Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

OxyNorm Dispersa 5 mg Orodispersible Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 4.5 mg of oxycodone as 5 mg of oxycodone hydrochloride.

Excipients with known effect:
Each 5mg tablet contains 2.7 mg of aspartame (E 951) and 14.2 mg of sucrose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Orodispersible tablet

White to off-white round, flat, bevelled edged tablets of approximately 8 mm in diameter marked O on one side and 5 on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

OxyNorm Dispersa 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 correct dosage per individual patient is the lowest dose which sufficiently controls the pain with no ortolerable side effects.
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
OxyNorm Dispersa should be taken at 4-6 hourly intervals. The dose should be adjusted to the intensity of the pain and the sensitivity of the individual patient. The patient's previous history of analgesic requirements, their body weight, and sex (higher plasma concentrations are produced in females), 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. The correct dosage per individual patient is that which controls the pain with no or tolerable side effects.

The usual starting dose for debilitated elderly patients, opioid naïve patients or patients presenting with severe pain uncontrolled with opioids is 5 mg 4-6 hourly. The dose should then be carefully titrated, every day if necessary, to achieve optimal pain relief.

Conversion from oral morphine
Patients receiving oral morphine before oxycodone therapy should have their daily dose based on the following ratio: 10 mg of oral oxycodone is equivalent to 20 mg of oral morphine. It must be emphasised that this is a guide to the dose of ***OxyNorm Dispersa*** required. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

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.

Elderly patients:
A dose adjustment is not usually necessary in elderly patients.
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.

Non-malignant pain:
Treatment with oxycodone should be short and intermittent to minimise the risk of dependence. The need for continued treatment should be assessed at regular intervals. Patients should not usually require more than 160 mg per day. For the long-term treatment of severe pain prolonged release formulations of oxycodone are available.

Cancer-related pain:
Patients should be titrated up to a dose which achieves pain relief unless unmanageable adverse drug reactions prevent this.

Patients with renal or hepatic impairment:
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. 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.

Other at-risk patients
Other at-risk patients, for example patients with low body weight or slow metabolism of medicinal products, should initially receive half the recommended adult dose if they are opioid naïve. Dose titration should be performed in accordance with the individual clinical situation

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.

Adolescents (from 12 years and older)
The usual starting dose for opioid-naïve patients presenting with severe pain uncontrolled by weak opioids is 5 mg oxycodone hydrochloride at 6-hour intervals.
The dose should then be carefully titrated, every day if necessary, to achieve pain relief.
During this process, the dosing interval of ***OxyNorm Dispersa*** may be reduced to 4 hours if required. However, ***OxyNorm Dispersa*** should not be taken more than 6 times a day.

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

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 Dispersa orodispersible tablets are for oral use.

The tablet is to be placed in the mouth where it should be allowed to disperse rapidly before being swallowed.

Missed dose:
If a patient forgets to take a dose, advise them to take a dose as soon as they remember, then go on as before. They must not take two doses within 4 hours. They must not take a double dose to make up for forgotten orodispersible tablets.

Treatment goals and discontinuation
Before initating treatment with ***OxyNorm Dispersa,*** 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 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, 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

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, adrenocortical insufficiency, prostate hypertrophy, raised intracranial pressure, intracranial lesions or head injury (due to the risk of raised intracranial pressure), convulsive disorders, delirium tremens, disorders of consciousness, sleep apnoea, hypotension, hypovolaemia. Use with caution in opioid dependent patients, diseases of the biliary tract, biliary or ureteric colic, pancreatitis, obstructive and inflammatory bowel disorders, constipation, chronic obstructive airways disease, reduced respiratory reserve, alcoholism or patients taking benzodiazepines, other CNS depressants (including alcohol) or MAO inhibitors. In patients in whom caution is required, a reduction in dosage may be advisable.

The primary risk of opioid excess is respiratory depression.

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. Opioids may also cause worsening of pre-existing sleep apnoea (see section 4.8).

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.

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).

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

OxyNorm Dispersa should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, ***OxyNorm Dispersa*** should be discontinued immediately (see section 4.3).

OxyNorm Dispersa should be used with caution pre-operatively and within the first 12-24 hours post-operatively.

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

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.

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 Dispersa*** 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 ***OxyNorm Dispersa*** 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 Dispersa*** 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.

Tolerance and withdrawal
The patient may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain control. There may also be cross-tolerance with other opioids.

A withdrawal syndrome may occur upon abrupt cessation of therapy following prolonged use of this product. 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, irritability, chills, hot flushes, piloerection, joint pain, diaphoresis, abdominal cramps, diarrhoea, convulsions and insomnia.

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.

Concomitant use of alcohol and ***OxyNorm Dispersa*** may increase the undesirable effects of ***OxyNorm Dispersa***; 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 analgesic preparations without clinical assessment and careful retitration as necessary. Otherwise, a continuous analgesic action is not ensured.

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

OxyNorm Dispersa contains a source of phenylalanine which may be harmful to patients with phenylketonuria.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase- isomaltase insufficiency should not take this medicine.

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.

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 affect the CNS include, but are not limited to: other opioids, gabapentinoids such as pregabalin, anxiolytics, hypnotics and sedatives (including benzodiazepines), antipsychotics, antidepressants, phenothiazines, anaesthetics, muscle relaxants, antihypertensives 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, antiemetics, antipsychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects such as constipation, dry mouth or micturition disorders. 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 Dispersa***, 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), azole-antifungals (e.g. ketoconazole, voriconazole, itraconazole, and posaconazole), protease inhibitors (e.g. boceprevir, ritonavir, indinavir, nelfinavir and saquinavir), cimetidine and grapefruit juice may cause a reduced clearance of oxycodone that could cause an increase of the plasma concentrations of oxycodone. Therefore the oxycodone dose may need to be 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, fluoxetine and quinidine, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations.

The effect of other relevant isoenzyme inhibitors on the metabolism of oxycodone is not known. Potential interactions should be taken into account.

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

There are no studies investigating the effect of oxycodone on CYP catalysed metabolism of other drugs.

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
Nohuman data on the effect of oxycodone on fertility are available. 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, both occurring in approximately 25 to 30% of patients. 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 Overdose section). 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		
Metabolism and nutrition disorders		decreased appetite	dehydration, weight fluctuation		
Psychiatric disorders		abnormal dreams, anxiety, confusional state, depression, insomnia, nervousness, abnormal thinking	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, hypoaethesia, hypotonia, involuntary muscle contractions, speech disorder, stupor, paraesthesia, dysgeusia, syncope		hyperalgesia
Eye disorders			visual impairment, lacrimation disorder, miosis		
Ear and labyrinth disorders			tinnitus, vertigo		
Cardiac disorders			palpitations (in the context of withdrawal syndrome)		
Vascular disorders			vasodilation	hypotension, orthostatic hypotension	
Respiratory, thoracic and mediastinal disorders		dyspnea, bronchospasm	rhinitis, epistaxis, hiccup, voice alteration, respiratory depression		central sleep apnoea syndrome
Gastrointestinal disorders	constipation, nausea, vomiting	abdominal pain, diarrhea, dry mouth, dyspepsia	dysphagia, flatulence, gastritis, mouth ulceration, eructation, ileus, stomatitis		dental caries
Hepatobiliary disorders			increased hepatic enzyme		biliary colic, cholestasis, Sphincter of Oddi dysfunction
Skin and subcutaneous tissue disorders	pruritis	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		asthenia, fever, fatigue	chills, chest pain, drug withdrawal syndrome (see sections 4.2 & 4.4), gait disturbance,		drug withdrawal

administration site conditions			malaise, oedema, peripheral oedema, drug tolerance, thirst		syndrome neonatal

Tolerance may occur in patients treated with oxycodone, although this has not been a significant problem in the clinical trial programme. Patients requiring marked dose escalation should have their pain control regimen carefully reviewed.

Drug dependence
Repeated use of ***OxyNormDispersa*** 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.
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. 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.

Gastric contents may need to be emptied as this can be useful in removing unabsorbed drug.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids ATC code: N02A A05

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. 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 Pharmacologic 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:
After administration of ***OxyNorm Dispersa***, peak oxycodone plasma concentrations are observed after approximately 1 hour (range 0.5 – 5.0 hours). Oxycodone has a high absolute bioavailability of up to 87% following oral administration.

Distribution:
Following absorption, oxycodone is distributed throughout the entire body. Approximately 45% is bound to plasma protein.

Metabolism:
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.

Elimination:
The active drug and its metabolites are excreted in both urine and faeces. It has an elimination half-life of approximately 3 hours.

Elderly:
The plasma concentrations of oxycodone are only nominally affected by age, being 15% greater in elderly as compared to young subjects.

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

Patients with hepatic impairment:
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.

Patients with renal impairment:

When compared to 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 development 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 did not induce any malformations in rats at doses as high as 8 mg/kg/day or in rabbits at doses as high as 125 mg/kg/day. Dose-related increases in developmental variations (increased incidences of extra (27) presacral verterbrae and extra pairs of ribs) were observed in rabbits when the data for individual foetuses were analysed. However, when the same data were analysed using litters as opposed to individual foetuses, 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 foetal 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.

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.

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 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sugar Spheres (contains sucrose and maize starch)
Polyacrylate dispersion 30%
Hypromellose
Mannitol
Silicon dioxide
Cellulose, microcrystalline
Crospovidone
Aspartame
Spearmint flavour (contains maltodextrin and spearmint oil)
Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Aluminium blister packs with a peelable aluminium backing foil.
Pack sizes: 14, 28 or 56 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Mundipharma Pharmaceuticals Limited
United Drug House
Magna Drive Magna Business Park
Citywest Road
Dublin 24
D24 XKE5
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1688/006/007

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16th July 2010

Date of latest renewal: 16th July 2015

10 DATE OF REVISION OF THE TEXT

March 2024