SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Morphine Kalceks 10 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ampoule (1 ml) contains 10 mg morphine hydrochloride trihydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless or yellowish liquid, pH 3-5.

4. CLINICAL PARTICULARS

WARNING: RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

• Concomitant use of benzodiazepines with other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see section 4.4].
• Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
• Limit dosages and durations to the minimum required.
• Follow patients for signs and symptoms of respiratory depression and sedation.

4.1 Therapeutic indications

Symptomatic relief of moderate to severe pain, especially that associated with neoplastic disease, myocardial infarction, and surgery.
Pre-operatively as an adjunct to anesthesia for pain relief and to allay anxiety. Alleviation of the anxiety associated with severe pain. It is useful as a hypnotic where sleeplessness is due to pain.

4.2 Posology and method of administration

Posology
Administration and posology should be adjusted according to the nature and severity of the pain as well as the general condition of the patient. Individual criteria for the dose are dependent on the patient's age, weight, pain severity and medical and analgesic history.

Adults

Subcutaneous or intramuscular injection
The usual dose by subcutaneous or intramuscular injection is 5-20 mg (0.5-2 ml) every 4 hours.

Intravenous injection

Doses of up to 15 mg (1.5 ml) have been given by slow intravenous injection, sometimes as a loading dose for continuous or patient controlled infusion.

Elderly
Because of the depressant effect on respiration, caution is necessary when giving morphine to the elderly. A reduction of dose is advisable.

Hepatic Impairment:

Morphine may precipitate coma in hepatic impairment – avoid or reduce dose.

Renal Impairment
A reduced maintenance dose may be necessary in moderate to severe impairment.

Discontinuation of therapy
An abstinence syndrome may be precipitated if opioid administration is suddenly discontinued. Therefore, the dose should be gradually reduced prior to discontinuation.

Method of administration
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

For intravenous, intramuscular or subcutaneous use.
The subcutaneous route is not suitable for oedematous patients.

Notes:
1. Resuscitative equipment and medications, including a specific antagonist (naloxone HCl injection) should be immediately available for management of respiratory depression or other complications that may arise from inadvertent morphine intravascular administration. Also, facilities for adequate monitoring of the patient's respiratory status must be available for 24 hours after each dose since delayed respiratory depression may occur.

2. Rapid I.V. injection of most opioid analgesics has caused chest wall rigidity, anaphylactoid reactions, severe respiratory depression, hypotension, peripheral circulatory collapse and cardiac arrest.
The patient usually should be lying down and should remain recumbent for a period of time to minimize side effects such as hypotension, dizziness, lightheadedness, nausea and vomiting. If these side effects occur in an ambulatory patient, they may be relieved if the patient lies down. An opioid antagonist and equipment for artificial ventilation should be available.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Acute respiratory depression
- Asthma attack or Chronic Obstructive Airways Disease
- Acute alcoholism
- Biliary colic (see section 4.4)
- Head injuries, comatose patients or increased intracranial pressure. The sedation and pupillary changes produced may interfere with accurate monitoring of the patient.
- Heart failure secondary to lung disease
- Monoamine oxidase inhibitors (including moclobemide), or within two weeks of their withdrawal
- Risk of paralytic ileus
- Phaeochromocytoma (due to the risk of pressor response to histamine release).
- Acute diarrhoeal conditions associated with antibiotic-induced pseudomembranous colitis or diarrhoea caused by poisoning (until the toxic material has been eliminated)
- Morphine is contraindicated in premature infants or during labor for delivery of a

premature infant

4.4 Special warnings and precautions for use

Repeated use can cause tolerance and dependence. Caution in use should be exercised and a reduction in dose may be advisable in the elderly and in the following cases:

- Hypotension
- Hypothyroidism
- Depressed respiratory reserve
- Prostatic hypertrophy
- Hepatic or renal impairment (avoid or reduce dose)
- Convulsive disorders
- Asthma (avoid during attack)
- Adrenocortical insufficiency
- Urethral stricture
- Inflammatory or obstructive bowel disorders

Opioids such as morphine should either be avoided in patients with biliary disorders or they should be given with an antispasmodic.

Hepatobiliary disorders
Morphine may cause dysfunction and spasm of the sphincter of Oddi, thus raising intrabiliary pressure and increasing the risk of biliary tract symptoms and pancreatitis.
Therefore, in patients with biliary tract disorders morphine may exacerbate pain (use in biliary colic is a contraindication, see 4.3).
In patients given morphine after cholecystectomy, biliary pain has been induced.
Palliative care - in the control of pain in terminal illness, these conditions should not necessarily be a deterrent to use.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:
Concomitant use of Morphine 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 Morphine 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).

Acute chest syndrome (ACS) in patients with sickle cell disease (SCD)
Due to a possible association between ACS and morphine use in SCD patients treated with morphine during a vaso-occlusive crisis, close monitoring for ACS symptoms is warranted.

Adrenal insufficiency
Opioid analgesics may cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of adrenal insufficiency may include e.g. nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure.

Decreased Sex Hormones and Increased prolactin
Long-term use of opioid analgesics may be associated with decreased sex hormone levels and increased prolactin. Symptoms include decreased libido, impotence or amenorrhea.
Hyperalgesia that does not respond to a further dose increase of morphine may occur in particular in high doses. A morphine dose reduction or change in opioid may be required.

Morphine has an abuse potential similar to other strong agonist opioids and should be used with particular caution in patients with a history of alcohol or drug abuse.

Opioid Use Disorder (abuse and dependence)
Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as Morphine Kalceks.

Repeated use of Morphine Kalceks can 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 Morphine 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).

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.

Plasma concentrations of morphine may be reduced by rifampicin. The analgesic effect of morphine should be monitored, and doses of morphine adjusted during and after treatment with rifampicin.

Oral P2Y12 inhibitor antiplatelet therapy
Within the first day of concomitant P2Y12 inhibitor and morphine treatment, reduced efficacy of P2Y12 inhibitor treatment has been observed (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.

Severe cutaneous adverse reactions (SCARs)
Acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, has been reported in association with morphine treatment. Most of these reactions occurred within the first 10 days of treatment. Patients should be informed about the signs and symptoms of AGEP and advised to seek medical care if they experience such symptoms.

If signs and symptoms suggestive of these skin reactions appear, morphine should be withdrawn and an alternative treatment considered.

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

4.5 Interaction with other medicinal products and other forms of interaction

Alcohol: Enhanced sedative and hypertensive effects.

Anti-arrhythmics: There may be delayed absorption of mexiletine.

Antibacterials: The opioid analgesic papaveretum has been shown to reduce plasma ciprofloxacin concentration. The manufacturer of ciprofloxacin advises that premedication with opioid analgesics be avoided.

Antidepressants, anxiolytics, hypnotics: Severe CNS excitation or depression (hypertension or hypotension) has been reported with the concurrent use of pethidine and monoamine oxidase inhibitors (MAOIs) including selegiline, moclobemide and linezolid. As it is possible that a similar interaction may occur with other opioid analgesics, morphine should be used with caution and consideration given to a reduction in dosage in patients receiving MAOIs.

The sedative effects of morphine (opioid analgesics) are enhanced when used with depressants of the central nervous system such as hypnotics, anxiolytics, tricyclic antidepressants and sedating antihistamines.

Morphine should be used with caution in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anaesthetics, phenothiazines, other tranquilisers, muscle relaxants, antihypertensives, gabapentin or pregabalin and alcohol. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with the usual doses of morphine.

Antipsychotics: possible enhanced sedative and hypotensive effect.

Antidiarrhoeal and antiperistaltic agents (such as loperamide and kaolin):
concurrent use may increase the risk of severe constipation.

Antimuscarinics: agents such as atropine antagonise morphine-induced respiratory depression and can partially reverse biliary spasm but are additive to the gastrointestinal and urinary tract effects. Consequently, severe constipation and urinary retention may occur during intensive antimuscarinic analgesic therapy.

Metoclopramide and domperidone: There may be antagonism of the gastrointestinal effects of metoclopramide and domperidone.

Oral P2Y12 inhibitor antiplatelet therapy
A delayed and decreased exposure to oral P2Y12 inhibitor antiplatelet therapy has been observed in patients with acute coronary syndrome treated with morphine. This interaction may be related to reduced gastrointestinal motility and apply to other opioids. The clinical relevance is unknown, but data indicate the potential for reduced P2Y12 inhibitor efficacy in patients co-administered morphine and a P2Y12 inhibitor (see section 4.4). In patients with acute coronary syndrome, in whom morphine cannot be withheld and fast P2Y12 inhibition is deemed crucial, the use of a parenteral P2Y12 inhibitor may be considered.

Sedative medicines such as benzodiazepines or related drugs:
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).

4.6 Fertility, pregnancy and lactation

Pregnancy:
Morphine should only be used when benefit is known to outweigh risk. As with all drugs it is not advisable to administer morphine during pregnancy. Morphine crosses the placental barrier. Administration during labour may cause respiratory depression in the new born infant and gastric stasis during labour, increasing the risk of inhalation pneumonia. Therefore, it is not advisable to administer morphine during labour.

Babies born to opioid-dependent mothers may suffer withdrawal symptoms including CNS hyperirritability, gastrointestinal dysfunction, respiratory distress and vague autonomic symptoms including yawning, sneezing, mottling and fever.

Newborns whose mothers received opioid analgesics during pregnancy should be monitored for signs of neonatal withdrawal (abstinence) syndrome.
Treatment may include an opioid and supportive care.

Breast-feeding:
While morphine can suppress lactation, the quantity from therapeutic doses that may reach the neonate via breast milk is probably insufficient to cause major problems of dependence or adverse effects.

Fertility
Animal studies have shown that morphine may reduce fertility (see section 5.3.)

4.7 Effects on ability to drive and use machines

Morphine causes drowsiness so patients should avoid driving or operating machinery.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you

4.8 Undesirable effects

The most serious hazard of therapy is respiratory depression (see section 4.9). The commonest side-effects of morphine are:

- Nausea
- Vomiting
- Constipation
- Drowsiness
- Dizziness

Tolerance generally develops with long term use, but not to constipation.
Other side effects include the following:

Psychiatric disorders

- Dependence.

Immune system disorders:

- Anaphylactic reactions following intravenous injection have been reported rarely, anaphylactoid reactions.

Cardiac disorders:

- Bradycardia
- Palpitations
- Tachycardia
- Orthostatic hypotension.

Nervous system disorders:

- Myoclonus
- Mental clouding
- Confusion (with large doses)
- Hallucinations
- Headache
- Vertigo
- Mood changes including dysphoria
- Euphoria
- Allodynia

- Hyperalgesia (see section 4.4)
- Hyperhidrosis

Gastrointestinal disorders:
- Dry mouth
- Biliary spasm
- Pancreatitis

Eye disorders:
- Blurred or double vision or other changes in vision
- Miosis

Reproductive system and breast disorders:
- Long term use may lead to a reversible decrease in libido or potency.
- Central sleep apnoea syndrome

Skin and subcutaneous tissue disorders:
- Pruritus
- Urticaria
- Rash
- Sweating.
- Contact dermatitis has been reported and pain and irritation may occur on injection.
- Facial flushing
- Acute generalised exanthematous pustulosis (AGEP)

Musculoskeletal and connective tissue disorders
- Muscle rigidity

Hepatobiliary disorders
- Spasm of sphincter of Oddi

Renal and urinary disorders:
- Difficulty with micturition
- Ureteric spasm
- Urinary retention
- Antidiuretic effect.

General disorders and administration site conditions:
- Drug withdrawal (abstinence) syndrome

Tolerance develops to the effects of opioids on the bladder.
The euphoric activity of morphine has led to its abuse and physical and psychological dependence may occur (see section 4.4).

Description of selected adverse reactions
Drug dependence and withdrawal (abstinence) syndrome.

Use of opioid analgesics may be associated with the development of physical and/or psychological dependence or tolerance. An abstinence syndrome may be precipitated when opioid administration is suddenly discontinued, or opioid antagonists administered or can sometimes be experienced between doses. For management, see 4.4.

Repeated use of Morphine Kalceks 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) .

Physiological withdrawal symptoms include Body aches, tremors, restless legs syndrome, diarrhoea, abdominal colic, nausea, flu-like symptoms, tachycardia and mydriasis. Psychological symptoms include dysphoric mood, anxiety and irritability. In drug dependence, "drug craving" is often involved.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

Toxic doses vary considerably with the individual, and regular users may tolerate large doses.

The triad of respiratory depression, coma and constricted pupils is considered indicative of opioid overdosage with dilatation of the pupils occurring as hypoxia develops. Death may occur from respiratory failure.

Other opioid overdose symptoms include hypothermia, confusion, severe dizziness, severe drowsiness, hypotension, bradycardia, circulatory failure pulmonary oedema, severe nervousness or restlessness, hallucinations, pneumonia aspiration, convulsions (especially in infants and children). Rhabdomyolysis, progressing to renal failure, has been reported in overdosage.

Death may occur from respiratory failure
Treatment: The medical management of overdose involves prompt administration of the specific opioid antagonist naloxone if coma or bradypnoea are present using one of the recommended dosage regimens. Both respiratory and cardiovascular support should be given where necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids, ATC Code: N02AA01

Morphine is a narcotic analgesic obtained from opium, which acts mainly on the central nervous system and smooth muscle.

Morphine is a potent analgesic with competitive agonist actions at the μ- receptor, which is thought to mediate many of its other actions of respiratory depression, euphoria, inhibition of gut motility and physical dependence. It is possible that analgesia, euphoria and dependence may be due to the effects of morphine on a μ-1 receptor subtype, while respiratory depression and inhibition of gut motility may be due to actions on a μ-2 receptor subtype.

Morphine is also a competitive agonist at the κ-receptor that mediates spinal analgesia, miosis and sedation. Morphine has no significant actions at the other two major opioid receptors, the δ- and the σ-receptors.
Morphine directly suppresses cough by an effect on the cough centre in the medulla. Morphine also produces nausea and vomiting by directly stimulating the chemoreceptor trigger zone in the area postrema of the medulla. Morphine provokes the release of histamine.

5.2 Pharmacokinetic properties

The pharmacokinetics of morphine is not dose dependent.

Absorption

Maximum blood concentration is reached within 10-20 minutes.

Distribution
The volume of distribution of morphine is approximately 3 L/kg with a plasma protein binding of about 35 %. Morphine is widely distributed throughout the body, mainly in the kidneys, liver, lungs and spleen: lower concentrations appear in the brain and the muscles. Morphine crosses the placenta and is excreted into the breast milk (see section 4.6).

Biotransformation
Morphine is metabolised in the liver to the two main metabolites morphine-3-glucuronide (lacks analgesic effect but can contribute with excitatory effects) and morphine-6-glucuronide (M6G) (more potent than morphine itself). Small amounts of morphine-3,6-diglucuronide can also be formed. Morphine and its metabolites undergo enterohepatic circulation.

Elimination
Morphine is primarily eliminated via glucuronidation, and the excretion of unchanged morphine in the urine is 5-10 %. Clearance is approximately 24 mL/min*kg and the half-life is about 2-3 hours.
Up to 10 % of a dose may be excreted via the bile into the faeces.
M6G is excreted via urine, which causes M6G accumulation in renal impairment.

Special population
The morphine bioavailability can increase in liver cancer patients.

Hepatic impairment
Impaired hepatic function influence the elimination of morphine.

Renal impairment
Impaired renal function influence the elimination of morphine. M6G is excreted via the urine. Accumulation of the active metabolite M6G occurs in patients with renal impairment.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity. There have been no long-term animal studies on the tumorigenic potential of morphine. Effects in non-clinical studies were observed for genotoxicity, and toxicity to reproduction and development.

Mutagenic and tumorigenic potential
There are clearly positive findings available with regards to mutagenicity, which indicate that morphine has a clastogenic effect and that, furthermore, this effect exerts an influence on gametes. Thus, morphine is to be regarded as a mutagenic substance and such an effect may also be assumed in humans.

Reproductive toxicity
Animal studies showed a potential for damage in offspring throughout the entire duration of gestation (CNS malformations, growth retardation, testicular atrophy, changes in neurotransmitter systems and behavioural patterns, dependence). In addition, morphine had an effect on male sexual behaviour and fertility in various animal species. In male rats, reduced fertility and chromosomal damage in gametes have been reported.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

Morphine salts are sensitive to pH changes and can precipitate in alkaline environment. Compounds incompatible with morphine salts include aminophylline, sodium salts of barbiturates, phenytoin and ranitidine hydrochloride.
Specialised references should be consulted for specific compatibility information.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C. Store in the original package in order to protect from light. Do not freeze.

6.5 Nature and contents of container

Type I colourless glass ampoules of 1 ml, 5 ampoules are packed in PVC liner. 2 liners are packed in a carton.
Pack size: 10 ampoules of 1 ml.

6.6 Special precautions for disposal and other handling

Splashes on the skin and in the eyes can cause burning pain, redness and pruritus. Avoid direct contact with the product.

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

7. MARKETING AUTHORISATION HOLDER

A.L.Medi-Market Ltd., 3 Hakatif St., Emek Hefer Industrial Park, 3877701

8. MARKETING AUTHORISATION NUMBER(S)

163-85-35523-00

9. MANUFACTURER

AS Kalceks, Krustpils iela 71E, Riga, LV-1057, Latvia

10. DATE OF REVISION OF THE TEXT

Revised in May 2025