PROFESSIONAL INFORMATION

SCHEDULING STATUS

S6

1 NAME OF THE MEDICINE

OxyContin® 5 mg Prolonged Release Tablets

OxyContin® 10 mg Prolonged Release Tablets

OxyContin® 20 mg Prolonged Release Tablets

OxyContin® 40 mg Prolonged Release Tablets

OxyContin® 80 mg Prolonged Release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each OxyContin® 5 mg contains 5 mg of oxycodone hydrochloride.

Each OxyContin® 10 mg contains 10 mg of oxycodone hydrochloride.

Each OxyContin® 20 mg contains 20 mg of oxycodone hydrochloride.

Each OxyContin® 40 mg contains 40 mg of oxycodone hydrochloride.

Each OxyContin® 80 mg contains 80 mg of oxycodone hydrochloride.

Contains sugar (lactose monohydrate).

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-Release Tablets.

OxyContin® 5 mg are pale blue, round, bi-convex, film coated tablets, imprinted with OC on one side and 5 on the other side.

OxyContin® 10 mg are white, round, bi-convex, film coated tablets, imprinted with OC on one side and 10 on the other side.

OxyContin® 20 mg are pink, round, bi-convex, film coated tablets, imprinted with OC on one side and 20 on the other side.

OxyContin® 40 mg are yellow, round, bi-convex, film coated tablets, imprinted with OC on one side and 40 on the other side.

OxyContin® 80 mg are green, round, bi-convex, film coated tablet, imprinted with OC on one side and 80 on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

OxyContin® is indicated for the treatment of moderate to severe pain in patients with cancer and post-operative pain after gastrointestinal function has returned.

OxyContin® is indicated for the treatment of severe pain requiring the use of a strong opioid analgesic.

4.2 Posology and method of administration

Treatment goals and discontinuation

Before initiating treatment with OxyContin®, 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 OxyContin®, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal (see also section 4.4 as well as section 4.8). 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.

Posology

Elderly and adults over 18 years:

OxyContin® must be swallowed whole and not chewed.

OxyContin® is not intended for use as a PRN analgesic.

OxyContin® should be taken at 12-hourly intervals. The dosage is dependent on the severity of the pain and the patient's previous history of analgesic requirements.

Increasing severity of pain will require an increased dose of OxyContin® using the 5 mg, 10 mg, 20 mg, 40 mg or 80 mg tablets strengths, either alone or in combination to achieve pain relief.

The correct dosage for any individual patient is that which controls the pain and is well tolerated for a full 12 hours. The lowest effective dose for analgesia should be selected. Patients should be titrated to pain relief unless unmanageable adverse drug reactions prevent this. If higher doses are necessary, increases should be made, where possible, in 25 % - 50 % increments. The need for escape medication more than twice a day indicates that the dosage of OxyContin® should be increased.

The usual starting dose for opioid naïve patients presenting with severe pain uncontrolled by weaker opioids is 10 mg, 12-hourly. 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, as frequently as once a day, if necessary, to achieve pain relief. For the majority of patients, the maximum dose is 200 mg 12-hourly. However, a few patients may require higher doses.

Transferring patients between pain products

Conversion from oral morphine

Patients receiving oral morphine before OxyContin® therapy should have their daily dose based on the following ratio: 10 mg of oral oxycodone is equivalent to 20 mg of oral morphine.

Conversion from parenteral oxycodone

Patients receiving parenteral oxycodone should have their dose based on the ratio 2 mg oral oxycodone is equivalent to 1 mg of parenteral oxycodone.

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

Special populations

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 (see section 5.2).

Adults with mild to moderate renal impairment and mild hepatic impairment:

The plasma concentration in this population may be increased. Therefore, dose initiation should follow a conservative approach. Opioid naïve patients should be started on OxyContin® 5 mg 12 hourly and titrated to pain relief as described (see section 5.2).

Paediatric population

Children under 18 years

The safety and efficacy of OxyContin® in patients under 18 years of age has not been established.

Method of administration

OxyContin® must be swallowed whole and not chewed.

4.3 Contraindications

OxyContin® is contraindicated in patients with known hypersensitivity to oxycodone or to any of the excipients or in any situation where opioids are contraindicated (see section 6.1).

OxyContin® is contraindicated in patients presenting with:

- respiratory depression,
- hypoxia and/or hypercapnia from any cause,
- paralytic ileus,
- acute abdomen,
- delayed gastric emptying,
- chronic obstructive lung disease,
- cor pulmonale,
- chronic bronchial asthma,
- moderate to severe hepatic impairment,
- severe renal impairment (creatinine clearance < 10 ml/min),
- chronic constipation.

OxyContin® is contraindicated in patients on concurrent administration of monoamine oxidase inhibitors or within 2 weeks of discontinuation of their use.

OxyContin® must not be used during pregnancy or lactation (see section 4.6).

OxyContin® is not recommended for pre-operative use or for the first 12 - 24 hours post-operatively.

Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 Special warnings and precautions for use

A reduction in dosage may be advisable in hypothyroidism.

OxyContin® should be used with caution in patients with:

- head injury (due to risk of increased intracranial pressure),
- hypotension,

- hypovolaemia,
- toxic psychosis,
- disease of the biliary tract,
- pancreatitis,
- inflammatory bowel disorders,
- prostatic hypertrophy,
- adrenocortical insufficiency,
- Addison's disease,
- myxoedema,
- delirium tremens,
- impaired renal or hepatic function,
- sleep apnoea,
- benzodiazepine, or other CNS depressants co administration (see below and section 4.5);
- psychological dependence (addiction), abuse profile and history of substance and/or alcohol abuse (see below);
- tolerance, physical dependence and withdrawal (see below);
- debilitated elderly and infirm patients.

Respiratory depression

The major risk is respiratory depression.

Sleep-related breathing disorders

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxaemia. Opioid use increases the risk of CSA in a dose-dependent fashion. Opioids may also cause worsening of pre-existing sleep apnoea (see section 4.8). In patients who present with CSA, consider decreasing the total opioid dosage.

CNS depressant co-administration

Concomitant use of 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).

MAOIs

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

OxyContin® should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, OxyContin® should be discontinued immediately. OxyContin® is not recommended for 24 hours before surgery or within the first 12 – 24 hours post-operatively.

Patients who are to undergo cordotomy or other pain-relieving surgical procedures should not receive OxyContin® for 24 hours before surgery or within the first 12 – 24 hours post-operatively. If further treatment with OxyContin® is then indicated the dosage should be adjusted to the new post-operative requirement.

Tolerance, Dependence and Opioid Use Disorder (abuse and dependence)

Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as oxycodone. Addiction following therapeutic use of opioids is known to occur. Abuse and addiction are separate and distinct from physical dependence

and tolerance. Healthcare providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

Tolerance may occur to both the desired and undesired effects of medicine and may develop at different rates for different effects. In the case of opioids, such as oxycodone, tolerance usually develops more slowly to analgesia than to respiratory depression, and tolerance to the constipating effects may not occur at all. Tolerance to the analgesic effects of opioids is variable in occurrence but not absolute.

The patient may develop analgesic tolerance to OxyContin® with chronic use and require progressively higher doses to maintain pain control (in the absence of disease progression or other external factors).

Prolonged use of OxyContin® may result in physical dependence, in which case a withdrawal syndrome may occur following abrupt cessation. (For symptoms of opioid withdrawal syndrome, please see section 4.8).

When a patient no longer requires therapy with oxycodone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

Given the increased risk for serious harms associated with increasing doses, opioid use should be limited to the minimum needed to manage pain which can help limit development of tolerance and therefore of withdrawal once opioids are discontinued.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed oxycodone hydrochloride tablets. Addiction can occur at recommended dosages and if the medicine is misused or abused. (See section 4.8 for risk of drug dependence).

Repeated use of OxyContin® may lead to Opioid Use Disorder (OUD). A higher dose and longer duration of opioid treatment may increase the risk of developing OUD. Abuse or intentional misuse of OxyContin® 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).

OxyContin® should be used with particular care in patients with a history of alcohol and drug abuse.

Before initiating treatment with OxyContin® 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 medical practitioner.

Patients will require monitoring for signs of drug-seeking behaviour (e.g. too early requests for refills). The prescriber should conduct a review of concomitant opioids and psycho-active medicines (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

OxyContin® must be swallowed whole and not broken, chewed or crushed. The administration of broken, chewed or crushed OxyContin® leads to a rapid release and absorption of a potentially fatal dose of oxycodone.

OxyContin® tablet should not be pre-soaked, licked or otherwise made wet prior to placing it in the mouth, and must be taken one tablet at a time with enough water to ensure complete swallowing immediately after placing it in the mouth.

*Opioid Use Disorder is a problematic pattern of opioid use leading to clinically significant impairment or distress. OUD has also been classified as Opioid Abuse or Opioid Dependence and has been referred to as “opioid addiction”. Diagnostic criteria for OUD include tolerance and withdrawal, yet these criteria are not considered to be met for individuals taking opioids solely under appropriate medical supervision.

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

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

OxyContin® 80 mg should not be used in patients not previously exposed to opioids. These tablets' strength may cause fatal respiratory depression when administrated to opioid naïve patients.

OxyContin® should be used with caution following abdominal surgery as opioids are known to impair intestinal motility and should not be used until the medical practitioner is assured of normal bowel function.

Infants who are born to dependent mothers may exhibit withdrawal symptoms and may have respiratory depression at birth.

Patients with underlying GI disorders such as oesophageal cancer or colon cancer with a small gastrointestinal lumen are at greater risk of developing complications (intestinal obstruction, and exacerbation of diverticulitis, which may require medical intervention to remove the tablet). Caution should be used when prescribing OxyContin® for patients who have difficulty swallowing or having underlying GI disorders that may predispose them to obstruction.

Opioids, such as oxycodone, 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.

Contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption etc. should not take OxyContin®.

4.5 Interaction with other medicines and other forms of interaction

The concomitant use of opioids with sedative medicines such as benzodiazepines or related medicine 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). Medicines 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.

Concomitant administration of oxycodone with anticholinergics or medications with anticholinergic activity (e.g. tricyclic antidepressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson medicines) may result in increased anticholinergic adverse effects.

Monoamine oxidase inhibitors are known to interact with narcotic analgesics, producing CNS excitation or depression with hypertensive or hypotensive crisis.

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.

Concurrent administration of quinidine, an inhibitor of cytochrome P450-2D6, resulted in an increase in oxycodone C_{max} by 11 %, AUC by 13 % and $t_{1/2}$ elimination by 14 %. Also, an increase in noroxycodone level was observed, (C_{max} by 50 %, AUC by 85 % and $t_{1/2}$ elimination

by 42 %). The pharmacodynamic effects of oxycodone were not altered. This interaction may be observed for other potent inhibitors of cytochrome P450-2D6 enzyme.

Oxycodone is metabolised mainly by cytochrome P450-3A4 with a contribution from cytochrome P450-2D6. The activities of these metabolic pathways may be inhibited or induced by various co-administered medicines or dietary elements. Oxycodone doses may need to be adjusted accordingly.

Cimetidine and inhibitors of cytochrome P450-3A4 such as azole-antifungal agents (e.g. ketoconazole), macrolide antibiotics (e.g. clarithromycin and erythromycin), protease inhibitors (e.g. ritonavir), and grapefruit juice may inhibit the metabolism of oxycodone, which could lead to an increase in oxycodone plasma concentrations.

Cytochrome P450-3A4 inducers, such as rifampin, carbamazepine, phenytoin and St. John's wort, may induce the metabolism of oxycodone and cause increased clearance of the medicine, resulting in a decrease in oxycodone plasma concentrations.

Medicines that inhibit cytochrome P450-2D6 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

Pregnancy

OxyContin® is contraindicated for use in pregnancy and during labour. Neonates born to mothers who have received OxyContin® during pregnancy should be monitored for respiratory depression (see section 4.3).

Prolonged use of oxycodone during pregnancy can result in neonatal opioid withdrawal syndrome in the neonate.

Breastfeeding

Oxycodone may be secreted in breast milk and may cause respiratory depression in the newborn. OxyContin® should therefore not be used by breastfeeding mothers.

Fertility

No human data on the effect of oxycodone on fertility are available. In rats, there was no effect on mating or fertility with oxycodone treatment (see section 5.3).

4.7 Effects on ability to drive and use machines

Oxycodone may modify patients' reactions to a varying extent depending on the dosage and individual susceptibility. Therefore, patients should not drive or operate machinery if affected.

4.8 Undesirable effects

Tabulated list of adverse reactions

Adverse medicine reactions are typical of full opioid agonists. Tolerance and dependence may occur (see section 4.4). Constipation may be prevented with an appropriate laxative. If nausea and vomiting are troublesome, OxyContin® may be combined with an anti-emetic. The reactions are listed as MeDRA preferred term by system organ class and absolute 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)

Infections and infestations

Rare: herpes simplex

Immune system disorders

Uncommon: hypersensitivity

Not known: anaphylactic reaction, anaphylactoid reaction

Metabolism and nutritional disorders

Common: decreased appetite

Uncommon: dehydration

Rare: increased appetite

Psychiatric disorders

Common: altered mood and personality changes (e.g. anxiety, depression), decreased activity, restlessness, psychomotor hyperactivity, nervousness, insomnia, thinking abnormal, confusional state

Uncommon: perception disturbances (e.g. hallucination, derealisation), libido decreased, affect lability, agitation, euphoric mood

Not known: Aggression, *drug dependence

**Frequency of drug dependence cannot be estimated. 'Not known' should not be interpreted as an indication of the rarity of the occurrence, but a reflection of the limitations of the available evidence*

Nervous system disorders

Very Common: headache, dizziness, sedation, somnolence

Common: tremor, lethargy

Uncommon: impaired concentration, migraine, dysgeusia, hypertonia, muscle contractions involuntary, hypoaesthesia, abnormal coordination, syncope, paraesthesia, amnesia, convulsion, speech disorder

Not known: hyperalgesia

Eye disorders

Uncommon: miosis, visual impairment

Ear and labyrinth disorders

Uncommon: impaired hearing, vertigo

Cardiac disorders

Uncommon: tachycardia, palpitations (in the context of withdrawal syndrome)

Vascular disorders

Uncommon: vasodilatation

Rare: hypotension, orthostatic hypotension

Respiratory, thoracic and mediastinal disorders

Common: dyspnoea

Uncommon: dysphonia, cough, respiratory depression, choking

Not known: central sleep apnoea syndrome

Gastrointestinal disorders

Very Common: constipation, nausea, vomiting

Common: abdominal pain, diarrhoea, dry mouth, hiccups, dyspepsia

Uncommon: mouth ulceration, stomatitis, flatulence, dysphagia (difficulty swallowing tablet), ileus, eructation, regurgitation, retching

Rare: melaena, tooth disorder, gingival bleeding

Not known: dental caries

Hepato-biliary disorders

Uncommon: biliary colic, hepatic enzymes increased

Not known: cholestasis

Skin and subcutaneous tissue disorders

Very common: pruritus

Common: skin reactions/rash, hyperhidrosis

Uncommon: dry skin

Rare: urticaria

Renal and urinary disorders

Common: dysuria, micturition urgency

Uncommon: urinary retention

Reproductive system and breast disorders

Uncommon: erectile dysfunction, hypogonadism

Not known: amenorrhoea

General disorders and administration site conditions

Common: asthenia, fatigue

Uncommon: chills, pain (e.g. chest pain), malaise, oedema, oedema peripheral, thirst, medicine tolerance

Rare: weight increase, weight decrease

Not known: drug withdrawal syndrome neonatal, opioid tolerance**, opioid withdrawal syndrome**

** *Frequency of opioid tolerance and opioid withdrawal cannot be estimated from available evidence, 'Not known' should not be interpreted as an indication of the rarity of the occurrence, but a reflection of the limitations of the available evidence that do not support a precise estimate.*

Injury, poisoning and procedural complications

Uncommon: injury from accidents, medication stuck in throat

Description of selected adverse reactions

Drug Dependence

The frequency of opioid tolerance and opioid withdrawal in the above table regarding drug dependence reflects the current evidence, including cumulative data from clinical trials and additional post marketing sources, and indicates that the risk of drug dependence with opioids is highly variable depending upon: definition of drug dependence; duration of treatment; dose; individual patient risk factors; and clinical settings. 'Not known' should not be interpreted as an indication of the rarity of the occurrence of drug dependence, but a reflection of the limitations in the available evidence that do not support a precise estimate of frequency. Repeated use of OxyContin® may 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 on monitoring and risk reduction interventions.). As an opioid, oxycodone exposes users to the risks of dependence (both physical and psychological), addiction, abuse, and misuse, as well as opioid use

disorder and problematic opioid use. Although the risk of addiction in any individual is unknown, it can and does occur in patients appropriately prescribed oxycodone. Addiction can occur at recommended doses, and if the drug is misused or abused. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The frequency of drug dependence also increases with longer term use or higher doses of oxycodone. (See section 4.4 on monitoring and risk reduction interventions).

Opioid Tolerance and Opioid Withdrawal Syndrome

The frequency of in the above table regarding opioid tolerance and opioid withdrawal syndrome reflects the high variability of risk depending upon: definition of tolerance and withdrawal syndrome; dose and duration of treatment; and assessment and monitoring methods (specific to withdrawal syndrome). 'Not known' should not be interpreted as an indication of the rarity of the occurrence of opioid tolerance and opioid withdrawal syndrome, but a reflection of the limitations in the available evidence that do not support a precise estimate of frequency. As an opioid, oxycodone exposes users to the risks of dependence (both physical and psychological), tolerance and withdrawal syndrome. The opioid withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia and mydriasis. Other symptoms may also develop, which includes: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea or increased blood pressure, increased respiratory rate or increased heart rate. (See section 4.4 on monitoring and risk reduction interventions).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med

Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Alternatively report to the following e-mail address: ZADrugsafety@mundipharma.co.za

4.9 Overdose

Signs of oxycodone toxicity and overdosage are miosis, respiratory depression, pulmonary oedema and hypotension and hallucinations. Circulatory failure and somnolence progressing to stupor or deepening coma, hypotonia, bradycardia and death may occur in more severe cases.

Toxic leukoencephalopathy has been observed with oxycodone overdose.

Treatment of oxycodone overdosage: primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation.

Administer naloxone intravenously (0,4 to 2 mg for an adult and 0,01 mg/kg body weight for children) if the patient is in a coma or respiratory depression is present. Repeat the dose at 2 minute intervals if there is no response. If repeat doses are required then an infusion of 60 % of the initial dose per hour is a useful starting point. A solution of 10 mg made up in 50 ml dextrose will produce 200 micrograms/ml for infusion using an IV pump (dose adjusted to the clinical response). Infusions are not a substitute for frequent review of the patient's clinical state. Intramuscular naloxone is an alternative in the event that IV access is not possible.

As the duration of action of naloxone is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established. Naloxone is a competitive antagonist and large doses (4 mg) may be required in seriously poisoned patients.

For less severe overdosage, 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 overdosage. Naloxone should be administered cautiously to persons who are known, or suspected, to be physically

dependant on oxycodone. In such cases, an abrupt or complete reversal of opioid effects may precipitate pain and an acute withdrawal syndrome.

Additional/other considerations: Consider activated charcoal (50 g for adults, 10 - 15 g for children), if a substantial amount has been ingested within 1 hour, provided the airway can be protected. It may be reasonable to assume that late administration of activated charcoal may be beneficial for prolonged-release preparations, however there is no evidence to support this.

OxyContin® will continue to release and add to the oxycodone load for up to 12 hours after administration and management of oxycodone overdosage should be modified accordingly.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 2.9 Other Analgesics

ATC code: N02A A05

Oxycodone is a full opioid agonist with no antagonist properties. It has affinity for kappa, mu and delta opiate receptors in the brain and spinal cord. Oxycodone is similar to morphine in its action. The therapeutic effect is mainly analgesic, anxiolytic and sedative (see section 4.1).

Gastrointestinal System

Opioids may induce spasm of the sphincter of Oddi.

5.2 Pharmacokinetic properties

Metabolism

Oxycodone has an absolute bioavailability of up to 87 % following oral administration. Oxycodone is metabolised principally to noroxycodone via CYP450-3A and oxymorphone via CYP450-2D6. Oxymorphone has some analgesic activity but is present in plasma in low concentrations and is not considered to contribute to oxycodone’s pharmacological effect.

Elimination

Oxycodone has an elimination half-life of approximately 3 hours.

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

The mean apparent elimination half-life of OxyContin® is 4,5 hours which leads to steady state being achieved in about one day.

Absorption

OxyContin® has an oral bioavailability comparable with conventional oral oxycodone, but the former achieve maximal plasma concentrations at about 3 hours rather than about 1 to 1,5 hours.

Peak and trough concentrations of oxycodone from OxyContin® 10 mg administered 12-hourly are equivalent to those achieved from conventional oxycodone 5 mg administered 6-hourly.

OxyContin® 5 mg, 10 mg, 20 mg, 40 mg and 80 mg are bioequivalent in terms of both rate and extent of absorption.

Ingestion of a standard high-fat meal does not alter peak oxycodone concentration or the extent of oxycodone absorption from OxyContin®.

Elderly: The AUC in elderly subjects is 15 % greater when compared with younger subjects.

Gender: Female subjects have, on average, plasma oxycodone concentrations up to 25 % higher than males on a body weight adjusted basis. The reason for this difference is unknown.

Patients with renal impairment: Preliminary data from a study of patients with mild to moderate renal dysfunction show peak plasma oxycodone and noroxycodone concentrations approximately 50 % and 20 % higher, respectively and AUC values of oxycodone, noroxycodone and oxymorphone approximately 60 %, 60 % and 40% higher than normal

subjects, respectively. There was an increase in $t_{1/2}$ of elimination for oxycodone of only 1 hour.

Patients with mild to moderate hepatic impairment: Patients with mild to moderate hepatic dysfunction showed peak plasma oxycodone and noroxycodone concentrations approximately 50 % and 20 % higher, respectively, than normal subjects. AUC values were approximately 95 % and 75 % higher, respectively. Oxymorphone peak plasma concentrations and AUC values were lower by 15 % to 50 %. The $t_{1/2}$ elimination for oxycodone increased by 2,3 hours.

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. There were no effects on physical, reflexological, or sensory developmental parameters or

on behavioural and reproductive indices in the F1 pups (the NOEL for F1 pups was 2 mg/kg/day based on body weight effects seen at 6 mg/kg/day). There were no effects on the F2 generation at any dose in the study.

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 produced a positive response in the *in vitro* mouse lymphoma assay in the presence of rat liver S9 metabolic activation at dose levels greater than 25 µg/ml. Two *in vitro* chromosomal aberrations assays with human lymphocytes were conducted. In the first assay, oxycodone was negative without metabolic activation but was positive with S9 metabolic activation at the 24-hour time point but not at 48 hours after exposure. In the second assay, oxycodone did not show any clastogenicity either with or without metabolic activation at any concentration or time point.

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

Tablet core: ammoniomethacrylate co-polymer, lactose monohydrate, magnesium stearate, povidone, stearyl alcohol, talc, triacetin.

Tablet coat: hypromellose, macrogol, talc, titanium dioxide.

OxyContin® 5 mg contains Brilliant blue FCF aluminium lake.

OxyContin® 10 mg contains hydroxypropylcellulose and no additional colourant.

OxyContin® 20 mg contains polysorbate and iron oxide red.

OxyContin® 40 mg contains polysorbate and iron oxide yellow.

OxyContin® 80 mg contains hydroxypropylcellulose, iron oxide yellow and indigo carmine.

Contains sugar (lactose monohydrate).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 ºC.

Store in original package in the outer carton in order to protect from light.

6.5 Nature and contents of container

OxyContin® Prolonged Release Tablets are supplied in clear PVC and aluminium foil blister packs of 28.

6.6 Special precautions for disposal <and other handling>

No special requirements

7 HOLDER OF CERTIFICATE OF REGISTRATION

Mundipharma (Pty) Ltd

Block D, Grosvenor Square,

Park Lane,

Century City,

7441

8 REGISTRATION NUMBERS

South Africa: S6

OxyContin® 5 mg Prolonged Release Tablets: 41/2.9/1098

OxyContin® 10 mg Prolonged Release Tablets: 41/2.9/1099

OxyContin® 20 mg Prolonged Release Tablets: 41/2.9/1100

OxyContin® 40 mg Prolonged Release Tablets: 41/2.9/1101

OxyContin® 80 mg Prolonged Release Tablets: 41/2.9/1102

Namibia: NS4

OxyContin® 5 mg Prolonged Release Tablets: 12/2.9/0259

OxyContin® 10 mg Prolonged Release Tablets: 12/2.9/0260

OxyContin® 20 mg Prolonged Release Tablets: 12/2.9/0261

OxyContin® 40 mg Prolonged Release Tablets: 12/2.9/0262

OxyContin® 80 mg Prolonged Release Tablets: 12/2.9/0263

Botswana: S1A

OxyContin® 5 mg Prolonged Release Tablets: BOT1402343

OxyContin® 10 mg Prolonged Release Tablets: BOT1402344

OxyContin® 20 mg Prolonged Release Tablets: BOT1402345

OxyContin® 40 mg Prolonged Release Tablets: BOT1402346

OxyContin® 80 mg Prolonged Release Tablets: BOT1402347

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

9 October 2009

10 DATE OF REVISION OF THE TEXT

12 February 2026

® = OxyContin is a registered trademark.