Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Morphine sulfate 15mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 15 mg of morphine sulfate.

Excipient with known effect: Also contains 2.89 mg of sodium per ml.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection).
Clear colourless or almost colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Morphine is used for the symptomatic relief of severe pain; relief of dyspnoea of left ventricular failure and pulmonary oedema of cardiogenic origin; pre-operative use in adults.

4.2 Posology and method of administration

Posology
Adults
The dosage should be based on the severity of the pain and the response and tolerance of the patient. The usual adult subcutaneous or intramuscular dose is 10 mg every 4 hours, if necessary, but may range from 5 mg to 20 mg.
The usual adult intravenous dose is 2.5 mg to 15 mg not more than 4-hourly, where necessary, but dosage and dosing interval must be titrated against the patient's response and adjustments made until analgesia is achieved.

Elderly
Because of the depressant effect on respiration, caution is necessary when giving morphine to the elderly and reduced doses may be required.

Paediatric population
Use in children is not recommended.

Hepatic impairment
A reduction in dosage should be considered in hepatic impairment.

Renal impairment
The dosage should be reduced in moderate to severe renal impairment.
For concomitant illnesses/conditions where dose reduction may be appropriate, see section 4.4.

Method of administration
The injection may be given by the intravenous, intramuscular or subcutaneous route.
The subcutaneous route is not suitable for oedematous patients.

Treatment goals and discontinuation
Before initiating treatment with Morphine sulfate, 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

Morphine sulfate, 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
Morphine sulfate 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.
- Acute respiratory depression
- Obstructive airways disease
- Concurrent treatment with monoamine oxidase inhibitors or within two weeks of their discontinuation of treatment with them
- Cerebral oedema
- Head injuries
- Coma
- Convulsive disorders
- Raised intracranial pressure
- Biliary colic
- Acute alcoholism
- Antibiotic induced pseudomembranous colitis
- Ulcerative colitis because of the risk of toxic megacolon
- Phaeochromocytoma
- Paralytic ileus
- Acute diarrhoea caused by poisoning or invasive pathogens.

4.4 Special warnings and precautions for use

Morphine is a potent medicine but with considerable potential for harmful effect, including addiction. It should be used only if other drugs with fewer hazards are inadequate, and with the recognition that it may possibly mask significant manifestations of disease which should be identified for proper diagnosis and treatment.

Use with caution or reduced doses
Morphine should be given in reduced doses or with caution to patients with asthma or a reduced respiratory reserve (including emphysema, chronic cor pulmonale, kyphoscoliosis, excessive obesity and sleep apnoea). Avoid use during an acute asthma attack (see section 4.3).
Opioid analgesics in general should be administered with caution or in reduced doses to patients with hypotension, hypothyroidism, adrenocortical insufficiency, impaired kidney or liver function, prostatic hypertrophy, urethral stricture, shock, inflammatory or obstructive bowel disorders, or convulsive disorders.

Caution is advised when giving morphine to patients with impaired liver function due to its hepatic metabolism (see section 4.2).

Severe and prolonged respiratory depression has occurred in patients with renal impairment who have been given morphine (see section 4.2).

Dosage should be reduced in elderly and debilitated patients.

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
Opioids such as morphine should either be avoided in patients with biliary disorders or they should be given with an antispasmodic.
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. [DK1] Therefore, in patients with biliary tract disorders morphine may exacerbate pain (use in biliary colic is a contraindication, see section 4.3). In patients given morphine after cholecystectomy, biliary pain has been induced.

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

Hyperalgesia
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.

Gastrointestinal disorders
An unexplained increase in abdominal pain associated with disturbed intestinal motility, symptoms of constipation, bloating, abdominal distension and increased gastroesophageal reflux during treatment with morphine sulfate, may indicate the development of opioid induced bowel dysfunction or narcotic bowel syndrome. In such situations consider the use of alternative analgesics and a morphine detoxification.

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

Palliative care
In the control of pain in terminal illness, these conditions should not necessarily be a deterrent to use.

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.

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 hypotensive 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 gabapentin or pregabalin, hypnotics, anxiolytics, tricyclic antidepressants and sedating antihistamines.

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 antimuscarinicanalgesic therapy.

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

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).

Cimetidine: inhibits the metabolism of morphine.

Rifampicin: Plasma concentrations of morphine may be reduced by rifampicin.

Ritonavir: Although there are no pharmacokinetic data available for concomitant use of ritonavir with morphine, ritonavir induces the hepatic enzymes responsible for the glucuronidation of morphine, and may possibly decrease plasma concentrations of morphine.

Oral P2Y12 inhibitors: 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.

4.6 Fertility, pregnancy and lactation

Pregnancy
Since morphine rapidly crosses the placental barrier, it is not advised to administer morphine during pregnancy and labour. It may reduce uterine contractions, cause respiratory depression in the foetus and new-born infant, and may have significant effects on foetal heart rate. 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.
As with all drugs it is not advisable to administer morphine during pregnancy.

Breastfeeding
The amount of morphine secreted in breast milk after a singledose administration seems to be compatible with breast feeding and insufficient to cause major problems or dependence. However longterm treatment with morphine in high doses may cause significant plasma concentration. That is why caution is advised on the use of morphine in breastfeeding patient and the benefit must outweigh the risk to the infant. If breast feeding is continued, the infant should be observed for possible 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 has major influence on the ability to drive and use machines. It may cause drowsiness so patients should avoid driving or operating machinery.

4.8 Undesirable effects

Adverse effects can be listed in terms of their frequency of occurrence: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), not known (cannot be estimated from the available data).

Morphine may cause the following adverse events:

Nervous system disorders:

Very common:	Drowsiness, hyperhidrosis.
Common:	Convulsion, headache, increased intracranial pressure, myoclonus; opioid induced hyperalgesia (or hyperaesthesia) (see section 4.4), vertigo.
Not known:	Allodynia (see section 4.4), coma.

Psychiatric disorders:

Very common:	Confusional state, hallucinations, physical and psychological dependence.
Common:	Decreased libido, mood swings, restlessness.

Eye disorders:

Common:	Blurred vision, miosis, nystagmus.

Respiratory, thoracic and mediastinal disorders:

Very common:	Respiratory depression.
Common:	Bronchospasm, pulmonary oedema, which can lead to death.
Not known:	Respiratory failure, which also can lead to death, central sleep apnoea syndrome.

Cardiac disorders:

Common:	Bradycardia, circulatory failure, tachycardia.
Uncommon:	Palpitations.

Vascular disorders:

Common:	Hypotension, orthostatic hypotension.

Gastrointestinal disorders:

Very common:	Constipation, nausea, vomiting.
Common:	Dry mouth, paralytic ileus.
Not known:	Intestinal functional disorder, narcotic bowel syndrome, pancreatitis.

Hepatobiliary disorders:

Common:	Biliary spasm.
Uncommon:	Hepatic enzyme increase.
Not known:	Spasm of the sphincter of Oddi.

Reproductive system and breast disorders:

Common:	Erectile dysfunction.

Renal and urinary disorders:

Common:	Urinary retention.
Uncommon:	Urethral spasm.
Not known:	Renal failure.

Immune system disorders:

Uncommon:	Anaphylactic reaction, hypersensitivity.
Not known:	Anaphylactoid reactions

Musculoskeletal and connective tissue disorders:

Not known:	Muscle rigidity, rhabdomyolysis.

Skin and subcutaneous tissue disorders:

Very common:	Pruritus.
Common:	Angioedema, contact dermatitis, rash, urticaria.
Not known:	Acute generalised exanthematous pustulosis (AGEP).

General disorders and administration site conditions:

Very common:	Drug tolerance
Common:	Fatigue, facial flushing, hypothermia, injection site pain, injection site irritation, drug withdrawal (abstinence) syndrome (babies born to opioid dependent mothers also at risk to present withdrawal syndrome).

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 Morphine sulfate 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 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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie

4.9 Overdose

Symptoms: respiratory depression, pinpoint pupils, pneumonia aspiration and coma. In addition, shock, reduced body temperature and hypotension may occur. In mild overdose, symptoms include nausea and vomiting, tremor, miosis, dysphoria, hypothermia, hypotension, confusion and sedation. In cases of severe poisoning, hypotension with circulatory failure, rhabdomyolysis progressing to renal failure, respiratory collapse may occur. Death may occur from respiratory failure.

Treatment: the patient must be given both respiratory and cardiovascular support and the specific antagonist, naloxone, should be administered using one of the recommended dosage regimens. Fluid and electrolyte levels should be maintained.

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.

5.2 Pharmacokinetic properties

Absorption
Variably absorbed after oral administration; rapidly absorbed after subcutaneous or intramuscular administration.

Blood concentration
After an oral dose of 10 mg as the sulfate, peak serum concentrations of free morphine of about 10 ng/ml are attained in 15 to 60 minutes.
After an intramuscular dose of 10 mg, peak serum concentrations of 70 to 80 ng/ml are attained in 10 to 20 minutes.
After an intravenous dose of 10 mg, serum concentrations of about 60 ng/ml are obtained in 15 minutes falling to 30 ng/ml after 30 minutes and to 10 ng/ml after three hours.
Subcutaneous doses give similar concentrations to intramuscular doses at 15 minutes but remain slightly higher during the following 3 hours; serum concentrations measured soon after administration correlate closely with the ages of the subjects studied and are increased in the elderly.

Half-life
Serum half-life in the period 10 minutes to 6 hours following intravenous administration, 2 to 3 hours; serum half-life in the period 6 hours onwards, 10 to 44 hours.

Distribution
Widely distributed throughout the body, mainly in the kidneys, liver, lungs and spleen; lower concentrations appear in the brain and muscles.
Morphine crosses the placenta and traces are secreted in sweat and milk.
Protein binding, about 35% bound to albumin and to immunoglobulins at concentrations within the therapeutic range.

Biotransformation
Mainly glucuronic acid conjugation to form morphine-3 and 6-glucuronides, with sulfate conjugation. N-demethylation, O-methylation and N-oxide glucuronide formation occurs in the intestinal mucosa and liver; N-demethylation occurs to a greater extent after oral than parental administration; the O-methylation pathway to form codeine has been challenged and codeine and norcodeine metabolites in urine may be formed from codeine impurities in the morphine sample studied.

Elimination
After an oral dose, about 60% is excreted in the urine in 24 hours, with about 3% excreted as free morphine in 48 hours.
After a parental dose, about 90% is excreted in 24 hours, with about 10% as free morphine, 65 to 70% as conjugated morphine, 1% as normorphine and 3% as normorphine glucuronide.
After administration of large doses to addicts about 0.1% of a dose is excreted as norcodeine.
Urinary excretion of morphine appears to be pH dependent to some extent; as the urine becomes more acidic more free morphine is excreted and as the urine becomes more alkaline more of the glucuronide conjugate is excreted; up to 10% of a dose may be excreted in the bile.

5.3 Preclinical safety data

Non-clinical data based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential reveal no special hazard additional to the known safety profile of morphine in humans. 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 may be precipitated in alkaline solution. Morphine sulfate is incompatible with oxidizing agents.
Physicochemical incompatibility (formation of precipitates) has been demonstrated between solutions of morphine sulfate and 5-fluorouracil.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Keep the ampoules in the outer carton in order to protect from light.

6.5 Nature and contents of container

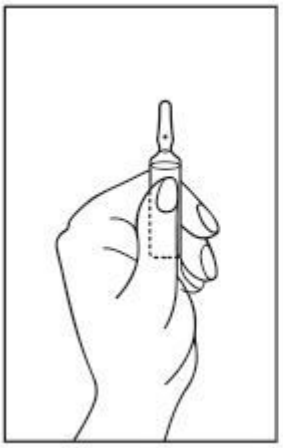
Type I amber glass ampoules of 1 ml with white open point cut. The ampoules are packed in transparent polyvinylchloride film liners. The liners together with leaflets are packed in cartons.
Pack size: 5 or 10 ampoules.
Not all pack sizes may be marketed.

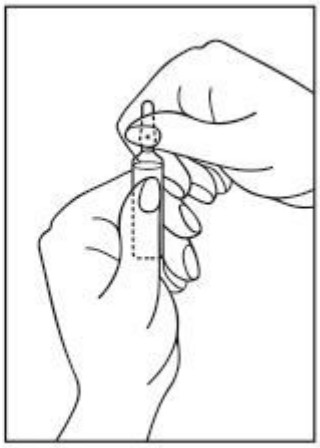
6.6 Special precautions for disposal and other handling

The medicinal product is for single use only; discard any remaining contents after use.

Instruction of ampoule opening:

1. Hold the ampoule upright. 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).





The required volume should be calculated based on the prescribed dose.

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

7 MARKETING AUTHORISATION HOLDER

AS Kalceks
Krustpils Iela 71e
Riga
1057
Latvia

8 MARKETING AUTHORISATION NUMBER

PA2165/003/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30th November 2018
Date of last renewal: 19th September 2023

10 DATE OF REVISION OF THE TEXT

May 2023