OxyNorm® Sterile Solution for Injection or Infusion

NAME OF THE MEDICINAL PRODUCT

OxyNorm® 10 mg/ml, solution for injection or infusion

QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

PHARMACEUTICAL FORM
Clear, colourless, sterile solution for injection or infusion.

CLINICAL PARTICULARS
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.

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:
The dose initiation should follow a conservative approach in these patients. The recommended adult starting dose should be reduced by 50% (for example a total daily dose of 10 mg orally in opioid naïve patients), and each patient should be titrated to adequate pain control according to their clinical situation.
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.

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.

Special warnings and precautions for use
The major risk of opioid excess is respiratory depression. Caution must be exercised when administering oxycodone to the debilitated elderly; patients with severely impaired pulmonary function, patients with impaired hepatic or renal function; patients with myxedema, hypothyroidism, Addison's disease, toxic psychosis, prostate hypertrophy, adrenocortical insufficiency, alcoholism, delirium tremens, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, hypotension, hypovolaemia, raised intracranial pressure, head injury (due to risk of increased intracranial pressure), reduced level of consciousness of uncertain origin, sleep apnoea or patients taking benzodiazepines, other CNS depressants (including alcohol) or Monoamine oxidase (MAO) inhibitors.

<u>Sleep related breathing disorders</u>
Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. Opioids may also cause worsening of pre-existing sleep apnoea (see *Undesirable effects*). In patients who present with CSA, consider decreasing the total opioid dosage.

Concomitant use of oxycodone and sedative medicines such as benzodiazepines may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs with opioids should be reserved for patients for whom alternative treatment options are not possible.
If a decision is made to prescribe benzodiazepines concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in *Posology and method of administration*).
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 environment to be aware of these symptoms (see *Interaction with other medicinal products and other forms of interaction*).

As with all opioids, a reduction in dosage may be advisable in hypothyroidism. Use with caution in patients with infirm patients.
OxyNorm® injection must be administered with caution in patients taking MAOIs or who have received MAOIs within the previous two weeks.

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.

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

As with all opioid preparations, oxycodone products 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. ***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.

<u>Drug dependence, tolerance and potential for abuse</u>
Opioid Use Disorder (abuse and dependence)
Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as oxycodone. Iatrogenic addiction following therapeutic use of opioids is known to occur.

Repeated use of ***OxyNorm***® injection may lead to Opioid Use Disorder (OUD). Abuse or intentional misuse of ***OxyNorm***® injection may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Patients will require monitoring for signs of drug-seeking behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.
A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Tolerance
Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse or addiction.

The clinical need for analgesic treatment should be reviewed regularly.

Drug withdrawal syndrome
Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with oxycodone.

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

If women take this drug during pregnancy there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

Oxycodone has an abuse profile similar to other strong opioids. Oxycodone 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. ***OxyNorm***® injection should be used with particular care in patients with a history of alcohol and drug abuse.

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

Hyperalgesia
Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and

less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

Concomitant use of alcohol and ***OxyNorm***® injection may increase the undesirable effects of ***OxyNorm***® injection; concomitant use should be avoided.

Opioids, such as oxycodone hydrochloride, 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 manifest from these hormonal changes.

Interaction with other medicinal products and other forms of interaction

The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs such with opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited (see *Special warnings and precautions for use*).

Drugs which affect the CNS include, but are not limited to: other opioids, gabapentinoids such as pregabalin, anxiolytics, hypnotics and sedatives (including benzodiazepines), antipsychotics, tranquillisers, anaesthetics, hypnotics, anti-depressants, non-benzodiazepine sedatives, phenothiazines, neuroleptic drugs, alcohol, other opioids, muscle relaxants and antihypertensives.

Concomitant administration of oxycodone with serotonin agents, such as a Selective Serotonin Re-uptake 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.

Concomitant administration of oxycodone with anticholinergics or medicines with anticholinergic activity (e.g. tricyclic anti-depressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects. Oxycodone should be used with caution and the dosage may need to be reduced in patients using these medications.

Monoamine oxidase inhibitors are known to interact with narcotic analgesics.MAO inhibitors cause CNS excitation or depression with hypertensive or hypotensive crisis. *(See Special warnings and precautions for use)* Co-administration with monoamine oxidase inhibitors or within two weeks of discontinuation of their use should be avoided.

Alcohol may enhance the pharmacodynamic effects of ***OxyNorm***® injection, concomitant use should be avoided.

Oxycodone is metabolised mainly by CYP3A4, with a contribution from CYP2D6. The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs or dietary elements.

CYP3A4 inhibitors, such as macrolide antibiotics (e.g. clarithromycin, erythromycin and telithromycin), azole-antifungals (e.g. ketoconazole, voriconazole, itraconazole, and posaconazole), protease inhibitors (e.g. boceprevir, ritonavir, indinavir, nelfinavir and saquinavir), cimetidine and grapefruit juice may cause a reduced clearance of oxycodone that could cause an increase of the plasma concentrations of oxycodone. Therefore the oxycodone dose may need to be adjusted accordingly.

Some specific examples are provided below:
• Itraconazole, a potent CYP3A4 inhibitor, administered 200 mg orally for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 2.4 times higher (range 1.5 - 3.4).
• Voriconazole, a CYP3A4 inhibitor, administered 200 mg twice-daily for four days (400 mg given as first two doses), increased the AUC of oral oxycodone. On average, the AUC was approximately 3.6 times higher (range 2.7 - 5.6).
• Telithromycin, a CYP3A4 inhibitor, administered 800 mg orally for four days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.8 times higher (range 1.3 – 2.3).

• Grapefruit Juice, a CYP3A4 inhibitor, administered as 200 ml three times a day for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.7 times higher (range 1.1 – 2.1).

CYP3A4 inducers, such as rifampicin, carbamazepine, phenytoin and St John´s Wort may induce the metabolism of oxycodone and cause an increased clearance of oxycodone that could cause a reduction of the plasma concentrations of oxycodone. The oxycodone dose may need to be adjusted accordingly.

Some specific examples are provided below:
• St Johns Wort, a CYP3A4 inducer, administered as 300 mg three times a day for fifteen days, reduced the AUC of oral oxycodone. On average, the
AUC was approximately 50% lower (range 37-57%).
• Rifampicin, a CYP3A4 inducer, administered as 600 mg once-daily for seven days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 86% lower

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

Fertility, pregnancy and lactation

Pregnancy
The effect of oxycodone in human reproduction has not been adequately studied. Infants born to mothers who have received opioids during the last 3 to 4 weeks before giving birth pregnancy should be monitored for respiratory depression. Withdrawal symptoms may be observed in the newborn of mothers undergoing treatment with oxycodone. If opioid use is required for a prolonged period in pregnant women, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

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. Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Breastfeeding
Oxycodone may be secreted in breast milk and may cause respiratory depression in the newborn. Oxycodone should therefore not be used in breastfeeding mothers.

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.

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

Body System

Immune system disorders	
Uncommon	Anaphylactic reaction, anaphylactoid reaction, Hypersensitivity
Gastrointestinal	
Very common	Constipation, nausea, vomiting.
Common	dry mouth, dyspepsia, abdominal pain, diarrhoea
Uncommon	Dysphagia, eructation, flatulence, gastrointestinal disorders, ileus, gastritis,
Hepato-biliary disorders	
Uncommon	Biliary colic, increased hepatic enzymes
Musculoskeletal and connective tissue disorders	
Common	
Uncommon	Muscular rigidity
Psychiatric disorders	
Common	Anxiety, confusional state, depression, insomia, nervousness, abnormal thinking, abnormal dreams
Uncommon	Affect lability, agitation, drug dependence, euphoric mood, hallucinations, decreased libido, disorientation, mood altered, restlessness, dysphoria
Eye Disorders	
Uncommon	Miosis, visual impairment
Ear and labyrinth disorders	
Uncommon	Vertigo
Cardiac disorders	
Common	orthostatic hypotension
Uncommon	Palpitation, supraventricular tachycardia, hypotension,
Metabolism and nutrition disorders	
Common	Decreased appetite
Uncommon	Dehydration
Respiratory, thoracic and mediastinal disorders	
Common	Bronchospasm, dyspnoea, cough decreased
Uncommon	Respiratory depression, hiccups
Skin and subcutaneous tissue disorders	

Very common	Pruritus
Common	Rash, hyperhidrosis
Uncommon	Dry skin, exfoliative dermatitis, urticaria
General disorders and administration site conditions	
Common	asthenia, fatigue
Uncommon	Pyrexia, oedema, peripheral oedema, thirst, malaise, drug withdrawal syndrome, drug tolerance, chills
Nervous system disorders	
Very common	Somnolence, dizziness, headache.
Common	Tremor, lethargy, sedation.
Uncommon	Amnesia, convulsion, hypertonia, hypoaesthesia, involuntary muscle contractions, speech disorder, syncope, paraesthesia, dysgeusia, hypotonia.
Vascular disorders	
Uncommon	Vasodilatation, facial flushing
Renal and urinary disorders	
Uncommon	Urinary retention, ureteral spasm.
Reproductive system and breast disorders	
Uncommon	Erectile dysfunction, hypogonadism, amenorrhea.

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, 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.

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.

Overdose
Symptoms of overdosage
Acute overdose with oxycodone can be manifested by miosis, 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. The pure opioid antagonists such as naloxone are specific antidotes against symptoms from opioid overdose. Other supportive measures should be employed as needed.

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.

PHARMACOLOGICAL PROPERTIES

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 manifested 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.

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.

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 mcg, 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 mcg/ ml, and in the in vivo bone marrow micronucleus assay in mice (at plasma levels of up to 48 mcg/ml). Mutagenic results occurred in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 mcg/ml) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 mcg/ml or greater with metabolic activation and at 400 mcg/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.

PHARMACEUTICAL PARTICULARS

Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned below under “Special precautions for disposal”.

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.

Shelf life
5 years unopened.
After opening use immediately.
For further information see below under “Special precautions for disposal”.

Special precautions for storage
Keep in a cool dry place below 30°C.
For further information on use after opening see below under “Special precautions for disposal”.

Nature and contents of container
Clear glass ampoules: 1 ml and 2 ml.
Pack size: 5 ampoules.

Special precautions for disposal
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 below 25ºC.

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 below 25ºC.

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.

MARKETING AUTHORISATION HOLDER

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