Package leaflet: Information for the user

Morphine sulfate 10 mg/ml, 15 mg/ml and 30 mg/ml solution for injection

morphine sulfate

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Morphine sulfate is and what it is used for

Morphine is one of a group of medicines called opioid analgesics, which are used to relieve moderate to severe pain.
Morphine is used for the relief of severe pain and it is also used to treat breathlessness caused by fluid in the lungs and as a pre-medication before operations in adults.

2. What you need to know before you are given Morphine sulfate

Do not use Morphine sulfate if you:
- are allergic to active substance or any of the other ingredients of this medicine (listed in section 6);
- have conditions that make breathing difficult, such as obstructive airways disease or your breathing is weak;
- are taking, or have recently taken (in the past two weeks) any drugs for depression known as monoamine oxidase inhibitors (MAOIs);
- have head injuries, headaches or have increased pressure in the skull (raised intracranial pressure);
- have problems related to fluid on the brain (cerebral oedema);
- suffer from convulsions (fits);
- have severe stomach cramps caused by a condition known as biliary colic;
- are suffering from acute alcoholism;
- suffer from antibiotic induced pseudomembranous colitis;
- have ulcerative colitis;
- have been told you have a tumour of the adrenal gland near your kidney called phaeochromocytoma;
- are at risk from a blocked intestine (paralytic ileus);
- are suffering from severe diarrhoea caused by food poisoning or an infection.

Morphine sulfate is never given to patients in a coma.
If any of the above applies to you, do not use this medicine and talk to your doctor or nurse.

Warnings and precautions
Talk to your doctor or nurse before you are given Morphine sulfate if you:

- have low blood pressure (hypotension);
- have a disease that causes difficulty in breathing as asthma, emphysema, cor pulmonale (high blood pressure causing failure of the right side of the heart), abnormal spinal shape and excessive obesity;
- have an under-active thyroid (hypothyroidism) or adrenal gland (adrenocortical insufficiency);
- have a liver or kidney disease;
- have an inflammatory or obstructive bowel disease such as Crohn`s disease or ulcerative colitis;
- are in circulatory collapse (shock);
- are male and have an enlarged prostate or have difficulty passing water (prostatic hypertrophy);
- have muscle weakness (myasthenia gravis);
- have biliary disorders;
- have a tendency to abuse drugs or have ever suffered from drug abuse;
- are elderly.

Talk to your doctor or nurse if you experience any of the following symptoms while using Morphine sulfate:
- increased sensitivity to pain despite the fact that you are taking increasing doses (hyperalgesia). Your doctor will decide whether you will need a change in dose or a change in strong analgesic ("painkiller"), (see section 2).
- weakness, fatigue, lack of appetite, nausea, vomiting or low blood pressure. This may be a symptom of the adrenals producing too little of the hormone cortisol, and you may need to take hormone supplement.
- loss of libido, impotence, cessation of menstruation. This may be because of decreased sex hormone production.
- severe upper abdominal pain possibly radiating to the back, nausea, vomiting or fever as this could be symptoms associated with inflammation of the pancreas (pancreatitis) and the biliary tract system.
- if you have once been dependent on drugs or alcohol. Also tell if you feel that you are becoming dependent on Morphine sulfate while you are using it. You may have started to think a lot about when you can take the next dose, even if you do not need it for the pain.
- abstinence symptoms or dependence. The most common abstinence symptoms are mentioned in section 3. If this occurs, your doctor may change the type of medicine or the times between doses.

<u>Tolerance, dependence, and addiction</u>
This medicine contains morphine which is an opioid medicine. Repeated use of opioids can result in the drug being less effective (you become accustomed to it, known as tolerance). Repeated use of Morphine sulfate can also lead to dependence, abuse, and addiction, which may result in life-threatening overdose. The risk of these side effects can increase with a higher dose and longer duration of use.
Dependence or addiction can make you feel that you are no longer in control of how much medicine you need to take or how often you need to take it.
The risk of becoming dependent or addicted varies from person to person. You may have a greater risk of becoming dependent on or addicted to Morphine sulfate if:
- you or anyone in your family have ever abused or been dependent on alcohol, prescription medicines or illegal drugs ("addiction").
- you are a smoker.
- you have ever had problems with your mood (depression, anxiety, or a personality disorder) or have been treated by a psychiatrist for other mental illnesses.

If you notice any of the following signs whilst using Morphine sulfate, it could be a sign that you have become dependent or addicted:
- you need to take the medicine for longer than advised by your doctor.
- you need to take more than the recommended dose.
- you are using the medicine for reasons other than prescribed, for instance, 'to stay calm' or 'help you sleep'.
- you have made repeated, unsuccessful attempts to quit or control the use of the medicine.
- when you stop taking the medicine you feel unwell, and you feel better once taking the medicine again ('withdrawal effects').

If you notice any of these signs, speak to your doctor to discuss the best treatment pathway for you, including when it is appropriate to stop and how to stop safely (see section 3, If you stop using Morphine sulfate).

Acute generalized exanthematous pustulosis (AGEP)
Acute generalized exanthematous pustulosis (AGEP) has been reported in association with Morphine sulfate treatment. Symptoms usually occur within the first 10 days of treatment. Tell your doctor if you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking Morphine sulfate or other opioids. Stop using Morphine sulfate and seek medical attention immediately, if you notice any of the following symptoms: blistering, widespread scaly skin or pus-filled spots together with fever.

Sleep-related breathing disorders
Morphine sulfate can cause sleep-related breathing disorders such as sleep apnoea (breathing pauses during sleep) and sleep related hypoxemia (low oxygen level in the blood). The symptoms can include breathing pauses during sleep, night awakening due to shortness of breath, difficulties to maintain sleep or excessive drowsiness during the day. If you or another person observe these symptoms, contact your doctor. A dose reduction may be considered by your doctor.

Children
This medicine is not recommended for use in children.

Other medicines and Morphine sulfate
Tell your doctor if you are taking have recently taken or might take any other medicines. In particular, tell your doctor if you are taking any of the following:
- monoamine oxidase inhibitors (MAOIs) such as moclobemide or phenelzine used in the treatment of depression.
- tricyclic antidepressants, which are used in the treatment of depression.
- gabapentin or pregabalin to treat epilepsy and pain due to nerve problems (neuropathic pain).
- tranquillising drugs or sleeping tablets such as diazepam, nitrazepam and temazepam.
- medicines used to treat mental illnesses, including schizophrenia (e.g. chlorpromazine, haloperidol).
- medicines used for diarrhoea (e.g. loperamide, kaolin).
- medicines which are used as premedication before operations and after heart attacks such as atropine.
- medicines used to treat nausea and vomiting, such as metoclopramide or domperidone.
- mexiletine, used to control heart rhythm.
- some antihistamines, used to treat allergies, hay fever and asthma.
- certain antibiotics, used to treat infections (e.g. ciprofloxacin and linezolid).
- selegiline, used in the treatment of Parkinson's disease.
- pethidine, used to treat pain.
- cimetidine, used as anti-ulcer drug.
- rifampicin to treat e.g. tuberculosis.
- ritonavir, used in the treatment of HIV.
- some medicines used to treat blood clots (e.g. clopidogrel, prasugrel, ticagrelor) may have delayed and decreased effect when taken together with morphine.
- concomitant use of Morphine sulfate and sedative medicines such as benzodiazepines or related drugs increases the risk of drowsiness, difficulties in breathing (respiratory depression), coma and may be life-threatening. Because of this, concomitant use should only be considered when other treatment options are not possible. However if your doctor does prescribe Morphine sulfate together with sedative medicines the dose and duration of concomitant treatment should be limited by your doctor. Please tell your doctor about all sedative medicines you are taking, and follow your doctor's dose recommendation closely. It could be helpful to inform friends or relatives to be aware of the signs and symptoms stated above. Contact your doctor when experiencing such symptoms.

Morphine sulfate with alcohol
You should not drink alcohol whilst being given Morphine sulfate, as it will increase its effects.

Pregnancy and breast-feeding

If you are pregnant, in labour or breastfeeding, Morphine sulfate will only be given to you if your doctor considers the benefit of treatment outweighs the risk to the infant foetus or new-born baby. Morphine may reduce contractions during labour, cause breathing problems to the infant foetus or new-born baby and affect the heart rate of the foetus. If Morphine sulfate is used for a long time during pregnancy, there is a risk of the new-born child having drug withdrawal (abstinence) symptoms which should be treated by a doctor.
If you are breast-feeding, ask your doctor for advice before using this medicine.

Driving and using machines
Morphine sulfate may cause drowsiness. If this happens to you, do not drive or use machinery.
This medicine can affect your ability to drive as it may make you sleepy or dizzy.

- do not drive while taking this medicine until you know how it affects you
- it is an offence to drive if this medicine affects your ability to drive
- however, you would not be committing an offence if:
    - the medicine has been prescribed to treat a medical or dental problem and
    - you have taken it according to the instructions given by the prescriber or in the information provided with the medicine and
    - it was not affecting your ability to drive safely.

Talk to your doctor or nurse if you are not sure whether it is safe for you to drive while taking this medicine.

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

3. How Morphine sulfate will be given to you

Morphine sulfate will be given to you by a doctor or nurse in hospital. Your doctor will choose the dose that is right for you.

Before starting treatment and regularly during treatment, your doctor will discuss with you what you may expect from using Morphine sulfate, when and how long you need to use it, when to contact your doctor, and when you need to stop it (see also, If you stop using Morphine sulfate, in this section).

Adults
- The recommended adult dose for relief of pain by subcutaneous injection (an injection underneath the skin) or intramuscular injection (an injection into a muscle) is 10 mg every four hours, if necessary.
- However, the amount may range from 5 mg to 20 mg depending on how severe your pain is and how you respond to the drug.
- If the drug is injected into a vein, the recommended dose for an adult is 2.5 mg to 15 mg with at least 4 hours between doses.
- Your doctor or nurse may adjust the dose of your medicine and the number of injections you are given each day until your pain is relieved.

Elderly
As this medicine make breathing difficult, your doctor or nurse may reduce dose of your medicine.

Use in children
Morphine sulfate is not recommended for use in children.

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.

If you think you have been given more Morphine sulfate than you should
As this medicine will be given to you whilst you are in hospital, it is unlikely that you will be given too little or too much, however, tell your doctor or nurse if you have any concerns.
Overdose may cause pneumonia from inhaling vomit or foreign matter, symptoms may include breathlessness, cough and fever. Symptoms of serious overdose include breathing difficulties leading to unconsciousness or even death, low blood pressure with your heart finding it difficult to pump blood around your body, a deepening coma, feeling cold, fits especially in infants and children and rapid break down of muscle tissue (characterized by dark coloured urine and muscle tenderness, stiffness or aching) progressing to kidney failure.
If you have these symptoms, you will be given another medicine called Naloxone to reverse the effects of Morphine sulfate.
If you have any further questions about the use of this medicine, ask your doctor or nurse.

If you stop using Morphine sulfate
Do not stop treatment with Morphine sulfate unless agreed with your doctor. If you want to stop the treatment with Morphine sulfate, ask your doctor how to slowly decrease the dose so you avoid abstinence symptoms. Abstinence symptoms may include body aches, tremors, diarrhoea, stomach pain, nausea, flu-like symptoms, fast heartbeat and large pupils. Psychological symptoms include an intense feeling of unsatisfaction, anxiety and irritability.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Seek immediate medical help if you have any of the following symptoms:
- Breathing difficulties (respiratory depression)
- Low blood pressure (hypotension) which may make you feel faint
- Your heart finding it difficult to pump blood around your body (circulatory failure) causing faintness, breathing difficulties, coughing up blood, excessive sweating and/or pale skin
- Serious allergic reaction which causes:
  - Swelling of hands, feet, lips, mouth, tongue or throat
  - Difficulty in breathing or dizziness
  - Itchy skin rash (hives)
- Stomach pains, bloating, vomiting and constipation (obstructive bowel disorder)
- Severe skin reaction with blistering, widespread scaly skin, pus-filled spots together with fever. This could be a condition called Acute Generalized Exanthematous Pustulosis (AGEP)

The other side effects which have been reported are:
Very common (may affect more than 1 in 10 people):
- Seeing or hearing things that are not there (hallucinations)
- Morphine is an addictive substance and its use can result in dependence
- Drowsiness and confusion
- Feeling (nausea) or being sick (vomiting)
- Constipation
- Sweating
- The drug no longer having the same effect as it used to (drug tolerance)

Common (may affect up to 1 in 10 people):
- Changes in your heart beat, such as slowing (bradycardia) or quickening (tachycardia) of the heart beat
- Low body temperature (hypothermia)
- Raised pressure in the skull (increased intracranial pressure)
- Abdominal pain (biliary spasms)
- Constriction of the pupil (miosis)

- Blurred vision
- Involuntary eye movements (nystagmus)
- A feeling of dizziness or "spinning" (vertigo)
- Dizziness/light headedness on standing (orthostatic hypotension)
- Difficulty passing urine
- Headaches
- Changes of mood
- Decreased libido (interest in sex) or inability to get an erection
- Dry mouth
- Facial flushing (warmth and redness of the skin)
- Restlessness
- Fits (convulsions)
- Increased sensitivity to pain
- Tiredness (fatigue)
- Stopping the drug can lead to withdrawal symptoms such as agitation, anxiety, shaking or sweating. This can also happen to babies born to mothers addicted to morphine.
- Pain and irritation may occur at the site of the injection

Uncommon (may affect up to 1 in 100 people):
- Being aware that your heart is beating or the rate has changed (palpitations)
- Abdominal pain (urethral spasms)
- An increase in liver enzymes may be noted during blood tests

Not known (cannot be estimated from the available data):
- Muscle stiffness with high doses
- Pain, generally on the skin, caused by something that would not normally cause pain such as light touch or pressure
- Coma
- Kidney failure
- Abstinence symptoms or dependence (for symptoms see section 3: If you stop using Morphine sulfate)
- Sleep apnoea (breathing pauses during sleep)
- Symptoms associated with inflammation of the pancreas (pancreatitis) and the biliary tract system, e.g. severe upper abdominal pain possibly radiating to the back, nausea, vomiting or fever

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via:
UK(NI): Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.
IE: HPRA Pharmacovigilance, Website: www.hpra.ie
MT: ADR Reporting, Website: www.medicinesauthority.gov.mt/adrportal.
By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Morphine sulfate

Keep this medicine out of the sight and reach of children.
Keep the ampoules in the outer carton in order to protect from light.

Product containing visible particles should not be used.

Do not use this medicine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Morphine sulfate contains
- The active substance is morphine sulfate 10 mg, 15 mg and 30 mg in each 1 ml of solution.
- The other ingredients are sodium chloride, hydrochloric acid (for pH adjustment), water for injections.

What Morphine sulfate looks like and contents of the pack
Clear colourless or almost colourless solution for injection.
Morphine sulfate 10 mg/ml, 15 mg/ml and 30 mg/ml are presented in 1 ml amber glass ampoules 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.

Marketing Authorisation Holder and Manufacturer
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The following information is intended for healthcare professionals only:

1. NAME OF THE MEDICINAL PRODUCT

Morphine sulfate 10 mg/ml solution for injection
Morphine sulfate 15 mg/ml solution for injection
Morphine sulfate 30 mg/ml solution for injection

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 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. 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 antimuscarinic analgesic 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 single-dose administration seems to be compatible with breast feeding and insufficient to cause major problems or dependence. However long-term treatment with morphine in high doses may cause significant plasma concentration. That is why caution is advised on the use of morphine in breast-feeding 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.
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
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
    - The medicine has been prescribed to treat a medical or dental problem and
    - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
    - It was not affecting your ability to drive safely

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:

UK(NI): Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

IE: HPRA Pharmacovigilance, Website: www.hpra.ie

MT: ADR Reporting, Website: www.medicinesauthority.gov.mt/adrportal.

4.9 Overdose

Symptoms: respiratory depression, pin-point 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.

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.

MARKETING AUTHORISATION HOLDER
AS KALCEKS, Krustpils iela 71E, Rīga, LV-1057, Latvia, Tel.: +371 67083320, E-mail: kalceks@kalceks.lv

MARKETING AUTHORISATION NUMBER(S)

	Malta	**United Kingdom (Northern Ireland)**	**Ireland**

Morphine Sulfate 10 mg/ml solution for injection	MA1207/00301	PL 47015/0003	PA2165/003/001
Morphine Sulfate 15 mg/ml solution for injection	MA1207/00302	PL 47015/0004	PA2165/003/002
Morphine Sulfate 30 mg/ml solution for injection	MA1207/00303	PL 47015/0005	PA2165/003/003