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OxyNorm 10 mg/ml solution for injection or infusion

Table of Contents

- 1. NAME OF THE MEDICINAL PRODUCT**
- 2. QUALITATIVE AND QUANTITATIVE COMPOSITION**
- 3. PHARMACEUTICAL FORM**
- 4. CLINICAL PARTICULARS**
 - 4.1 Therapeutic indications**
 - 4.2 Posology and method of administration**
 - 4.3 Contraindications**
 - 4.4 Special warnings and precautions for use**
 - 4.5 Interaction with other medicinal products and other forms of interaction**
 - 4.6 Pregnancy and lactation**
 - 4.7 Effects on ability to drive and use machines**
 - 4.8 Undesirable effects**
 - 4.9 Overdose**
- 5. PHARMACOLOGICAL PROPERTIES**
 - 5.1 Pharmacodynamic properties**
 - 5.2 Pharmacokinetic properties**
 - 5.3 Preclinical safety data**
- 6. PHARMACEUTICAL PARTICULARS**
 - 6.1 List of excipients**
 - 6.2 Incompatibilities**
 - 6.3 Shelf life**
 - 6.4 Special precautions for storage**
 - 6.5 Nature and contents of container**
 - 6.6 Special precautions for disposal and other handling**
- 7. MARKETING AUTHORISATION HOLDER**
- 8. MARKETING AUTHORISATION NUMBER(S)**
- 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
- 10. DATE OF REVISION OF THE TEXT**
- 11. LEGAL CATEGORY**

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. For the treatment of severe pain requiring the use of a strong opioid.

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.

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



OxyNorm injection is contraindicated in patients with known hypersensitivity to oxycodone or any of the other constituents, or in any situation where opioids are contraindicated; 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, delirium 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.

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. **OxyNorm** injection 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.

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

4.5 Interaction with other medicinal products and other forms of interaction



There is an enhanced CNS depressant effect with drugs such as 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.


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 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. 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 (see Tolerance and Dependence, below). Constipation may be prevented with an appropriate laxative. If nausea or vomiting are troublesome, oxycodone may be combined with an antiemetic.

Common (incidence of $\geq 1\%$) and uncommon (incidence of $\leq 1\%$) adverse drug reactions to oxycodone are listed in the table below.

Body System	Common	Uncommon
Gastrointestinal	Constipation	Biliary spasm
	Nausea	Dysphagia
	Vomiting	Eructation
	Dry mouth	Flatulence
	Anorexia	Gastrointestinal disorders
	Dyspepsia	Ileus
	Abdominal pain	Taste perversion

	Diarrhoea	Gastritis
		Hiccups
Central Nervous System	Headache	Vertigo
	Confusion	Hallucinations
	Asthenia	Disorientation
	Faintness	Mood changes
	Dizziness	Restlessness
	Sedation	Agitation
	Anxiety	Depression
	Abnormal dreams	Tremor
	Nervousness	Withdrawal syndrome
	Insomnia	Amnesia
	Thought abnormalities	Hypoaesthesia
	Drowsiness	Hypertonia

	Twitching	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	Overdose may produce respiratory depression
	Dyspnoea	
	Decreased cough reflex	

Dermatological	Rash	Dry skin
	Pruritus	Exfoliative dermatitis
		Urticaria
General	Sweating	Facial flushing
	Chills	Miosis
		Allergic reaction
		Fever
		Anaphylaxis

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** injection 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 and mydriasis. 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.

The development of psychological dependence (addiction) to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of psychological dependence (addiction) in chronic pain patients.

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

4.9 Overdose



Symptoms of overdosage

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 of opioid analgesics. 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 drugs

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 intravenously (0.4 to 2mg for an adult and 0.01mg/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 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.

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.

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 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.

Opioids 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 be manifest from these hormonal changes.

In vitro and animal studies indicate various effects of natural opioids, such as morphine, on components of the immune system; the clinical significance of these findings is unknown. Whether oxycodone, a semisynthetic opioid, has immunological effects similar to morphine is unknown.

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 mg, 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 mg/ml, and in the *in vivo* bone marrow micronucleus assay in mice (at plasma levels of up to 48 mg/ml). Mutagenic results occurred in the presence of metabolic activation in the human chromosomal aberration test

(at greater than or equal to 1250 mg/ml) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 mg/ml or greater with metabolic activation and at 400 mg/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

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

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 size: 5 ampoules.

6.6 Special precautions for disposal and other 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 has been shown to be **compatible** with the following drugs:

Hyoscine butylbromide

Hyoscine hydrobromide

Dexamethasone sodium phosphate

Haloperidol

Midazolam hydrochloride

Metoclopramide hydrochloride

Levomepromazine hydrochloride

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(S) 

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14 April 2003

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May 2007


11. LEGAL CATEGORY 

CD (Sch 2) POM

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<http://emc.medicines.org.uk/emc/assets/c/html/displaydoc.asp?documentid=12151>

SUPPORTING INFORMATION 

Patient Information Leaflet:

[OxyNorm 10 mg/ml solution for injection or infusion](#)

Alternative format PIL:

[View X-PIL \(new window\)](#)