SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

OxyNorm 5 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 4.5 mg of oxycodone as 5 mg of oxycodone hydrochloride. For excipients, see section 6.1

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard.

Descriptions*:* Opaque white/beige size 4 hard gelatin capsules printed with ONR and 5 in black ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of moderate to severe pain in patients with cancer and post-operative pain. For the treatment of severe pain requiring the use of a strong opioid.

4.2 Posology and method of administration

Route of administration:
Oral

In common with other strong opioids, 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 dosage 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 drug reactions prevent this.

The usual starting dose for opioid naive 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 oxycodone therapy should have their daily dose based on the following ratio: 10 mg of oral oxycodone is equivalent to 20 mg of oral morphine. It must be emphasised that this is a guide to the dose of ***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 oxycodone is only slightly reduced. No untoward adverse drug reactions were seen based on age, therefore adult doses and dosage intervals are appropriate.

Adults with mild to moderate renal impairment and mild hepatic impairment
The plasma concentration in this patient population may be increased. Therefore, dose initiation should follow a conservative approach. The starting dose for opioid naïve patients is 2.5 mg oxycodone 6-hourly, given as ***OxyNorm*** liquid.

Children under 18 years:
OxyNorm capsules should not be used in patients under 18 years.

Use in non-malignant pain:
Opioids are not first-line therapy for chronic non-malignant pain, nor are they recommended as the only treatment. Types of chronic pain which have been shown to be alleviated by strong opioids include chronic osteoarthritic pain and intervertebral disc disease. The need for continued treatment in non-malignant pain should be assessed at regular intervals.

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.

4.3 Contraindications

Hypersensitivity to any of the constituents, respiratory depression, head injury, paralytic ileus, acute abdomen, delayed gastric emptying, chronic obstructive airways disease, cor pulmonale, chronic bronchial asthma, hypercarbia, known oxycodone sensitivity or in any situation where opioids are contraindicated, moderate to severe hepatic impairment, severe renal impairment (creatinine clearance <10 ml/min), chronic constipation, concurrent administration of monoamine oxidase inhibitors or within 2 weeks of discontinuation of their use. Pregnancy.

4.4 Special warnings and precautions for use

The major risk of opioid excess is respiratory depression. As with all narcotics, a reduction in dosage may be advisable in hypothyroidism. Use with caution in opioid- dependent patients and in patients with raised intracranial pressure, hypotension, hypovolaemia, toxic psychosis, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, prostatic hypertrophy, adrenocortical insufficiency, acute alcoholism, delirium tremens, chronic renal and hepatic disease, or severe pulmonary disease, and debilitated elderly and infirm patients. ***OxyNorm*** capsules

should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, ***OxyNorm*** capsules should be discontinued immediately. As with all opioid preparations, patients about to undergo additional pain-relieving procedures (e.g. surgery, plexus blockade) should not receive ***OxyNorm*** capsules for 6 hours prior to the intervention. If further treatment with oxycodone is indicated then the dosage should be adjusted to the new post- operative requirement.

Oxycodone 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 appropriate patients who suffer with 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. There is potential for development of psychological dependence (addiction) to opioid analgesics, including oxycodone. ***OxyNorm*** capsules, like all opioids, 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 of opioid, but rather to achieve a dose which provides adequate pain relief with a minimum of side effects. There must be frequent contact between physician and patient so that dosage adjustments can be made. It is strongly recommended 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.

Sunset yellow, a constituent of the 5mg capsule, can cause allergic-type reactions such as asthma. This is more common in people who are allergic to aspirin.
Oxycodone has an abuse profile similar to other strong opioids. Oxycodone may be sought and abused by people with latent or manifest addiction disorders.

As with other opioids, infants who are born to dependent mothers may exhibit withdrawal symptoms and may have respiratory depression at birth.

The capsules should be swallowed whole, and not chewed or crushed. Abuse of oral dosage forms by parenteral administration can be expected to result in serious adverse events, which may be fatal.

4.5 Interaction with other medicinal products and other forms of interaction

Oxycodone, like other opioids, potentiates the effects of tranquillisers, anaesthetics, hypnotics, anti-depressants, sedatives, phenothiazines, neuroleptic drugs, alcohol, other opioids, muscle relaxants and antihypertensives. Monoamine oxidase inhibitors are known to interact with narcotic analgesics, producing CNS excitation or depression with

hypertensive or hypotensive crisis. Concurrent administration of quinidine, an inhibitor of cytochrome P450-2D6, resulted in an increase in oxycodone C_{max} by 11%, AUC by 13%, and $t_{½}$ elim. by 14%. Also an increase in noroxycodone level was observed, (C_{max} by 50%; AUC by 85%, and $t_{½}$ elim. by 42%). The pharmacodynamic effects of oxycodone were not altered. This interaction may be observed for other potent inhibitors of cytochrome P450-2D6 enzyme. Cimetidine and inhibitors of cytochrome P450-3A such as ketoconazole and erythromycin may inhibit the metabolism of oxycodone.

4.6 Pregnancy and lactation

OxyNorm capsules are not recommended for use in pregnancy nor during labour. Infants born to mothers who have received opioids during pregnancy should be monitored for respiratory depression.

Oxycodone may be secreted in breast milk and may cause respiratory depression in the newborn. ***OxyNorm*** capsules should, therefore, not be used in breast-feeding mothers.

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

Adverse drug reactions are typical of full opioid agonists. Tolerance and dependence may occur (see *Tolerance and Dependence,* below). Constipation may be prevented with an appropriate laxative. If nausea and vomiting are troublesome, oxycodone may be combined with an anti-emetic.

Common (incidence of ≥1%) and uncommon (incidence of ≤1%) adverse drug reactions are listed in the table below.

Body System	Common	Uncommon
Immune system disorders		Anaphylactic reaction Anaphylactoid reaction Hypersensitivity
Metabolism and nutritional disorders	Anorexia	Dehydration
Psychiatric disorders	Anxiety	Affect lability
	Confusional state Insomnia Nervousness Thinking disturbances Abnormal dreams	Agitation Depression Drug dependence Euphoria Hallucinations

		Disorientation Mood altered Restlessness Dysphoria
Nervous system disorders	Headache	Amnesia
	Dizziness Sedation Somnolence	Hypertonia Tremor Hypoaesthesia Hypotonia Paraesthesia Speech disorder Convulsions Muscle contractions involuntary Taste perversion Syncope
Eye disorders		Miosis
		Visual disturbance
Ear and labyrinth disorders		Vertigo
Cardiac disorders		Supraventricular tachycardia
Vascular disorders		Hypotension
		Orthostatic hypotension Vasodilatation Facial flushing
Respiratory, thoracic and mediastinal disorders	Bronchospasm	Respiratory depression
	Dyspnoea Cough decreased	Hiccups
Gastrointestinal disorders	Constipation	Dysphagia
	Nausea	Eructation

Body System	Common	Uncommon
	Vomiting Dry mouth Dyspepsia Abdominal pain Diarrhoea	Flatulence Gastrointestinal disorders Ileus Gastritis
Hepato-biliary disorders		Biliary colic Increased hepatic enzymes
Skin and subcutaneous tissuedisorders	Hyperhidrosis	Dry skin
	Pruritus Rash	Exfoliative dermatitis Urticaria
Musculoskeletal and connective tissue disorders		Muscular rigidity
Renal and urinary disorders		Urinary retention Ureteral spasm
Reproductive system and breast disorders		Amenorrhoea Libido decreased Erectile dysfunction
General disorders and administration site conditions	Asthenia Chills	Drug tolerance Oedema Oedema peripheral Malaise Thirst Pyrexia Drug withdrawal syndrome

Tolerance and Dependence:
The patient may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain control. Prolonged use of ***OxyNorm*** capsules may lead to physical dependence and a withdrawal syndrome may occur upon abrupt cessation of therapy. When a patient no longer requires therapy with oxycodone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. The opioid abstinence or withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis, and palpitations. Other symptoms also 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare providers are asked to report any suspected adverse reactions to the marketing authorization holder or if available via the national reporting system (See details below);

Paper based reporting: TMDA yellow card
Online reporting: https://sqrt.tmda.go.tz/
*USSD reporting: send a simple short text message to report any suspected Adverse Drug Reaction by dialing *152*00# and follow the instructions*.

4.9 Overdose

Signs of oxycodone toxicity and overdosage are pin-point pupils, respiratory depression and hypotension. Circulatory failure and somnolence progressing to stupor or deepening coma, skeletal muscle flaccidity, bradycardia and death may occur in more severe cases.

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

In the 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 2minute intervals if there is no response. If repeated 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 dependent 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.
- Gastric contents may need to be emptied as this can be useful in removing unabsorbed drug.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids ATC code: N02A A05
Oxycodone is a full opioid agonist with no antagonist properties. It has an affinity for kappa, mu and delta opiate receptors in the brain and spinal cord. The therapeutic effect is mainly analgesic, anxiolytic and sedative.

5.2 Pharmacokinetic properties

Compared with morphine, which has an absolute bioavailability of approximately 30%, oxycodone has a high absolute bioavailability of up to 87% following oral administration. Oxycodone has an elimination half-life of approximately 3 hours and is metabolised principally to noroxycodone via CYP450-3A and oxymorphone via CYP450-2D6. Oxymorphone has some analgesic activity but is present in the plasma in low concentrations and is not considered to contribute to oxycodone's pharmacological effect.

5.3 Preclinical safety data

Oxycodone was not mutagenic in the following assays: Ames Salmonella and *E. coli* test with and without metabolic activation at doses of up to 5000 µg, chromosomal aberration test in human lymphocytes (in the absence of metabolic activation and with activation after 48 hours of exposure) at doses of up to 1500 µg g/ml, and in the *in vivo* bone marrow micronucleus assay in mice (at plasma levels of up to 48 µg g/ml). Mutagenic results occurred in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 µg g/ml) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 µg g/ml or greater with metabolic activation and at 400 µg/ml or greater without metabolic activation. The data from these tests indicate that the genotoxic risk to humans may be considered low.

Studies of oxycodone in animals to evaluate its carcinogenic potential have not been conducted owing to the length of clinical experience with the drug substance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, microcrystalline Magnesium stearate Titanium dioxide (E171) Iron oxide (E172)
Indigo carmine (E132) Sunset Yellow (E110) Sodium laurylsulphate Gelatin

The capsules are printed with ink containing shellac, iron oxide (E172) and propylene glycol.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

PVdC coated PVC blister packs with aluminium backing foil. Polypropylene containers with polyethylene lids.

PVC/PVdC blister of 4 x 14's

6.6 Instructions for use/handling

None stated.

6.7 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Napp Pharmaceuticals Limited
Cambridge Science Park, Milton Road, Cambridge, CB4 OGW
United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

TAN 20 HM 0490

9 DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

25/09/2020

10 DATE OF REVISION OF THE TEXT