PROFESSIONAL INFORMATION

SCHEDULING STATUS

S6

1 NAME OF THE MEDICINE

OxyNorm® 5 mg Capsules

OxyNorm® 10 mg Capsules

OxyNorm® 20 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

OxyNorm® 5 mg Capsules contains 5 mg of oxycodone hydrochloride each.

OxyNorm® 10 mg Capsules contains 10 mg of oxycodone hydrochloride each.

OxyNorm® 20 mg Capsules contains 20 mg of oxycodone hydrochloride each.

Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsules, hard.

OxyNorm® 5 mg Capsules (capsule size 4) has an orange body and beige cap imprinted with ONR 5 in black ink, and filled with white to off-white powder.

OxyNorm® 10 mg Capsules (capsule size 4) has a white body and beige cap imprinted with ONR 10 in black ink, and filled with white to off-white powder.

OxyNorm® 20 mg Capsules (capsule size 4) has a pink body and beige cap imprinted with ONR 20 in black ink, and filled with white to off-white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

OxyNorm® Capsules are indicated for the treatment of severe pain requiring the use of a strong opioid analgesic.

4.2 Posology and method of administration

Posology

The need for continued treatment should be assessed at regular intervals.

Treatment goals and discontinuation

Before initiating treatment with OxyNorm® Capsules, 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 medical practitioner 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 OxyNorm® Capsules, 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.

Elderly and adults over 18 years

OxyNorm® Capsules should be taken at 4-6 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 OxyNorm® Capsules.

The correct dosage for any individual patient is that which controls the pain and is well tolerated throughout the dosing period. Patients should be titrated to pain relief unless unmanageable adverse medicine reactions prevent this.

The usual starting dose for opioid naïve patients or patients presenting with severe pain uncontrolled by weaker opioids is 5 mg, 4-6 hourly.

The dose should then be carefully titrated, as frequently as once a day, if necessary, to achieve pain relief. The majority of patients will not require a daily dose greater than 400 mg. However, a few patients may require higher doses.

Transferring patients between pain products

Conversion from oral morphine

Patients receiving oral morphine before OxyNorm® Capsules 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 approximately equivalent to 1 mg of parenteral oxycodone.

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

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

Special populations

Elderly

Controlled pharmacokinetic studies in elderly patients (aged over 65 years) have shown that compared with younger adults, the clearance of OxyNorm® Capsules is only slightly reduced. No untoward adverse medicine 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 OxyNorm® 5 mg Capsules 6 hourly.

Paediatric population

Children under 18 years

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

Method of administration

OxyNorm® Capsules should be swallowed whole and not chewed or crushed.

4.3 Contraindications

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

OxyNorm® Capsules are contraindicated in patients who are pregnant or breastfeeding; or patients on concurrent administration of monoamine oxidase inhibitors or within 2 weeks of discontinuation of their use.

OxyNorm® Capsules are contraindicated in patients suffering from:

- severe respiratory depression with hypoxia and/or hypercapnia;
- head injury;

- paralytic ileus;
- acute abdomen;
- delayed gastric emptying;
- severe chronic obstructive lung disease;
- cor pulmonale;
- chronic bronchial asthma;
- moderate to severe hepatic impairment;
- severe renal impairment (creatinine clearance < 10 ml/min);
- chronic constipation.

4.4 Special warnings and precautions for use

OxyNorm® Capsules should be swallowed whole and not chewed or crushed. Abuse of oral dosage forms through parenteral administration can be expected to result in other serious adverse events that might be fatal.

A reduction in dosage may be advisable in hypothyroidism.

OxyNorm® Capsules should be used with caution in patients with:

- respiratory depression;
- sleep apnoea;
- benzodiazepines, or other CNS depressants co-administration (see below and section 4.5);
- monoamine oxidase inhibitors (MAOIs, see below and section 4.5);
- tolerance, physical dependence and withdrawal (see below);
- psychological dependence (addiction), abuse profile and history of substance and/or alcohol abuse (see below);
- head injury (due to risk of increased intracranial pressure), reduced level of consciousness of uncertain origin;

- 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;
- severe impaired pulmonary function;
- debilitated elderly and infirm patients.

Respiratory depression

The major risk of all opioid excess 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 may increase 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 depressants co-administration

Concomitant use of oxycodone and sedative medicines such as benzodiazepines or related medicines 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 patient 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

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

OxyNorm® Capsules should be used with caution or completely avoided when using certain medicines (refer to section 4.5).

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 OxyNorm® 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 OxyNorm® may result in physical dependence, in which case a withdrawal syndrome may occur following abrupt cessation.

When a patient no longer requires therapy with oxycodone, it is 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 OxyNorm® 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 OxyNorm® 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).

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

Before initiating treatment with OxyNorm® 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.

*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. See Section 4.2 for additional information on treatment goals and discontinuation.

OxyNorm® Capsules should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus occur, or be suspected during use, OxyNorm® Capsules should be discontinued immediately.

Patients who are to undergo cordotomy or other pain relieving surgical procedures should not receive OxyNorm® Capsules for 6 hours before surgery or within the first 12 – 24 hours post-operatively. If further treatment with OxyNorm® Capsules is then indicated, the dosage should be adjusted to the new post-operative requirement.

OxyNorm® Capsules 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 opioid dependent mothers may exhibit withdrawal symptoms and may have respiratory depression at birth (refer to section 4.6).

Constipation may be prevented with an appropriate laxative. If nausea and vomiting are troublesome, OxyNorm® Capsules may be combined with an anti-emetic.

Opioids, such as OxyNorm® Capsules, 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.

Hyperalgesia that will not respond to a further dose increase of oxycodone may occur in particular in high doses. An oxycodone dose reduction or change in opioid may be required.

For more information on tolerance and dependence please refer to section 4.2 as well as section 4.8.

4.5 Interaction with other medicines and other forms of interaction

The concomitant use of opioids with sedative medicines such as benzodiazepines or related medicines 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 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 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 (see section 4.3).

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

OxyNorm® Capsules are not recommended for use in pregnancy nor during labour (see section 4.3). Neonates born to mothers who have received opioids 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. (also refer to section 4.4 and section 4.8).

Breastfeeding

Oxycodone is not recommended as it may be secreted in breast milk and may cause respiratory depression in the newborn. OxyNorm® Capsules should therefore not be used by breastfeeding mothers.

Fertility

No human data on the effect of oxycodone on fertility is 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

OxyNorm® Capsules 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 drug reactions are typical of full opioid agonists. Tolerance and dependence may occur (see Section 4.4, 4.8).

The reactions are listed as MedDRA 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), and 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: mood altered, and personality change (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: concentration impaired, 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: hearing impaired, vertigo

Cardiac disorders

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

Vascular disorders

Uncommon: vasodilatation

Rare: hypotension, hypotension orthostatic

Respiratory, thoracic and mediastinal disorders

Common: dyspnoea

Uncommon: dysphonia, cough, respiratory depression

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, ileus, eructation

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, peripheral oedema, 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

Description of selected adverse reactions

Drug Dependence

The frequency of drug dependence in the above list 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 OxyNorm® 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 opioid tolerance and opioid withdrawal in the above list 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).

Adverse reactions from spontaneous reporting

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care 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: ZADrugSafety@mundipharma.co.za

4.9 Overdose

Signs of oxycodone toxicity and overdosage are miosis, respiratory depression, pulmonary oedema, hypotension and hallucinations. Nausea and vomiting are common in less severe cases. Non-cardiac pulmonary oedema and rhabdomyolysis are particularly common after intravenous injection. 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.

The effects of overdosage will be potentiated by the simultaneous ingestion of alcohol or other psychotropic medicines.

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

In case of massive overdosage (if the patient is in a coma or respiratory depression is present), administer naloxone intravenously (0,4 to 2 mg for an adult and 0,01 mg/kg body weight for children). 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 a less severe overdosage, administer naloxone 0,2 mg intravenously followed by increments of 0,1 mg every 2 minutes if required.

The patient should be observed for at least 6 hours after the last dose of naloxone.

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. Other supportive measures should be employed as needed.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 2.9 Other Analgesics.

ATC code: N02A A05

Oxycodone is a full opioid agonist with no antagonistic 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

Absorption

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

Distribution

Oxycodone is metabolised primarily to noroxycodone and oxymorphone via CYP450-3A and CYP450-2D6 respectively. 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.

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, 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 one 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

Inactive ingredients: gelatine, indigo carmine, iron oxide, magnesium stearate, microcrystalline cellulose, sodium laurylsulphate, Sunset Yellow, and titanium dioxide.

The capsules are sugar free.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 30 °C.

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

6.5 Nature and contents of container

OxyNorm® Capsules are supplied in clear PVdC coated 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, Cape Town,

South Africa

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8 REGISTRATION NUMBER(S)

South Africa: S6

OxyNorm® 5 mg Capsules: 41/2.9/1103

OxyNorm® 10 mg Capsules: 41/2.9/1104

OxyNorm® 20 mg Capsules: 41/2.9/1105

Namibia: NS4

OxyNorm® 5 mg Capsules: 12/2.9/0256

OxyNorm® 10 mg Capsules: 12/2.9/0257

OxyNorm® 20 mg Capsules: 12/2.9/0258

Botswana: S1A

OxyNorm® 5 mg Capsules: BOT1402578

OxyNorm® 10 mg Capsules: BOT1402579

OxyNorm® 20 mg Capsules: BOT1402580

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 August 2009

10 DATE OF REVISION OF THE TEXT

10 September 2026

® = **OxyNorm®** is a registered trademark