SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Morfin Kalceks, 10 mg/ml, solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Morphine hydrochloride trihydrate 10 mg/ml equivalent to morphine 7.6 mg/ml.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless or yellowish liquid, pH 3-5.
Osmolarity 0.035-0.055 Osmol/L.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Severe pain conditions which can be adequately managed only with opioid analgesics.

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: 1-1.5 ml solution for injection (10-15 mg morphine hydrochloride trihydrate) subcutaneously or intramuscularly 1-3 times daily. In urgent cases morphine can be administered slowly intravenously.

Elderly
Caution should be exercised and the dose initially reduced in morphine treatment.

Hepatic and renal impairment
Caution should be exercised and the dose initially reduced in morphine treatment.

The dose may need reduction in patients with bronchial asthma, upper respiratory tract obstruction, skull injuries, peritoneal dialysis, hypotension associated with hypovolemia, hypothyroidism, inflammatory bowel diseases, pancreatitis, biliary passage or ureter spasms.

Treatment monitoring
Nausea, vomiting and obstipation can sometimes be counteracted by 0.25-0.5 mg atropine subcutaneously. Respiratory depression can be reversed with naloxone.

Method of administration
For intravenous, intramuscular or subcutaneous use.

Treatment goals and discontinuation
Before initiating treatment with Morfin Kalceks, 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 Morfin Kalceks, 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
Morfin Kalceks should not be used longer than necessary.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1,
- secretion stagnation in the respiratory tract,
- respiratory depression,
- acute liver disease,
- anxiety conditions during affect by alcohol or hypnotic medicines.

4.4 Special warnings and precautions for use

Caution should be exercised in patients with prostate hypertrophy, myasthenia gravis.
Morphine should not be used in idiopathic pain or in pain with psychopathological characteristics (related to the lack of pain relief).
Morphine alone should not be administered during biliary or renal colic attacks as it may increase the cramp. In these cases morphine should be given in combination with a spasmolytic.
Following encephalitis, the effects of morphine can be enhanced.
Treatment with MAO inhibitors, see section 4.5.

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.

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.

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.

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.

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

Repeated use of Morfin 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 Morfin 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 initiating treatment with Morfin Kalceks 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 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.

Withdrawal (abstinence) syndrome
The risk of withdrawal syndrome increases with the time the drug is used, and with higher doses. Symptoms can be minimised with adjustments of dose or dosage form, and gradual withdrawal of morphine. For individual symptoms, see section 4.8.

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.

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

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).

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

Combinations that should be avoided

Barbiturates

Barbiturates enhance the respiratory depressive effect of opiates and opioids. The combination should therefore be avoided.

Small amounts of alcohol
Small amounts of alcohol can largely increase the weak respiratory depressive effect of morphine. The combination should therefore be avoided.

MAO inhibitors
MAO inhibitors can potentiate the effects of morphine (respiratory depression and hypotension). Serotonin syndrome has been reported during concomitant treatment with pethidine and MAO inhibitors, and the emergence of the same reaction cannot be ruled out during concomitant treatment with morphine and MAO inhibitors.

Combinations that may require dose adjustment

Gabapentin and pregabalin
Morphine should be used with caution in patients who are concurrently receiving gabapentin or pregabalin. Attention should be paid to the risk of CNS symptoms in the choice of treatment. If gabapentin and morphine are given concomitantly, consider reducing the gabapentin dose. Patients should therefore be monitored carefully regarding signs of CNS depression such as somnolence, and the gabapentin or morphine dose should be reduced accordingly.

Rifampicin
Rifampicin decreases the plasma concentration of *oral* morphine strongly enough that higher doses than normal are required for analgesic effect.

Amitriptyline, clomipramine and nortriptyline
Amitriptyline, clomipramine and nortriptyline enhance the analgesic effect of morphine, probably caused by increased bioavailability. Dose adjustment may be necessary.

Combined morphine agonists/antagonists
Combined morphine agonists/antagonists (*buprenorphine, nalbuphine, pentazocine*) decrease the analgesic effect through competitive inhibition of receptors, which increase the risk of withdrawal symptoms.

Combinations with unclear clinical relevance

Baclofen
The combination of morphine and intrathecal administration of Lioresal caused decreased blood pressure in one patient. The risk for this combination to cause apnoea or other CNS symptoms cannot be excluded.

Hydroxyzine
Concomitant administration of hydroxyzine and morphine can via additive effect cause increased CNS depression and drowsiness. Switching to a non-sedative antihistamine should be considered.

Methylphenidate
Methylphenidate can increase the analgesic effect of morphine. During concomitant administration a reduction of the morphine dose should be considered.

Nimodipine
Nimodipine can increase the analgesic effect of morphine. During concomitant administration a reduction of the morphine dose should be considered.

Ritonavir

Morphine levels can decrease due to induction of glucuronidation by concomitantly administered ritonavir dosed as an antiretroviral medicinal product or pharmacokinetic booster of other protease inhibitors.

Oral P2Y12 inhibitor
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

Men and women of childbearing potential
Due to the mutagenic properties of morphine, it should not be administered to men and women of child-producing/child bearing potential unless effective contraception is assured (see section 5.3).

Pregnancy
There are limited amount of data from the use of morphine in pregnant women. Morphine crosses the placenta. Studies in animals have shown reproductive toxicity (see section 5.3).
For this reason, morphine must only be used during pregnancy in cases where the maternal benefit clearly outweighs the risk for the child.

Long term use of morphine during pregnancy may result in a neonatal opioid withdrawal state. Morphine can prolong or shorten the duration of labour. Morphine can produce respiratory depression in the neonate, if it is administered during labour. New-borns 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. Especially during the 2 to 3 hours before expected partum Morfin Kalceks should only be administered on strict indication and following a mother benefit versus baby risk analysis.

Breast-feeding
Morphine is excreted into breast milk, where it reaches higher concentrations than in maternal plasma. Since clinically relevant concentrations of morphine may be reached in nursing infants, breast-feeding is not recommended (see section 5.2).

Fertility
There are no clinical data on the effects of morphine on male or female fertility.
Animal studies have shown that morphine may reduce fertility (see 5.3 Preclinical safety data).

4.7 Effects on ability to drive and use machines

Morfin Kalceks has major influence on the ability to drive and use machines.

4.8 Undesirable effects

Approximately 20 % of the patients suffer from nausea and vomiting. Most undesirable effects are dose dependent.

The adverse reactions are presented below in accordance with the MedDRA system organ classification. The frequencies have been assessed in accordance with the following convention: 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:
Not known: anaphylactoid reactions.

Endocrine disorders:
Common: increased ADH release.

Psychiatric disorders:
Uncommon: dysphoria.
Not known: euphoria, sleep, memory and concentration disturbances, dependence.

Nervous system disorders:
Common: sedation, dizziness.
Uncommon: respiratory depression, disorientation.
Not known: allodynia, hyperalgesia (see section 4.4), hyperhidrosis, convulsions, myoclonus.

Eye disorders:
Common: miosis.

Cardiac disorders:
Rare: palpitations, tachycardia, syncope.

Vascular disorders:
Rare: orthostatic hypotension, hypertension, hypotension, peripheral oedema.

Respiratory, thoracic and mediastinal disorders:
Uncommon: bronchoconstriction.
Not known: central sleep apnoea syndrome.

Gastrointestinal disorders:
Common: obstipation, nausea, vomiting.
Not known: pancreatitis, dry mouth.

Hepatobiliary disorders:
Uncommon: biliary tract spasm.
Not known: spasm of sphincter of Oddi.

Skin and subcutaneous tissue disorders:
Uncommon: pruritus.
Not known: acute generalised exanthematous pustulosis (AGEP), urticaria.

Renal and urinary disorders:
Common: urinary retention.
Uncommon: urinary tract spasm.

General disorders and administration site conditions:
Uncommon: light-headedness.
Not known: drug withdrawal (abstinence) syndrome.

Sedation normally decreases after a few days of administration. Nausea and vomiting usually decrease in long term treatment. Spasms in biliary or urinary tract can occur in predisposed persons. The respiratory depressive effect is dose dependent and is rarely a clinical problem.

Dependence and tolerance do normally not cause problems in treatment of severe cancer pain.

Drug dependence and withdrawal (abstinence) syndrome
Use of opioid analgesics may be associated with the development of physical and/or psychological dependence or tolerance. Repeated use of Morfin 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).
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.
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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms of overdose
Signs of overdose are pin-point pupils, respiratory depression and low blood pressure, pneumonia aspiration. Circulatory disturbances and coma may occur in serious cases. Death may occur from respiratory failure.

Treatment of overdose
If justified, gastric lavage, charcoal, laxative when orally administered. Respiratory depression caused by morphine intoxication can be reversed with naloxone, initially 0.4 mg for adults (children 0.01 mg/kg) slowly intravenously, the dose is gradually increased if necessary.
Continuous infusion of naloxone can sometimes be a useful alternative.
Respirator treatment on when indicated (with PEEP in pulmonary edema). Naloxone cannot replace respirator treatment in serious intoxication. Intravenous fluid (electrolyte solution, glucose), blood gas control, acidosis correction. Symptomatic therapy.

Toxicity
A potential lethal dose for adults (without tolerance development) is usually in the range of 40-60 mg orally (30 mg parenterally). Scopolamine, hypnotics and alcohol potentiate toxic effects.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids, ATC code: N02AA01

Morphine is an opioid analgesic with potent analgesic effect. The analgesic effect is partly due to an altered pain perception and partly on a raised pain threshold. Morphine probably exerts its analgesic effect at different levels within the CNS. In elderly patients the pain relieving effect of morphine increases. The central nervous system effects of morphine also include respiratory depression, psychiatric symptoms, nausea and vomiting, miosis and antidiuretic hormone release.
The respiratory depressive effect of morphine is caused by the inhibition of the carbon dioxide stimulating effect on the respiratory centre in the medulla oblongata. This effect can lead to respiratory insufficiency in patients with impaired ventilation ability caused by pulmonary disease or other pharmaceuticals. Elderly may be more sensitive to the side effects.
Intoxication with morphine requires respiratory supporting treatment and administration of antidote.

Morphine is metabolised via conjugation to the two main metabolites morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G). Small amounts of morphine-3,6-diglucuronide can also be formed. M3G has a small affinity to opioid receptors, i.e. no documented analgesic effect, but can contribute to excitatory effects. M6G is twice as potent as morphine when systemically administered, and the pharmacologic effects of M6G cannot be separated from those of morphine. During chronic treatment it contributes with a significant part of the analgesic effects of morphine.

As a result of stimulation of dopamine receptors in the “trigger zone” in medulla oblongata, nausea and vomiting can occur. The increased release of antidiuretic hormone contributes to decreased urine volumes during morphine treatment. Morphine increases tonus in smooth muscles in the gastrointestinal tract. This causes obstipation due to a slower passage of food through the gastrointestinal tract. Further the pressure in the biliary passage and the urinary tract increases which makes morphine less suitable in biliary passage or urinary tract spasms.
Morphine has addictive properties and tolerance can develop against the morphine effects. However, normally this causes no problem in treatment of severe pain related to cancer.

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, concentrated (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.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Colourless glass ampoules 10 x 1 ml.
5 ampoules are packed in a polyethylene film liner. 2 liners are packed in a carton.

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

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

2024-12-23

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