PROFESSIONAL INFORMATION

SCHEDULING STATUS

S6

1 NAME OF THE MEDICINE

OxyNorm® 10 mg Injection (Solution for Injection or Infusion)

OxyNorm® 20 mg Injection (Solution for Injection or Infusion)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Qualitative declaration

Oxycodone hydrochloride.

Quantitative declaration

Each OxyNorm® 10 mg Injection contains 10 mg/1 ml of oxycodone hydrochloride equivalent to 9 mg/1 ml oxycodone.

Each OxyNorm® 20 mg Injection contains 20 mg/2 ml of oxycodone hydrochloride equivalent to 18 mg/2 ml oxycodone.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

OxyNorm® 10 mg Injection: 1 ml Type 1 Ph. Eur clear glass ampoules with white break ring and yellow identification ring in cardboard boxes of 5 ampoules per box.

OxyNorm® 20 mg Injection: 2 ml Type 1 Ph. Eur clear glass ampoules with white break ring and red identification ring in cardboard boxes of 5 ampoules per box.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

OxyNorm® Injection is indicated for the short-term treatment of moderate to severe pain in patients with cancer and post-operative pain.

OxyNorm® Injection is indicated for the short-term treatment of severe pain requiring the use of a strong opioid analgesic.

4.2 Posology and method of administration

Posology

The dose should be adjusted according to the severity of pain, the total condition of the patient and previous or concurrent medication.

Adults over 18 years: The following starting doses are recommended. A gradual increase in dose may be required if analgesia is inadequate or if pain severity increases.

i.v. (Bolus): Dilute to 1 mg/ml in 0,9 % saline, 5 % dextrose or water for injections. Administer a bolus dose of 1 to 10 mg slowly over 1-2 minutes. Doses should not be administered more frequently than every 4 hours.

i.v. (Infusion): Dilute to 1 mg/ml in 0,9 % saline, 5 % dextrose or water for injections. A starting dose of 2 mg/hour is recommended.

i.v. (PCA): Dilute to 1 mg/ml in 0,9 % saline, 5 % dextrose or water for injections. Bolus doses of 0,03 mg/kg should be administered with a minimum lock-out time of 5 minutes.

Transferring patients between oral and parenteral oxycodone: The dose should be based on the following ratio: 2 mg of oral oxycodone is approximately 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.

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

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.

Preparation, dilution, administration and disposal:

OxyNorm® Injection must not be mixed with other medicinal products except with the following compatible medicines: hyoscine butylbromide, hyoscine hydrobromide, dexamethasone sodium phosphate, haloperidol, midazolam hydrochloride, metoclopramide hydrochloride, levomepromazine.

OxyNorm® Injection is formulated at acidic pH and is likely to be incompatible with alkaline pH formulations such as Fluoracil (5-FU) which may lead to precipitation.

Cyclizine at concentrations of 3 mg/ml or less, when mixed with OxyNorm® Injection, either undiluted or diluted with water for injections, shows no sign of precipitation over a period of 24 hours storage at room temperature. Precipitation has been shown to occur in mixtures with OxyNorm® Injection and cyclizine at concentrations greater than 3 mg/ml, or when diluted with sterile 0,9 % sodium chloride solution. It is recommended that water for injections is used as a diluent when cyclizine and OxyNorm® Injection are co-administered intravenously as an infusion.

Prochlorperazine is chemically incompatible with OxyNorm® Injection.

Each ampoule is for single use in a single patient. The injection should be given immediately after opening the ampoule and any unused portion shall be discarded. If not used immediately, in-use storage times and conditions prior to use should not be longer than 24 hours at 2 – 8 °C, unless reconstitution, dilution etc. has taken place in controlled and validated aseptic conditions.

OxyNorm® Injection undiluted or diluted to 1 mg/ml with 0,9 % *w/v* saline, 5 % *w/v* dextrose or water for injections, is physically and chemically stable when in contact with respective brands of polypropylene or polycarbonate syringes, polyethylene or PVC tubing and PVC or EVA infusion bags over a 24-hour period at room temperature.

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

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

Special populations

Elderly: Elderly patients should be treated with caution. The lowest dose should be administered with careful titration to pain control.

Adult patients with renal or hepatic impairment: The dose initiation should follow a conservative approach in these patients. The recommended starting dose should be reduced by 50 % and each patient should be titrated to adequate pain control according to their clinical situation (also refer to section 4.4 as well as section 4.3).

Paediatric population

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

Method of administration

OxyNorm® Injection should be administered intravenously as a bolus or infusion.

4.3 Contraindications

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

OxyNorm® Injection is contraindicated in patients suffering from respiratory depression, head injury, paralytic ileus, acute abdomen, delayed gastric emptying, chronic obstructive airways disease, cor pulmonale, chronic bronchial asthma, hypercarbia, moderate to severe hepatic impairment, severe renal impairment (creatinine clearance < 30 ml/min), chronic constipation, pregnancy, concurrent administration of monoamine oxidase inhibitors or within 2 weeks of discontinuation of their use.

4.4 Special warnings and precautions for use

The major risk of OxyNorm® Injection is respiratory depression. A reduction in dosage may be advisable in hypothyroidism.

OxyNorm® Injection should be used with caution in debilitated elderly and infirm patients or patients with opioid dependence, raised intracranial pressure, hypotension, hypovolaemia, toxic psychosis, disease of the biliary tract, pancreatitis, inflammatory bowel disorders, prostatic hypertrophy, adrenocortical insufficiency, alcoholism, delirium tremens, chronic renal and hepatic disease, myxoedema, Addison's disease, reduced level of consciousness of uncertain origin, sleep apnoea, severe pulmonary disease, patients taking benzodiazepines, or other CNS depressants (see below and section 4.5).

Opioids may cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use may increase the risk of CSA in a dose-dependent manner in some patients. 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 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).

OxyNorm® Injection should be used with caution or completely avoided when using certain medicines (refer to section 4.5). OxyNorm® Injection should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected of occurring during use, OxyNorm® Injection should be discontinued immediately.

Tolerance, physical dependence and withdrawal

The patient may develop tolerance to OxyNorm® Injection with chronic use and require progressively higher doses to maintain pain control.

Prolonged use of OxyNorm® Injection may result in physical dependence, in which case a withdrawal syndrome may occur following abrupt cessation. The withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, or increased blood pressure, respiratory rate, or heart rate.

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

OxyNorm® Injection has an abuse profile similar to other strong opioids and should be used with caution in opioid-dependent patients. OxyNorm® Injection may be sought and abused by people with latent or manifest addiction disorders and therefore OxyNorm® Injection should be used with particular care in patients with a history of alcohol and drug abuse.
For appropriate patients who suffer from chronic non-malignant pain, opioids, such as OxyNorm® Injection, should be used as part of a comprehensive treatment programme involving other medications and modalities. A crucial part of the assessment of a patient with chronic non-malignant pain is the patient's addiction and substance abuse history.
There is potential for development of psychological dependence (addiction) to opioid analgesics, including OxyNorm® Injection.

If opioid treatment is considered appropriate for the patient, then the main aim of treatment is not to minimise the dose of opioid but rather to achieve a dose that provides adequate pain relief with minimum side effects.
There must be frequent contact between the doctor and patient so that the dosage adjustments can be made. It is strongly suggested that the doctor defines treatment outcomes in accordance with pain management guidelines. The doctor and patient can then agree to discontinue treatment if these objectives are not met.

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® Injection may be combined with an anti-emetic.

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

OxyNorm® Injection should be used with caution pre- or intra-operatively and within the first 12-24 hours post-operatively.

Opioids may influence the hypothalamic-pituitary-adrenal or gonadal axes. Some changes that can be seen include an increase in serum prolactin and decrease in plasma cortisol and testosterone. Clinical symptoms may manifest from these hormonal changes.

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.

Co-administration with monoamine oxidase inhibitors or within two weeks of discontinuation of their use is inappropriate.
Monoamine oxidase inhibitors are known to interact with narcotic analgesics, producing CNS excitation or depression with hypertensive or hypotensive crisis (refer to section 4.3).

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.

Oxycodone is metabolised in part via the CYP2D6 and CYP3A4 pathways. The activity of these pathways may be inhibited or induced by medicines and/or dietary elements. It might be required to adjust the dose of oxycodone accordingly.

CYP3A4 inhibitors, such as macrolide antibiotics (e.g. clarithromycin), azole-antifungals (e.g. ketoconazole), protease inhibitors (e.g. ritonavir) and grapefruit juice may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations.

CYP3A4 inducers, such as rifampicin, carbamazepine, phenytoin and St. John's Wort, may induce the metabolism of oxycodone and cause increased clearance of oxycodone, resulting in a decrease in oxycodone plasma concentrations.

CYP2D6 inhibitors such as paroxetine and quinidine, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations.

Concomitant administration of oxycodone with serotonin agents, such as a Selective Serotonin Reuptake 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.

OxyNorm® Injection is incompatible with certain diluents and certain parenteral preparations (refer to section 4.2).

4.6 Fertility, pregnancy and lactation

Pregnancy

OxyNorm® Injection is not recommended for the use in pregnancy nor during labour. Infants born to mothers who have received opioids during pregnancy should be monitored for respiratory depression (refer to 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 may be secreted in breast milk and may cause respiratory depression in the newborn. OxyNorm® Injection should therefore not be used by breast-feeding 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

OxyNorm® Injection 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

The reactions are listed as MeDRA preferred term by system organ class and absolute frequency.

Body System	**Frequency of Occurrence**	
	Common *≥ 1 %*	Uncommon *≥ 0,1 % and < 1 %*
Psychiatric disorders	anxiety, confusional state, depression, insomnia, nervousness, thinking disturbances, abnormal dreams	affect lability, agitation, drug dependence, euphoria, hallucinations, libido decreased, disorientation, mood altered, restlessness, dysphoria, aggression
Nervous system disorders	headache, dizziness, sedation, somnolence, tremor, lethargy	amnesia, hypertonia, hypoaesthesia, hypotonia, paraesthesia, speech disorder, convulsions, involuntary muscle contractions, taste perversion, syncope, dysgeusia, hyperalgesia, sleep apnoea syndrome
Immune system disorders		anaphylactic reaction, anaphylactoid reaction, hypersensitivity
Metabolism and nutritional disorders	anorexia / decreased appetite	dehydration
Eye disorders		miosis, visual disturbances
Ear and labyrinth disorders		vertigo

Body System	**Frequency of Occurrence**	
	Common *≥ 1 %*	Uncommon *≥ 0,1 % and < 1 %*
Cardiac disorders		supraventricular tachycardia, palpitations (in the context of withdrawal syndrome)
Vascular disorders		hypotension, orthostatic hypotension, vasodilatation, facial flushing
Respiratory, thoracic and mediastinal disorders	bronchospasm, dyspnoea, decreased cough	respiratory depression, hiccups
Skin and subcutaneous tissue disorders	hyperhidrosis, pruritus, rash	dry skin, exfoliative dermatitis, urticaria
Gastrointestinal disorders	constipation, nausea, vomiting, dry mouth, dyspepsia, abdominal pain, diarrhoea	dysphagia, eructation, flatulence, gastrointestinal disorders, ileus, gastritis, dental caries
Hepato-biliary disorders		biliary colic, increased hepatic enzymes, cholestasis
Musculoskeletal and connective tissue disorders		muscular rigidity
Renal and urinary disorders		urinary retention, urinary spasm

Body System	Frequency of Occurrence	
	Common *≥ 1 %*	Uncommon *≥ 0,1 % and < 1 %*
Reproductive system and breast disorders		amenorrhoea; erectile dysfunction, hypogonadism
General disorders and administration site conditions	asthenia, fatigue	oedema, peripheral oedema, malaise, thirst, pyrexia, drug withdrawal syndrome, chills, tolerance, neonatal opioid withdrawal syndrome

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 asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

Alternatively report to: ZADrugSafety@mundipharma.co.za

4.9 Overdose

Signs of oxycodone toxicity and overdosage are pin-point pupils, respiratory depression, 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 coma, skeletal muscle flaccidity, bradycardia and death may occur in more severe cases.

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 institution of assisted or controlled ventilation.

In case of massive overdosage, 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.

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 dependent 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.

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.

Endocrine system - Please refer to section 4.4.

5.2 Pharmacokinetic properties

Absorption:

Equivalent exposure of oxycodone was demonstrated after administration of OxyNorm® Injection by either subcutaneous- or intravenous route, as a single bolus dose or a continuous infusion over 8 hours respectively.

The analgesic effects of the metabolites are clinically insignificant.

Distribution:

Following administration, oxycodone is distributed throughout the entire body.

Approximately 45 % is bound to plasma protein.

Biotransformation:

Oxycodone is metabolised in the liver principally to noroxycodone via CYP450-3A and oxymorphone via CYP450-2D6 and various conjugated glucuronides.

Elimination:

Oxycodone and its metabolites are excreted in both urine and faeces.

Oxycodone penetrates the placenta and can be found in breast milk (refer to section 4.6).

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.

Patients with renal impairment: 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 oxycodone effects.

Patients with mild to severe hepatic impairment: When compared to normal subjects, patients with mild to severe hepatic dysfunction may have higher plasma concentrations of oxycodone and noroxycodone and lower plasma concentrations of oxymorphone. There may be an increase in the elimination half-life of oxycodone and this may be accompanied by an increase in oxycodone effects.

5.3 Preclinical safety data

5.3.1. 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.

5.3.2. 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: Citric acid monohydrate; sodium citrate, sodium chloride and water for injections.

6.2 Incompatibilities

OxyNorm® Injection must not be mixed with medicinal products that are incompatible. Also see section 4.2 Posology.

OxyNorm® Injection is formulated at acidic pH and is likely to be incompatible with alkaline pH formulations which may lead to precipitation.

Cyclizine at concentrations greater than 3 mg/ml, or when diluted with sterile 0,9 % sodium chloride solution can cause precipitation.

Prochlorperazine is chemically incompatible with OxyNorm® Injection.

6.3 Shelf life

60 months.

6.4 Special precautions for storage

Store at or below 25 ˚C in original package in the outer carton.

For single use only. Discard any unused portion.

Do not refrigerate or freeze.

6.5 Nature and contents of container

OxyNorm® Injection is a clear, colourless solution, practically free from particulates.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Mundipharma (Pty) Ltd

Block D, Grosvenor Square,

Park Lane, Century City,

7441, Cape Town,

South Africa

8 REGISTRATION NUMBER(S)

South Africa: S6

OxyNorm® 10 mg Injection: 46/2.9/0718

OxyNorm® 20 mg Injection: 46/2.9/0719

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 September 2016

10 DATE OF REVISION OF THE TEXT

17 January 2021

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