsomes resulted in no significant inhibition of CYP2D6 and CYP3A4 activities, which suggest that noroxymorphone may not alter the metabolism of other drugs that are metabolized by CYP2D6 and CYP3A4. .

Elimination
The plasma elimination half-life is approximately 4.5 hours. The active drug and its metabolites are excreted in both urine and faeces.

When compared with 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 with normal subjects, patients with mild to severe renal dysfunction (creatinine clearance <60 ml/min) 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

Reproductive and Developmental Toxicology

Oxycodone had no effect on fertility or early embryonic development in male and female rats at doses as high as 8 mg/kg/day. Also, oxycodone was not teratogenic in rats in doses of as high as 8 mg/kg/day or in rabbits in doses as high as 125 mg/kg/day. Dose-related increases in developmental variations (increased incidences of extra (27) presacral vertebrae and extra pairs of ribs) were observed in rabbits when the data for individual fetuses were analyzed. However, when the same data were analyzed using litters as opposed to individual fetuses, there was no dose-related increase in developmental variations although the incidence of extra presacral vertebrae remained significantly higher in the 125 mg/kg/day group compared to the control group. Since this dose level was associated with severe pharmacotoxic effects in the pregnant animals, the fetal findings may have been a secondary consequence of severe maternal toxicity.

In a prenatal and postnatal development study in rats, maternal body weight and food intake parameters were reduced for doses ≥2 mg/kg/day compared to the control group. Body weights were lower in the F1 generation from maternal rats in the 6 mg/kg/day dosing group.

Genotoxicity

The results of *in vitro* and *in vivo* studies indicate that the genotoxic risk of oxycodone to humans is minimal or absent at the systemic oxycodone concentrations that are achieved therapeutically. Oxycodone was not genotoxic in a bacterial mutagenicity assay or genotoxic in an *in vivo* micronucleus assay in the mouse. Oxycodone was genotoxic in the *in vitro* mouse lymphoma assay in the presence of rat liver S9 metabolic activation at dose levels greater than 25 µg/mL and two *in vitro* chromosomal aberrations assays with human lymphocytes provided equivocal results.

Carcinogenicity

Carcinogenicity was evaluated in a 2-year oral gavage study conducted in Sprague-Dawley rats. Oxycodone did not increase the incidence of tumours in male and female rats at doses up to 6 mg/kg/day. The doses were limited by opioid-related pharmacological effects of oxycodone.

Mutagenicity

Oxycodone was not mutagenic in bacterial mutation tests or in in-vivo micronucleus assay(s) in mice. As is the case with other opioids, oxycodone was shown to be genotoxic in some in-vitro assays (e.g. mouse lymphoma and human lymphocyte chromosomal aberration assays).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate
Sodium citrate
Sodium chloride
Hydrochloric acid, dilute
Sodium hydroxide
Water for injections

6.2 Incompatibilities

When cyclizine at concentrations of up to 3 mg/ml is mixed with OxyNorm injection, no sign of precipitation has been shown over a period of 24 hours storage at room temperature. When cyclizine at concentrations greater than 3 mg/ml is mixed with OxyNorm injection, precipitation has been shown to occur.

It is recommended that water for injection is used as a diluent, as cyclizine will precipitate in the presence of 0.9 % saline.

Prochlorperazine is chemically incompatible with OxyNorm injection.

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

6.3 Shelf life

5 years unopened.
After opening use immediately.
For further information see Section 6.6.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light.

For further information on use after opening see section 6.6.

6.5 Nature and contents of container

1 ml - Clear, Type I Ph Eur glass ampoules with a white breakline and a yellow identification line.
2 ml - Clear, Type I Ph Eur glass ampoules with a white breakline and a red identification line.
Pack sizes: 5 ampoules.

20 ml - Clear, Type I Ph Eur glass ampoules with a white breakline and a white identification line
Pack size: 4 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Each ampoule is for single use in a single patient. The injection should be given immediately after opening the ampoule, and any unused portion should be discarded. Chemical and physical in-use stability has been demonstrated for 24 hours at 15 – 25°C 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 use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution, dilution, etc has taken place in controlled and validated aseptic conditions.

No evidence of incompatibility was observed between OxyNorm injection and representative brands of injectable forms of the following drugs, when stored in high and low dose combinations in polypropylene syringes over a 24-hour period at ambient temperature.

Hyoscine butylbromide
Hyoscine hydrobromide
Dexamethasone sodium phosphate
Haloperidol
Midazolam hydrochloride
Metoclopramide hydrochloride
Levomepromazine hydrochloride
Glycopyrronium bromide
Ketamine hydrochloride

OxyNorm injection, undiluted or diluted to 1 mg/ml with 0.9% w/v saline, 5% w/v dextrose or water for injections, is physically and chemically stable when in contact with representative brands of polypropylene or polycarbonate syringes, polyethylene or PVC tubing and PVC or EVA infusion bags, over a 24 hour period at room temperature.

The injection, whether undiluted or diluted to 1 mg/ml in the infusion fluids used in these studies and contained in the various assemblies, does not need to be protected from light.

Inappropriate handling of the undiluted solution after opening of the original ampoule, or of the diluted solutions may compromise the sterility of the product.

7 MARKETING AUTHORISATION HOLDER

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