SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

OxyNorm 10 mg/ml, solution for injection or infusion

2. Qualitative and Quantitative Composition

Oxycodone hydrochloride 10 mg/ml
(equivalent to 9 mg/ml oxycodone)

For excipients, see section 6.1

3. Pharmaceutical Form

Solution for injection or infusion.

4. Clinical Particulars

4.1. Therapeutic indications

For the treatment of moderate to severe pain in patients with cancer and post-operative pain.

4.2. Posology and method of administration

Route of administration:

Subcutaneous injection or infusion
Intravenous injection or infusion.

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.

s.c. (Bolus): Use as 10 mg/ml concentration. A starting dose of 5 mg is recommended, repeated at 4-hourly intervals as required.

s.c. (Infusion): Dilute in 0.9% saline, 5% dextrose or water for injections if required. A starting dose of 7.5 mg/day is recommended in opioid naïve patients, titrating gradually according to symptom control. Cancer patients transferring from oral oxycodone may require much higher doses (see below).

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

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

Patients with renal and hepatic impairment:
Patients with mild to moderate renal impairment and/or mild hepatic impairment should be treated with caution. The lowest dose should be given with careful titration to pain control.

Children under 18 years:
There are no data on the use of ***OxyNorm*** injection in patients under 18 years of age.

4.3. Contraindications

OxyNorm injection is contraindicated in patients with known hypersensitivity to oxycodone or any of the other constituents; respiratory depression; head injury; paralytic ileus; acute abdomen; chronic obstructive airways disease; cor pulmonale; chronic bronchial asthma; hypercarbia; 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 opioids, a reduction in dosage may be advisable in hypothyroidism. Use with caution in patients with raised intracranial pressure, hypotension, hypovolaemia, toxic psychoses, diseases of the biliary tract, inflammatory bowel disorders, prostatic hypertrophy, adrenocortical insufficiency, acute alcoholism, delerium tremens, pancreatitis, chronic renal and hepatic disease or severe pulmonary disease and debilitated, elderly and infirm patients. ***OxyNorm*** injection should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, ***OxyNorm*** injection should be discontinued immediately.

The patient may develop tolerance to oxycodone with chronic use and require progressively higher doses to maintain pain control. The patient may develop physical dependence in which case an abstinence syndrome may be seen following abrupt cessation.

Oxycodone has an abuse liability similar to other strong opioids and should be used with caution in opioid dependent patients.

4.5. Interactions with other medicinal products and other forms of interaction

There is an enhanced CNS depressant effect with drugs such as tranquillisers, anaesthetics, hypnotics, sedatives, alcohol, muscle relaxants and antihypertensives. Monoamine oxidase inhibitors are known to interact with narcotic analgesics, producing CNS excitation or depression with hypertensive or hypotensive crisis.

Oxycodone is metabolised in part via the CYP2D6 and CYP3A4 pathways. While these pathways may be blocked by a variety of drugs, such blockade has not yet been shown to be of clinical significance with this agent.

4.6 Pregnancy and lactation

The effect of oxycodone in human reproduction has not been adequately studied. No studies on fertility or the post-natal effects of intrauterine exposure have been carried out. However, studies in rats and rabbits with oral doses of oxycodone equivalent to 3 and 47 times an adult dose of 160 mg/day respectively, did not reveal evidence of harm to the foetus due to oxycodone. ***OxyNorm*** injection is not recommended for use in pregnancy.

Oxycodone may be secreted in breast milk and may cause respiratory depression in the newborn. Oxycodone 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. Constipation may be prevented with an appropriate laxative. If nausea or vomiting are troublesome, oxycodone may be combined with an antiemetic.

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

Body System	**Common**	**Uncommon**
Gastrointestinal	Constipation Nausea Vomiting Dry mouth Anorexia Dyspepsia Abdominal pain Diarrhoea	Biliary spasm Dysphagia Eructation Flatulence Gastrointestinal disorders Ileus Taste perversion Gastritis Hiccups
Central Nervous System	Headache Confusion Asthenia Faintness Dizziness Sedation Anxiety Abnormal dreams Nervousness Insomnia Thought abnormalities Drowsiness Twitching	Vertigo Hallucinations Disorientation Mood changes Restlessness Agitation Depression Tremor Withdrawal syndrome Amnesia Hypoaesthesia Hypertonia Hypotonia Malaise Paraesthesia Speech disorder Euphoria Dysphoria Seizure Vision abnormalities

Genitourinary		Urinary retention Ureteric spasm Impotence Amenorrhoea Decreased libido
Cardiovascular	Orthostatic hypotension	Palpitations Supraventricular tachycardia Hypotension Syncope Vasodilation
Metabolic and Nutritional		Dehydration Oedema Peripheral oedema Thirst
Respiratory	Bronchospasm Dyspnoea Decreased cough reflex	Overdose may produce respiratory depression
Dermatological	Rash Pruritus	Dry skin Exfoliative dermatitis Urticaria
General	Sweating Chills	Facial flushing Miosis Allergic reaction Fever

4.9. Overdose

Symptoms of overdosage
Signs of oxycodone toxicity and overdosage are pin-point pupils, respiratory depression and hypotension. Circulatory failure and somnolence progressing to stupor or coma, skeletal muscle flaccidity, 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 institution of assisted or controlled ventilation.

In the case of massive overdosage, administer naloxone 0.8 mg intravenously. Repeat at 2-3 minute intervals as necessary, or by an infusion of 2 mg in 500 ml of normal saline or 5% dextrose (0.004 mg/ml).

The infusion should be run at a rate related to the previous bolus doses administered and should be in accordance with the patient's response.

However, because the duration of action of naloxone is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established. Monitoring for a further 24-48 hours is then recommended in case of possible relapse.

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.

5. Pharmacological Properties

5.1. Pharmacodynamic properties

N02A A05 Narcotic analgesic

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

5.2. Pharmacokinetic properties

Pharmacokinetic studies in healthy subjects demonstrated an equivalent availability of oxycodone from ***OxyNorm*** injection when administered by the intravenous and subcutaneous routes, as a single bolus dose or a continuous infusion over 8 hours.

Following absorption, oxycodone is distributed throughout the entire body. Approximately 45% is bound to plasma protein. It is metabolised in the liver to produce noroxycodone, oxymorphone and various conjugated glucuronides. The analgesic effects of the metabolites are clinically insignificant.

The active drug and its metabolites are excreted in both urine and faeces.

The plasma concentrations of oxycodone are only minimally affected by age, being 15% greater in elderly as compared to young subjects.

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis.

The drug penetrates the placenta and can be found in breast milk.

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 drug effects.

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 drug effects.

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/ml, and in the *in vivo* bone marrow micronucleus assay in mice (at plasma levels of up to 48 μg/ml). Mutagenic results occurred in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 μg/ml) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 μg/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

Citric acid monohydrate
Sodium citrate
Sodium chloride
Hydrochloric acid, dilute
Sodium hydroxide
Water for injections

6.2. Incompatibilities

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 at cyclizine concentrations greater than 3 mg/ml or when diluted with 0.9% saline.
It is recommended that water for injections be used as a diluent when cyclizine and oxycodone hydrochloride are co-administered either intravenously or subcutaneously as an infusion.

Prochlorperazine is chemically incompatible with ***OxyNorm*** injection.

6.3. Shelf life

3 years unopened.
After opening use immediately.
For further information see section 6.6.

6.4. Special precautions for storage

No special precautions for storage prior to opening.
For further information on use after opening see section 6.6.

6.5. Nature and contents of container

Clear glass ampoules: 1 ml and 2 ml.

Pack sizes: 5 ampoules.

6.6. Instruction for use and handling

The injection should be given immediately after opening the ampoule. Once opened any unused portion should be discarded. Chemical and physical in-use stability has been demonstrated for 24 hours at room temperature.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 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 representative 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 undiluted or diluted 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.

7. Marketing Authorisation Holder

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8. Marketing Authorisation Number

PL 16950/0128

9. Date of First Authorisation

10. Date of Revision of the Text