SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Oxycodone Molteni 50 mg/ml solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Oxycodone Molteni 50 mg/ml (equivalent to 45 mg of oxycodone base).

Each 1 ml ampoule contains 50 mg of oxycodone hydrochloride.

Excipients with known effect:

This medicinal product contains 0.038 mmol sodium (0.874 mg) per ml.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion.

A clear, colourless solution with a pH between 4.5-5.5.

The osmolality is between 267-310 mOsm/Kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults over 18 years

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

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 for opioid-naïve patients. The initial dose should be adjusted to previous or concurrent medication (especially if the patient has been treated with other opioids before), the total condition of the patient, and the severity of pain. A gradual increase in dose may be required if analgesia is inadequate or if pain severity increases.

- **i.v. (bolus):** Dilute in 0.9% saline, 5% dextrose or water for injections. Administer a bolus dose of 1 to 10 mg slowly over 1-2 minutes in opioid-naïve patients.

  Doses should not be administered more frequently than every 4 hours.

- **i.v. (infusion):** Dilute in 0.9% saline, 5% dextrose or water for injections. A starting dose of 2 mg/hour is recommended for opioid-naïve patients.

- **i.v. (PCA):** Dilute 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 for opioid-naïve patients.

- **s.c. (Bolus)**: Dilute in 0.9% saline, 5% dextrose or water for injections. A starting dose of 5 mg is recommended at 4-hourly intervals as required for opioid-naïve patients.

- **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 or 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.

  Pediatric population:

  There are no data on the use of Oxycodone 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.

  <u>Method of administration</u>

  Subcutaneous injection or infusion.

Intravenous injection or infusion.

Treatment goals and discontinuation

Before initiating treatment with Oxycodone Molteni, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider

discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with

oxycodone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In

absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of

underlying disease should be considered (see section 4.4).

Duration of treatment:

Oxycodone should not be used for longer than necessary.

For instruction on dilution of the medicinal product before administration, see section 6.6

4.3 Contraindications

Oxycodone injection is contraindicated in patients with known hypersensitivity to oxycodone or any of the excipients listed in section 6.1.

Oxycodone must not be used in any situation where opioids are contraindicated: severe respiratory depression with hypoxia; paralytic ileus; acute abdomen; severe chronic obstructive lung disease; cor pulmonale; severe bronchial asthma; elevated carbon dioxide levels in the blood; moderate to severe hepatic impairment; chronic constipation.

4.4 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 myxoedema, 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) or patients taking benzodiazepines, other CNS depressants (including alcohol) or MAO inhibitors.

Oxycodone injection should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, Oxycodone injection should be discontinued immediately (see section 4.3).
Oxycodone 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.
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.
The patient may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain control. Prolonged use of this product 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.

Hyperalgesia that will not respond to a further dose increase of oxycodone may occur, particularly in high doses. An oxycodone dose reduction or change to an alternative opioid may be required.

Hepatobiliary disorders

Oxycodone may cause dysfunction and spasm of the sphincter of Oddi, thus increasing the risk of biliary tract symptoms and pancreatitis. Therefore, oxycodone has to be administered with caution in patients with pancreatitis and diseases of the biliary tract.

Opioid Use Disorder (abuse and dependence)

Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as oxycodone.

Repeated use of Oxycodone Molteni may lead to Opioid Use Disorder (OUD). A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of Oxycodone Molteni 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).

Before initiating treatment with Oxycodone Molteni and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician.

Patients will require monitoring for signs of drug-seeking behavior (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.

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

Concomitant use of Oxycodone Molteni and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are

not possible. If a decision is made to prescribe Oxycodone Molteni concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.
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 caregivers to be aware of these symptoms (see section 4.5).

Sleep-related breathing disorders
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. In patients who present with CSA, consider decreasing the total opioid dosage.

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

4.5 Interaction with other medicinal products and other forms of interaction

The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).
Drugs which affect the CNS include, but are not limited to: tranquillisers, anaesthetics, hypnotics, anti-depressants, non-benzodiazepine sedatives, phenothiazines, neuroleptic drugs, alcohol, other opioids, muscle relaxants and antihypertensives.
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 (MAOIs) are known to interact with narcotic analgesics. MAOIs cause CNS excitation or depression associated with hypertensive or hypotensive crisis (see section 4.4).
Alcohol may enhance the pharmacodynamic effects of Oxycodone 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.

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 serotoin 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.

4.6 Fertility, Pregnancy and lactation

Pregnancy

There are limited data from the use of oxycodone in pregnant women. 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.

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 fetus due to oxycodone

Oxycodone Molteni injection is not recommended for use in pregnancy nor during labour..

Breast-feeding

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.

Fertility

No information on fertility is available in humans. Studies in animals showed no effects on fertility.

4.7 Effects on ability to drive and use machines

Oxycodone may impair the ability to drive and use machines. Oxycodone may modify patients' reactions to a varying extent depending on the dosage and individual susceptibility. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

Adverse drug reactions are typical of full opioid agonists. Tolerance and dependence may occur (see Section 4.4). Constipation may be prevented with an appropriate

laxative. If nausea or vomiting are troublesome, oxycodone may be combined with an antiemetic.

Adverse reactions reported either spontaneously or observed in clinical trials are depicted in the following table. Within each system organ class, the adverse drug reactions are ranked under headings of frequency, using the following convention: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), not known (cannot be estimated from the available data).

System Organ Class	**Frequency**	**Adverse Reaction**
Immune system disorders	Uncommon	Hypersensitivity.
	Frequency not known	Anaphylactic responses, anaphylactoid reaction.
Metabolism and nutritional disorders	Common	Anorexia (decreased appetite).
	Uncommon	Dehydration.
Psychiatric disorders	Common	Anxiety, confusional state, depression, insomnia, nervousness, abnormal thinking, abnormal dreams.
	Uncommon	Agitation, affect lability, euphoric mood, hallucinations, decreased libido, drug dependence (see section 4.4), disorientation, mood altered, restlessness, dysphoria.
	Frequency not known	Aggression.
Nervous System Disorders	Very Common	Headache, dizziness, somnolence.
	Common	Tremor, lethargy, sedation.
	Uncommon	Amnesia, convulsions, hypertonia, hypoaesthesia, involuntary muscle contractions, speech disorder, syncope, paraesthesia, dysgeusia, hypotonia.
	Frequency not known	Hyperalgesia.
Eye disorders	Uncommon	Miosis, visual impairment.
Ear and labyrinth disorders	Uncommon	Vertigo.
Cardiac disorders	Uncommon	Palpitations (in the context of withdrawal syndrome), supraventricular tachycardia.
Vascular disorders	Uncommon	Vasodilatation, facial flushing.
	Rare	Hypotension, orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Uncommon	Respiratory depression, hiccups.
	Common	Bronchospasm, dyspnoea, cough decreased.
	Frequency not known	Central sleep apnoea syndrome.

Gastrointestinal disorders	Very Common Common Uncommon Frequency not known	Constipation, nausea, vomiting. Dry mouth, dyspepsia, abdominal pain, diarrhoea. Dysphagia, eructation, flatulence, ileus, gastritis. Dental caries
Hepato-biliary disorders	Uncommon Frequency not known	Biliary colic, increased hepatic enzymes Cholestasis. Sphincter of Oddi dysfunction
Skin and subcutaneous tissue	Very common Common Uncommon Rare	Pruritus. Hyperhidrosis, rash. Dry skin, exfoliative dermatitis. Urticaria.
Renal and urinary disorders	Uncommon	Urinary retention, ureteral spasm.
Reproductive system and breast disorders	Uncommon Frequency not known	Erectile dysfunction, hypogonadism Amenorrhoea,
General disorders and administration site conditions	Common Uncommon Frequency not known	Asthenia, fatigue. Drug tolerance, oedema, peripheral oedema, malaise, thirst, pyrexia, drug withdrawal syndrome, chills. Drug withdrawal syndrome neonatal.

Description of selected adverse reactions

Drug dependence

Repeated use of Oxycodone Molteni can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

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 professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: ww.mhra.gov.uk/yellowcard.

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 (hypotonia), bradycardia, pulmonary oedema 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.

Toxic leukoencephalopathy has been observed with oxycodone overdose.

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 reestablished. 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 alkaloid, opioid, analgesics.

ATC code: N02A A05

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

Gastrointestinal System

Opioids may induce spasm of the sphincter of Oddi.

Endocrine system

See section 4.4.

Other pharmacological effects

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 semi-synthetic 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 Oxycodone 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.

Oxycodone is metabolized in the liver to produce noroxycodone, oxymorphone and noroxymorphone, which are subsequently glucuronidated. 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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and genotoxicity.

Teratogenicity

Oxycodone had no effect on fertility or early embryonic development in male and female rats at doses as high as 8 mg/kg/d. In addition, oxycodone did not induce any deformities in rats at doses as high as 8 mg/kg/d or in rabbits at doses as high as 125 mg/kg/d. Dose-related increases in developmental variations (increased incidences of extra (27) presacral vertebrae and extra pairs of ribs) were observed in rabbits when the data for individual fetuses were analyzed. However, when the same data were analyzed using litters as opposed to individual fetuses, there was no dose-related increase in developmental variations although the incidence of extra presacral vertebrae remained significantly higher in the 125 mg/kg/d group compared to the control group. Since this dose level was associated with severe pharmacotoxic effects in the pregnant animals, the fetal findings may have been a secondary consequence of severe maternal toxicity.

In a study of peri- and postnatal development in rats, maternal body weight and food intake parameters were reduced for doses ≥ 2 mg/kg/d compared to the control group. Body weights were lower in the F1 generation from maternal rats in the 6 mg/kg/d dosing group. There were no effects on physical, reflexological, or sensory developmental parameters or on behavioural and reproductive indices in the F1 pups (the NOEL for F1 pups was 2 mg/kg/d based on body weight effects seen at 6 mg/kg/d). There were no effects on the F2 generation at any dose in the study.

Mutagenicity

The results of *in vitro* and *in vivo* studies indicate that the genotoxic risk of OxyNorm to humans is minimal or absent at the systemic oxycodone concentrations that are achieved therapeutically.

Oxycodone was not genotoxic in a bacterial mutagenicity assay or in an in vivo micronucleus assay in the mouse.

Oxycodone produced a positive response in the in vitro mouse lymphoma assay in the presence of rat liver S9 metabolic activation at dose levels greater than 25 μg/mL. Two in vitro chromosomal aberrations assays with human lymphocytes were conducted. In the first assay, oxycodone was negative without metabolic activation but was positive with S9 metabolic activation at the 24 hour time point but not at other time points or at 48 hour after exposure. In the second assay, oxycodone did not show any clastogenicity either with or without metabolic activation at any concentration or time point.

No animal studies to evaluate the carcinogenic potential of oxycodone have been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate

Sodium citrate

Sodium chloride

Hydrochloric acid, dilute (for pH adjustment)

Sodium hydroxide (for pH adjustment)

Water for injections

6.2 Incompatibilities

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

When cyclizine at concentrations of up to 3 mg/ml is mixed with Oxycodone injection, no sign of precipitation has been shown over a period of 24 hours storage at room temperature. When cyclizine at concentrations greater than 3 mg/ml is mixed with Oxycodone injection, precipitation has been shown to occur.

It is recommended that water for injection is used as a diluent, as cyclizine will precipitate in the presence of 0.9 % saline.

Prochlorperazine is chemically incompatible with Oxycodone injection.

6.3 Shelf life

36 months unopened.

After opening use immediately.

For further information, see section 6.6.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light.

For further information on use after opening, see section 6.6.

6.5 Nature and contents of container

1 ml - Clear, Type I Ph Eur glass ampoules.

Pack sizes: 5 ampoules.

6.6 Special precautions for disposal

Each ampoule is for single use in a single patient. The injection should be given immediately after opening the ampoule, and any unused portion should be discarded. Chemical and physical in-use stability has been demonstrated for 24 hours at 15 – 25°C 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.

No evidence of incompatibility was observed between Oxycodone injection and representative brands of injectable forms of the following drugs, when stored in high and low dose combinations in polypropylene syringes over a 24 hour period at ambient temperature:

- Hyoscine butylbromide
- Hyoscine hydrobromide
- Dexamethasone sodium phosphate
- Haloperidol
- Midazolam hydrochloride
- Metoclopramide hydrochloride
- Levomepromazine hydrochloride
- Glycopyrronium bromide
- Ketamine hydrochloride

Oxycodone 50 mg/ml injection, undiluted or diluted to 3 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 50 mg/ml injection, whether undiluted or diluted to 3 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

L. Molteni & C. dei F.lli Alitti Società di Esercizio SpA - Strada Statale 67, Fraz. Granatieri – 50018 Scandicci (Firenze) – Italy

8 MARKETING AUTHORISATION NUMBER(S)

PL 16046/0025

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/01/2024

10 DATE OF REVISION OF THE TEXT

09/04/2025