PACKAGE INSERT

OXYNORM® CAPSULES

SCHEDULING STATUS

S6

PROPRIETARY NAMES and DOSAGE FORM

OxyNorm® 5 mg Capsules

OxyNorm® 10 mg Capsules

OxyNorm® 20 mg Capsules

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.

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

The capsules are sugar free.

PHARMACOLOGICAL CLASSIFICATION

A 2.9 Other Analgesics.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

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 **INDICATIONS**).

Pharmacokinetic properties

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

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. 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.

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.

CONTRAINDICATIONS

OxyNorm® Capsules are contraindicated in patients with known hypersensitivity to oxycodone or to any of the excipients (see **COMPOSITION**) 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.

WARNINGS and SPECIAL PRECAUTIONS

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

The major risk of all opioid excess is respiratory depression.

A reduction in dosage may be advisable in hypothyroidism.

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

- opioid dependence;

- 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
- alcoholism;
- delirium tremens;
- impaired renal or hepatic function;
- severe impaired pulmonary function;
- debilitated elderly and infirm patients.

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 physician is assured of normal bowel function.

For patients who suffer from chronic non-malignant pain, opioids should be used as part of a comprehensive treatment programme involving other medications and treatment modalities.

A crucial part of the assessment of a patient with chronic non-malignant pain is the patient's addiction and substance abuse history.

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

If opioid treatment is considered appropriate for the patient, then the main aim of treatment is not to minimise the dose, but rather to achieve a dose that provides adequate pain relief with minimum side effects.

There must be frequent contact between the physician and the patient so that the dosage adjustments can be made. It is strongly suggested that the physician defines treatment outcomes in accordance with pain management guidelines. The physician and patient can then agree to discontinue treatment if these objectives are not met.

Tolerance and dependence:

The patient may develop tolerance to the medicine with chronic use which will require progressively higher doses to maintain pain control. Prolonged use of **OxyNorm® Capsules** may also lead to physical dependence and a withdrawal syndrome may occur upon abrupt cessation of therapy. When a patient no longer requires therapy with **OxyNorm® Capsules**, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

OxyNorm® Capsules has an abuse liability similar to other strong opioids and may be sought and abused by people with latent or manifest addiction disorders.

There is potential for development of psychological dependence (addiction) to opioid analgesics, including oxycodone. 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 **DOSAGE AND DIRECTIONS FOR USE** as well as **SIDE EFFECTS**.

Effects on the 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.

INTERACTIONS

OxyNorm® Capsules potentiates the effects of tranquillisers, anaesthetics, hypnotics, anti-depressants, sedatives, phenothiazines, neuroleptic medicines, alcohol, other opioids, muscle relaxants and antihypertensives.

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 **CONTRAINDICATIONS**).

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 P450-3A 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 P450-3A 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 P450-3A 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.

PREGNANCY AND LACTATION

OxyNorm® Capsules are not recommended for the use in pregnancy nor during labour (see **CONTRAINDICATIONS**). Infants born to mothers who have received opioids during pregnancy should be monitored for respiratory depression (see **CONTRAINDICATIONS**)**.** Prolonged use of oxycodone during pregnancy can result in neonatal opioid withdrawal syndrome.

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

DOSAGE AND DIRECTIONS FOR USE

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

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.

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. 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.

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 **Pharmacokinetic properties** under **PHARMACOLOGICAL ACTION**).

Children under 18 years:

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

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.

Cessation of therapy:

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 **WARNINGS AND SPECIAL PRECAUTIONS** as well as **SIDE EFFECTS**).

SIDE EFFECTS

Adverse medicine reactions are typical of full opioid agonists.

Tolerance and dependence may also occur (see **WARNINGS AND SPECIAL PRECAUTIONS**).

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

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

Body System	**Frequency of Occurrence**					
	Very Common *> 10 %*	Common *> 1 % and < 10 %*	Uncommon *> 0,1 % and < 1 %*	Rare *> 0,01 % and < 0,1 %*	Very Rare *< 0,01 %*	Not known (cannot be estimated from the available data)
Gastrointestinal disorders	constipation, nausea, vomiting	abdominal pain, diarrhoea, dry mouth, hiccups, dyspepsia	mouth ulceration, stomatitis, flatulence, dysphagia, ileus, eructation	melaena, tooth disorder, gingival bleeding		dental caries
Hepatobiliary disorders			biliary colic, hepatic enzymes increased			cholestasis

Metabolism and nutrition disorders		decreased appetite	dehydration	increased appetite		
Nervous system disorders	headache, dizziness, sedation, somnolence	tremor, lethargy	concentration impaired, migraine, dysgeusia, hypertonia, muscle contractions involuntary, hypo-aesthesia, abnormal coordination, syncope, paraesthesia, amnesia, convulsion, speech disorder			hyperalgesia

Psychiatric disorders		altered mood and personality change (e.g. anxiety, depression), decreased activity, restlessness, psychomotor hyperactivity, nervousness, insomnia, thinking abnormal, confusional state	perception disturbances (e.g. hallucination, derealisation), libido decreased, affect lability, agitation, euphoric mood, medicine dependence			aggression
Infections and infestations				herpes simplex		

Immune system disorders			hypersensitivity			anaphylactic reaction, anaphylactoid reaction
Eye disorders			miosis, visual impairment			
Ear and labyrinth disorders			hearing impaired, vertigo			
Renal and urinary disorders		dysuria, micturition urgency	urinary retention			
Reproductive system and breast disorders			erectile dysfunction, hypogonadism			amenorrhoea
Cardiac disorders			tachycardia, palpitations (in the context of withdrawal syndrome)			
Vascular disorders			vasodilatation	hypotension, orthostatic hypotension		

Respiratory, thoracic and mediastinal disorders		dyspnoea	dysphonia, cough, respiratory depression			
Skin and subcutaneous tissue disorders	pruritus	skin reactions / rash, hyperhidrosis	dry skin	urticaria		
Injury, poisoning and procedural complications			injury from accidents			
General disorders and administration site conditions		asthenia, fatigue	chills, medicine withdrawal syndrome, pain (e.g. chest pain), malaise, oedema, oedema peripheral, thirst, medicine tolerance	weight increase, weight decrease		medicine withdrawal syndrome neonatal

Symptoms of withdrawal:

The opioid abstinence or withdrawal syndrome (see also **WARNINGS AND SPECIAL PRECAUTIONS** as well as **DOSAGE AND DIRECTIONS FOR USE**) 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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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

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.

Naloxone should 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.

IDENTIFICATION

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.

PRESENTATION

OxyNorm® Capsules are supplied in clear PVdC coated PVC and aluminium foil blister packs of 28.

STORAGE INSTRUCTIONS

Store at or below 30 ˚C.

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

Store this medicine out of the reach of children.

REGISTRATION NUMBERS

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: S4

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

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