Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

OxyContin 5 mg prolonged release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient:
Each 5 mg tablet contains 77.30 mg of lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release tablets.
Each 5 mg tablet is light blue, round, convex of approximately 7 mm in diameter marked OC on one side and 5 on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

OxyContin 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.

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:
OxyContin tablets should be taken at 12-hourly intervals. The dose should be adjusted to the intensity of the pain and the sensitivity of the individual patient. The correct dosage per individual patient is the lowest dose which sufficiently controls the pain with no ortolerable side effects.

The usual starting dose for debilitated elderly patients, opioid naïve patients or patients presenting with severe pain uncontrolled with weaker opioids is 10 mg 12-hourly. Generally, the lowest effective dose for analgesia should be selected. Some patients may benefit from a starting dose of 5 mg to minimise the incidence of side effects. The dose should then be carefully titrated, every day if necessary, to achieve pain relief. Given the time to reach steady state, patients' doses should only be titrated up after 24 hours and increases should be made, where possible, in 25% - 50% increments. The correct dosage for any individual patient is that which controls the pain with no or tolerable side effects, for a full 12 hours. The need for escape medication more than twice a day indicates that the dosage of ***OxyContin*** tablets should be increased.

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 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 ***OxyContin*** tablets 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. Patients should not usually require more than 160 mg per day.

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.

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)
If a prolonged release formulation is required as initial treatment for opioid naive patients, the usual starting dose is 10 mg oxycodone hydrochloride per dose at 12-hour intervals. Considering the guidance for other special populations, some paediatric patients may benefit from a starting dose of 5 mg to minimize the incidence of adverse reactions.

Patients already receiving opioids may be initiated on higher OxyContin 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.

Method of administration

OxyContin tablets are for oral use.

***OxyContin* tablets must be swallowed whole and are not to be broken, chewed or crushed. Taking broken, chewed or crushed *OxyContin* tablets may lead to a rapid release and absorption of a potentially fatal dose of oxycodone**.

It is recommended that patients take the medication in a consistent manner in relation to the timing of meals. (See section 5.2)

Treatment goals and discontinuation
Before initiating treatment with ***OxyContin*** tablets, 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).

Missed dose:
If a patient forgets to take a dose but remembers within 4 hours of the time the dose was due to be taken, the tablets can be taken straight away. The next dose should be taken at the normal time. Beyond 4 hours the prescriber may need to consider alternative rescue medicine until the next dose is due.

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 the active substance or to any of the excipients listed in section 6.1.
- Severe chronic obstructive lung disease,
- Cor pulmonale,
- Severe bronchial asthma,
- Severe respiratory depression with hypoxia,
- Elevated carbon dioxide levels in the blood (hypercarbia),
- Paralytic ileus,
- Acute abdomen,
- Delayed gastric emptying,
- Head injury,
- Known sensitivity to morphine or other opoids

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 Opioid Use Disorder below)
- Psychological dependence [addiction], abuse profile and history of substance and/or alcohol abuse (see Opioid Use Disorder 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.

Respiratory depression
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.

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).

Doses of ***OxyContin*** tablets in excess of 60 mg may cause fatal respiratory depression when administered to patients not previously exposed to opioids and should only be used in opioid-tolerant patients. Care should be taken in the prescription of daily oxycodone dosages of 120 mg or more.

OxyContin tablets should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, ***OxyContin*** tablets should be discontinued immediately (see section 4.3). As with all opioid preparations, patients about to undergo additional pain relieving procedures (e.g. surgery, plexus blockade) should not receive oxycodone for 12 hours prior to the intervention. If further treatment with ***OxyContin*** tablets is indicated then 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.

OxyContinis not recommended for pre-operative use or within the first 12-24 hours post-operatively.

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 ***OxyContin*** tablets 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 ***OxyContin*** tablets 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 ***OxyContin*** *tablets* 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. 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.

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 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.

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.

The prolonged release tablets must be swallowed whole, and not be broken, chewed or crushed.
The administration of broken, chewed or crushed controlled release oxycodone tablets leads to a rapid release and absorption of a potentially fatal dose of oxycodone (see section 4.9).

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

Parenteral abuse of dosage forms not approved for parenteral administration can be expected to result in serious adverse events, which may be fatal.

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.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Empty matrix (tablets) may be seen in the stool.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

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 ***OxyContin***; 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.gavir 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, carbamazepin, 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:
CYP3A4 inducers, such as rifampicin, carbamazepin, 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
No human data on the effect of oxycodone on fertility are available. 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 section 4.9). This is most likely to occur in elderly, debilitated or opioid-intolerant patients.

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 Very rare	≥1/10,000 to <1/1,000 <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, gastrointestinal disorders, 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**,** 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 ***OxyContin*** *tablets* 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. ***OxyContin*** tablets will continue to release and add to the oxycodone load for up to 12 hours after administration and the management of oxycodone overdose should be modified accordingly.

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, particularly when a prolonged release formulation has been taken.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids, opioids, 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. 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.

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.

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
Oxycodone has a high absolute bioavailability of up to 87% following oral administration.

The release of oxycodone from ***OxyContin*** tablets is biphasic with an initial relatively fast release providing an early onset of analgesia followed by a more controlled release which determines the 12 hour duration of action.

Release of oxycodone from ***OxyContin*** tablets is independent of pH.

OxyContin tablets have an oral bioavailability comparable with conventional oral oxycodone, but the former achieve peak plasma concentrations within 3-5 hours rather than about 1 to 1.5 hours. Peak and trough concentrations of oxycodone from ***OxyContin*** tablets 10 mg administered 12-hourly are equivalent to those achieved from conventional oxycodone 5 mg administered 6-hourly.

All strengths of ***OxyContin*** are bioequivalent in terms of both rate and extent of absorption. Following ingestion of a high fat meal, peak plasma concentrations may be increased, relative to dosing in the fasting state. It is recommended that patients take the medication in a consistent manner in relation to the timing of meals.

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

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

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.

Paediatric population
The pharmacokinetic properties of oral oxycodone in infants and children were examined in 3 studies including a total of 63 infants and children aged 0.5 to 7.6 years. In addition pharmacokinetics of buccal and sublingual oxycodone was studied in 30 children aged 0.5-7.5 years. These studies did not reveal significant different results in comparison to adults. Oral oxycodone was tolerated well in these pharmacokinetic studies with only minor adverse events.

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 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 vertebrae 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.

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.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Povidone
Ammoniomethacrylate polymer dispersion
Sorbic acid
Glycerol triacetate
Stearyl alcohol
Talc
Magnesium stearate
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol
Brilliant blue (E133)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Three years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

PVC blister packs with aluminium foil backing (containing 10, 28, 30, 56 or 112 tablets).

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

No special 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

PA1688/005/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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