PACKAGE INSERT

1. NAME OF THE MEDICINAL PRODUCT

OXYCODONE KALCEKS SOLUTION FOR INJECTION OR INFUSION 10 MG/ML

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml ampoule contains 10 mg of oxycodone hydrochloride (equivalent to 9 mg of oxycodone).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection/infusion.
Clear, colourless or yellowish solution, free from visible particles.
pH of solution is 4.5-5.5.
Osmolality is approximately 285 mOsmol/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of moderate to severe pain in patients with cancer and postoperative pain.
For the treatment of severe pain requiring the use of a strong opioid.
OXYCODONE KALCEKS is indicated in adults only.

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. A gradual increase in dose may be required if analgesia is inadequate or if pain severity increases.

IV (Bolus): Dilute to 1 mg/ml in sodium chloride 9 mg/ml (0.9%) solution for injection, 50 mg/ml (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.

IV (Infusion): Dilute to 1 mg/ml in sodium chloride 9 mg/ml (0.9%) solution for injection, 50 mg/ml (5%) dextrose or water for injections. A starting dose of 2 mg/hour is recommended.

IV (PCA): Dilute to 1 mg/ml in sodium chloride 9 mg/ml (0.9%) solution for injection, 50 mg/ml (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.

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

SC (Infusion): Dilute in sodium chloride 9 mg/ml (0.9%) solution for injection, 50 mg/ml (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. The patient should be monitored closely until stable when switching opioid medications.

Elderly patients:
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 (see section 5.2).

Paediatric 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. The need for continued treatment in non-malignant pain should be assessed at regular intervals.

Duration of treatment:
Oxycodone should not be used for longer than necessary.

Discontinuation of treatment:
When a patient no longer requires therapy with oxycodone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

For instructions on dilution of the medicinal product before administration, see section 6.7.

Method of administration
Subcutaneous injection or infusion.
Intravenous injection or infusion.

4.3 Contraindications

Hypersensitivity to oxycodone or to any of the excipients listed in section 6.1.
Oxycodone must not be used in any situation where opioids are contraindicated:
- known sensitivity to morphine or other opioids;
- severe respiratory depression with hypoxia;
- head injury;
- chronic obstructive airways disease;
- cor pulmonale;
- severe bronchial asthma;
- moderate or severe hepatic impairment;
- severe renal impairment (creatinine clearance < 10 ml/min);
- elevated carbon dioxide levels in the blood;

- paralytic ileus;
- acute abdomen;
- chronic constipation;
- concurrent administration of monoamine oxidase (MAO) 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. 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) or patients taking MAO inhibitors.

OXYCODONE KALCEKS must not be administered to patients taking MAOIs or who have received MAOIs within the previous two weeks (see section 4.3).

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. Opioids may also cause worsening of pre-existing sleep apnoea (see section 4.8). In patients who present with CSA, consider decreasing the total opioid dosage.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs
Concomitant use of benzodiazepines and opioids 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 section 4.2). 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 section 4.5).

OXYCODONE KALCEKS should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, OXYCODONE KALCEKS should be discontinued immediately.

Surgical procedures
OXYCODONE KALCEKS 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.

Non-malignant pain
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. 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.

Endocrine system
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.
As with all opioids, a reduction in dosage may be advisable in hypothyroidism. Use with caution in infirm patients.

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 OXYCODONE KALCEKS may lead to Opioid Use Disorder (OUD). Abuse or intentional misuse of OXYCODONE KALCEKS 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.

Tolerance
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.

Withdrawal syndrome
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.
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.

Alcohol
Concomitant use of alcohol and OXYCODONE KALCEKS may increase the undesirable effects of oxycodone; concomitant use should be avoided.

Excipients
This medicinal product contains less than 1 mmol sodium (23 mg) per 1 ml, that is to say essentially ‘sodium free’.

4.5 Interaction with other medicinal products and other forms of interaction

The concomitant use of 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 section 4.4). Drugs which affect the CNS include, but are not limited to: tranquillisers, anaesthetics, hypnotics, antidepressants, 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.

MAO inhibitors are known to interact with narcotic analgesics. MAO inhibitors cause CNS excitation or depression associated with hypertensive or hypotensive crisis (see section 4.4). Oxycodone should be used with caution in patients administered MAO inhibitors or who have received MAO inhibitors during the last two weeks (see section 4.4).

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.

Alcohol may enhance the pharmacodynamics effects of oxycodone, 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 John's 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.

4.6 Fertility, pregnancy and lactation

Use of this medicinal product should be avoided to the extent possible in patients who are pregnant or lactating, or during labour.

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 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.

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 studies on fertility or the post-natal effects of intrauterine exposure have been carried out.

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. 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 section 4.4). Constipation may be prevented with an appropriate laxative. If nausea or vomiting are troublesome, oxycodone may be combined with an antiemetic.

The following frequency categories form the basis for classification of the undesirable effects:

Very common	≥ 1/10
Common	≥ 1/100 to < 1/10
Uncommon	≥ 1/1,000 to < 1/100
Rare	≥ 1/10,000 to < 1/1,000
Very rare	< 1/10,000
Not known	Cannot be estimated from the available data

Immune system disorders
Uncommon: hypersensitivity.

Not known: anaphylactic reaction, anaphylactoid reaction.

Metabolism and nutrition disorders
Common: 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.
Not known: aggression.

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.
Not known: hyperalgesia.

Eye disorders
Uncommon: visual impairment, miosis.

Ear and labyrinth disorders
Uncommon: vertigo.

Cardiac disorders
Common: orthostatic hypotension.
Uncommon: palpitations (in the context of withdrawal syndrome), supraventricular tachycardia, hypotension.

Vascular disorders
Uncommon: vasodilatation, facial flushing.

Respiratory, thoracic and mediastinal disorders
Common: dyspnoea, bronchospasm, cough decreased.
Uncommon: respiratory depression, hiccups.
Not known: central sleep apnoea syndrome.

Gastrointestinal disorders
Very common: constipation, nausea, vomiting.
Common: abdominal pain, diarrhoea, dry mouth, dyspepsia.
Uncommon: dysphagia, flatulence, eructation, ileus, gastritis.
Not known: dental caries.

Hepatobiliary disorders
Uncommon: increased hepatic enzymes, biliary colic.
Not known: cholestasis.

Skin and subcutaneous tissue disorders
Very common: pruritus.
Common: rash, hyperhidrosis.
Uncommon: dry skin, exfoliative dermatitis, urticaria.

Renal and urinary disorders
Uncommon: urinary retention, ureteral spasm.

Reproductive system and breast disorders
Uncommon: erectile dysfunction, hypogonadism, amenorrhoea.

General disorders and administration site conditions
Common: asthenia, fatigue.
Uncommon: drug withdrawal syndrome, malaise, oedema, peripheral oedema, drug tolerance, thirst, pyrexia, chills.
Not known: drug withdrawal syndrome neonatal.

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 national reporting system.

4.9 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, 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.

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 2 mg for an adult and 0.01 mg/kg body weight for children) if the patient is in a coma or respiratory depression is present. Repeat the dose at 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: N02AA05

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.

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 semisynthetic opioid, has immunological effects similar to morphine is unknown.

5.2 Pharmacokinetic properties

Absorption
Pharmacokinetic studies in healthy subjects demonstrated an equivalent availability of oxycodone when administered as a 5 mg dose by the intravenous and subcutaneous routes, as a single bolus dose or a continuous infusion over 8 hours.
Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis.

Distribution
Following absorption, oxycodone is distributed throughout the entire body. Approximately 45% is bound to plasma protein. The drug penetrates the placenta and can be found in breast milk.

Biotransformation and elimination
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.

Specific patient populations

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

Hepatic and renal impairment
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.

Unlike morphine preparations, the administration of oxycodone does not result in significant levels of active metabolites. However, the plasma concentration of oxycodone in this patient population may be increased compared with patients having normal renal or hepatic function. Studies involving other intravenous oxycodone preparations, administered by bolus injection to six patients with end-stage

liver cirrhosis and ten patients with end-stage renal failure have been reported in the literature. In each case, the elimination of oxycodone was impaired.

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 micrograms, 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 micrograms/ml, and in the *in vivo* bone marrow micronucleus assay in mice (at plasma levels of up to 48 micrograms/ml). Mutagenic results occurred in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 micrograms/ml) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 micrograms/ml or greater with metabolic activation and at 400 micrograms/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
Sodium hydroxide (for pH adjustment)
Hydrochloric acid, concentrated (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 6.7.

Cyclizine at concentrations of 3 mg/ml or less, when mixed with OXYCODONE KALCEKS, 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 OXYCODONE KALCEKS at cyclizine concentrations greater than 3 mg/ml or when diluted with sodium chloride 9 mg/ml (0.9%) solution for injection. However, if the dose of OXYCODONE KALCEKS injection is reduced and the solution is sufficiently diluted with water for injections, concentrations greater than 3 mg/ml are possible. 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 OXYCODONE KALCEKS.

6.3 Shelf life

Unopened ampoule: 4 years

Shelf life after opening the ampoule: The medicinal product should be used immediately.

6.4 Shelf life after dilution

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C and at 2-8°C.

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 dilution has taken place in controlled and validated aseptic conditions.

6.5 Special precautions for storage

Do not store above 30 °C.

For storage conditions after opening the ampoule see section 6.3.
For storage conditions after dilution of the medicinal product, see section 6.4.

6.6 Nature and contents of containers

Type I colourless glass ampoules of 1 ml.

Pack size: 10 ampoules

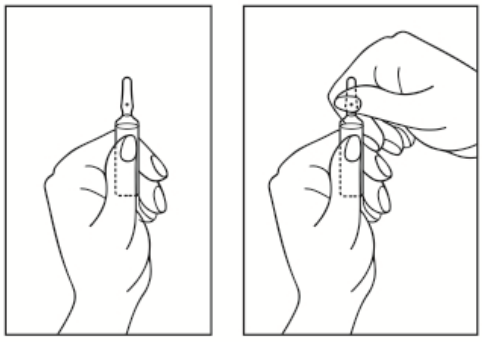
6.7 Special precautions for disposal and other handling

The injection should be given immediately after opening the ampoule. Once opened, any unused portion should be discarded.
OXYCODONE KALCEKS 10 MG/ML, undiluted or diluted to 1 mg/ml with sodium chloride 9 mg/ml (0.9%) solution for injection, 50 mg/ml (5%) 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 (25°C) and at 2-8°C.
OXYCODONE KALCEKS, whether undiluted or diluted in the infusion fluids used in these studies and contained in the various assemblies, does not need to be protected from light.
As well as product is compatible with following medicinal products: hyoscine butylbromide, hyoscine hydrobromide, dexamethasone sodium phosphate, haloperidol, midazolam hydrochloride, metoclopramide hydrochloride, levomepromazine hydrochloride.

Inappropriate handling of the undiluted solution after opening of the original ampoule, or of the diluted solutions may compromise the sterility of the product.

This medicine should not be used if there are any visible signs of deterioration (e.g. particles).

Instruction of ampoule opening:
1) Turn the ampoule with coloured point up. If there is any solution in the upper part of the ampoule, gently tap with your finger to get all the solution to the lower part of the ampoule.
2) Use both hands to open; while holding the lower part of the ampoule in one hand, use the other hand to break off the upper part of the ampoule in the direction away from the coloured point (see the pictures below).



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

7. PRODUCT OWNER AND MANUFACTURER

Product Owner:
AS KALCEKS
Krustpils iela 71E, Rīga, LV-1057, Latvia

Manufacturer:
HBM Pharma s.r.o.
Sklabinska 30, 036 80 Martin, Slovakia

8. MARKETING AUTHORISATION NUMBER(S)

SINXXXXXX

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

06/2022