APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S6

1 NAME OF THE MEDICINE

Morphine Sulphate 10 mg/1 ml Fresenius solution for injection/infusion.

Morphine Sulphate 15 mg/1 ml Fresenius solution for injection/infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml ampoule contains 10 mg or 15 mg morphine sulphate.

Excipients with known effect:

Morphine Sulphate 10 mg/1 ml Fresenius: Each 1 ml contains 3 mg sodium.

Morphine Sulphate 15 mg/1 ml Fresenius: Each 1 ml contains 2,7 mg sodium.

Contains no sugar or preservatives.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion.

A clear, colourless or almost colourless or light straw to yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Relief of intractable pain not controlled with non-narcotic analgesics.

4.2 Posology and method of administration

Posology

Subcutaneous or intramuscular injection:

Adults: 5 to 20 mg every 4 hours

Children: 1 to 5 years: 2,5 to 5 mg

6 to 12 years: 5 to 10 mg.

Slow intravenous injection or as loading dose for continuous or patient-controlled infusions:

Adults: up to 15 mg.

Maintenance dose for continuous intravenous administration and continuous subcutaneous infusion:

From 0,8 to 80 mg per hour.

Intrathecal dose ranges from 0,2 to 1,0 mg and must only be given as a single dose.

Method of Administration

Doses should generally be reduced in the elderly, debilitated patients or in patients with renal impairment.

Administer with caution or in reduced doses to patients with hypothyroidism, adrenocortical insufficiency, impaired liver function and prostatic hypertrophy or shock.

4.3 Contraindications

- Hypersensitivity to morphine sulphate or to any of the excipients of **Morphine Sulphate Fresenius** listed in section 6.1.
- Patients taking monoamine oxidase inhibitors or within 10 days of stopping such treatment**.**
- Acute respiratory depression, and obstructive airway disease especially in the presence of cyanosis and excessive bronchial secretion.
- In the presence of acute alcoholism, convulsive disorders, head injuries, comatose patients and conditions in which intracranial pressure is raised.

- During an attack of bronchial asthma or in heart failure secondary to chronic lung disease.
- Biliary colic (see section 4.4).
- Paralytic ileus.
- Phaeochromocytoma
- Acute diarrhoeal caused by poisoning or invasive pathogens.

4.4 Special warnings and precautions for use

The euphoric activity of morphine may lead to abuse. Dependence and tolerance to **Morphine Sulphate Fresenius** may occur.

Morphine Sulphate Fresenius should be used with extreme caution in patients with decreased respiratory reserve.

In the case of geriatric or debilitated patients, and in patients with hypotension, hypothyroidism, convulsive disorders, adrenocortical insufficiency, myasthenia gravis, urethral stricture, impaired kidney or liver function, prostatic hypertrophy, shock or inflammatory or obstructive bowel disorders, it should be used with caution and the dosage reduced.

Hepatobiliary disorders

Opioids such as **Morphine Sulphate Fresenius** should either be avoided in patients with biliary disorders, or they should be given with an antispasmodic.

Morphine Sulphate Fresenius 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 contraindicated, see section 4.3).

In patients given **Morphine Sulphate Fresenius** after cholecystectomy, biliary pain has been induced.

Risk from concomitant use of sedative medicines such as benzodiazepines or related medicines

Concomitant use of **Morphine Sulphate Fresenius** and sedative medicines such as benzodiazepines or related medicines 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 Sulphate Fresenius** 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 treatment with a P2Y12 inhibitor and morphine, as in **Morphine Sulphate Fresenius**, 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 amenorrhoea.

Opioid Use Disorder (abuse and dependence)

Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as **Morphine Sulphate Fresenius.**

Repeated use of **Morphine Sulphate Fresenius** 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 Sulphate Fresenius** 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 (eg. major depression, anxiety and personality disorders).

Before initiating treatment with **Morphine Sulphate Fresenius** and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient. 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 doctor.

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.

Symptoms can be minimised with adjustments of dose or dosage form and gradual withdrawal of morphine. For individual symptoms, see section 4.8.

Hyperalgesia that does not respond to a further dose increase of morphine may occur, particularly at high doses. A dose reduction or change in opioid may be required.

Treatment goals and discontinuation

Before initiating treatment with **Morphine Sulphate Fresenius**, 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 doctor 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 Sulphate Fresenius**, 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.

Duration of treatment

Morphine Sulphate Fresenius should not be used longer than necessary.

Morphine Sulphate Fresenius contains sodium

Morphine Sulphate Fresenius contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially sodium free.

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.

4.5 Interaction with other medicines and other forms of interaction

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

Alcohol: Enhanced sedative and hypertensive effects.

Dysrhythmics: 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 9MAOI's) including selegiline, moclobemide and linezolid. As it is 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 MAOI's.

The sedative effects of **Morphine Sulphate Fresenius** are enhanced when used with central nervous system depressants such as alcohol, anaesthetics, hypnotics, sedatives, tricyclic antidepressants and phenothiazines.

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

Antipsychotics: Possible enhanced sedative and hypotensive effect.

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

Antimuscarinics: Medicines 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 medicines: The concomitant use of opioids with sedative medicines such as benzodiazepines or related medicines 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.

4.6 Fertility, pregnancy, and lactation

Pregnancy

The safety of **Morphine Sulphate Fresenius** during pregnancy has not been established. Regular use during pregnancy may cause physical dependence in the f**o**etus, leading to withdrawal symptoms in the neonate. Use during labour may cause respiratory depression in the neonate.

Breastfeeding

The safety of **Morphine Sulphate Fresenius** has not been established in breastfeeding women.

4.7 Effects on ability to drive and use machines

Drowsiness may affect the ability to perform skilled tasks. Those affected should not drive a vehicle or operate machinery.

4.8 Undesirable effects

Side effects have been ranked according to frequency within each system organ class. The following adverse reactions have been reported with **Morphine Sulphate Fresenius:**

MedDRA system organ class	**Frequency**	**Adverse reactions**
Immune system disorders:	Frequent	Histamine release (decreased blood pressure, fast heartbeat, increased sweating, redness or flushing of the face, wheezing or troubled breathing).
	Less frequent	Allergic reaction (skin rash, hives, and/or itching, swelling of face).
Metabolism and nutritional disorders:	Less frequent	Loss of appetite.
Psychiatric disorders:	Less frequent:	False sense of wellbeing, general feeling of discomfort or illness, nervousness or restlessness, insomnia, confusion, hallucinations, mental depression. Decreased libido, mood swings, restlessness.
	Frequency unknown	Nightmares or unusual dreams
Nervous system disorders:	Frequent	Drowsiness, hyperhidrosis.
	Less frequent	Headache, paradoxical CNS stimulation (unusual excitement or restlessness, especially in children).

MedDRA system organ class	**Frequency**	**Adverse reactions**
	Frequency unknown	Convulsions, allodynia
Eye disorders	Less frequent	Miosis, nystagmus.
	Frequency unknown	Blurred or double vision or other changes in vision
Ear and labyrinth disorders	Frequency unknown	Tinnitus (ringing or buzzing in the ears).
Cardiac disorders	Less frequent	Bradycardia, tachycardia, pounding heartbeat.
	Frequency unknown	Palpitations.
Vascular disorders	Less frequent	Dizziness, feeling faint or light-headedness, hypotension, orthostatic hypotension.
	Frequency unknown	Increased blood pressure.
Respiratory, thoracic, and mediastinal disorders	Less frequent	Atelectasis, bronchospastic allergic reaction, laryngeal oedema, allergic laryngospasm, respiratory depression.
		Central sleep apnoea syndrome.
Gastrointestinal	Frequent	Nausea and vomiting, constipation.

MedDRA system organ class	**Frequency**	**Adverse reactions**
disorders	Less frequent	Dry mouth, gastrointestinal irritation (stomach cramps or pain), paralytic ileus or toxic megacolon.
	Frequency unknown	Intestinal functional disorder, narcotic bowel syndrome, pancreatitis.
Hepato-biliary disorders	Less frequent	Biliary spasm, hepatic enzyme increase.
	Frequency unknown	Hepatotoxicity, spasm of the sphincter of Oddi.
Skin and subcutaneous tissue disorder	Frequent	Pruritus
	Less frequent	Urticaria, rash, angioedema, contact dermatitis.
		Acute generalised exanthematous pustulosis (AGEP).
Musculoskeletal and connective tissue disorders	Less frequent	Muscle rigidity (especially in muscles of respiration), trembling or uncontrolled muscle movements.
	Frequency unknown	Rhabdomyolysis.
Renal and	Frequent	Urinary retention.

MedDRA system organ class	**Frequency**	**Adverse reactions**
urinary disorders	Less frequent	Ureteral spasm (difficult or painful urination, frequent urge to urinate), antidiuretic effect.
	Frequency unknown	Renal failure.
Reproductive system and breast disorders	Frequent	Erectile dysfunction.
General disorders and administration site conditions	Frequent	Unusual tiredness or weakness, medicine tolerance
	Less frequent	Redness, swelling, pain or burning at the site of injection, medicine withdrawal (abstinence) syndrome (babies born to opioid-dependent mothers also at risk of present withdrawal syndrome).

Description of selected adverse reactions:

Dependence and withdrawal (abstinence) syndrome.

Repeated use of opioid analgesics may be associated with the development of physical and/or psychological dependence or tolerance, even at therapeutic doses. An abstinence syndrome may be precipitated when opioid administration is suddenly discontinued, or opioid antagonists administered, or can sometimes be experienced between doses. The

risk of dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4). 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 dependence, “drug craving” is often involved.

Post-marketing data

Less frequent: increased risk of abdominal pain, including pancreatitis has been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of **Morphine Sulphate Fresenius** is important. It allows continued monitoring of the benefit/risk balance of **Morphine Sulphate Fresenius**. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Healthcare providers are asked to report any suspected Adverse Drug Reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com, and to the relevant medicines’ regulatory authority in the country where the product is marketed.

4.9 Overdose

Signs and symptoms of overdose indicating need for medical attention: cold and clammy skin, confusion, convulsions, severe dizziness, severe drowsiness, low blood pressure,

nervousness or severe restlessness, pinpoint pupils of eyes, slow heartbeat, slow or troubled breathing, unconsciousness, severe weakness (see section 4.8).

Intensive supportive therapy may be required to correct respiratory failure and shock. Death may occur from respiratory failure. The specific antagonist naloxone hydrochloride is used. A dose of 0,4 to 2 mg is given intravenously every 2 to 3 minutes, if necessary up to 10 mg. For children, the initial dose is 0,01 mg/kg. It may also be given by subcutaneous or intramuscular injection. Additional doses may be required to prevent relapse.

The circulation should be maintained with infusions of dextrose injection and suitable electrolyte solutions. Assisted respiration may be necessary.

The use of opioid antagonists such as naloxone, nalorphine, and levallorphan in persons physically dependent on morphine or related medicines may induce withdrawal symptoms.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.9 Other analgesics.

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

Morphine salts are well absorbed from the gastrointestinal tract but have poor oral bioavailability, since they undergo extensive first-pass metabolism in the liver and gut.

After subcutaneous or intramuscular injection morphine is rapidly absorbed into the blood.

Distribution

Morphine is distributed throughout the body but mainly in the kidneys, liver, lungs and spleen, with lower concentrations appearing in the brain and muscles. Morphine crosses the blood-brain barrier less readily than more lipid-soluble opioids such as diamorphine, but it has been detected in the cerebrospinal fluid (CSF) as its highly polar metabolites morphine-3-glucuronide and morphine-6-glucuronide.

Morphine diffuses across the placenta and traces also appear in breast milk and sweat.

About 35 % is protein bound to albumin and to immunoglobulins at concentrations within the therapeutic range.

Biotransformation

The majority of a dose of morphine is conjugated with glucuronic acid in the liver and gut to produce morphine-3-glucuronide and morphine-6-glucuronide, with sulphate conjugation. The latter is considered to contribute to the analgesic effect of morphines.

Morphine-3-glucuronide on the other hand may antagonise the analgesic action and might be responsible for the paradoxical pain observed in some patients given morphine.

Other active metabolites include normorphine, codeine, and morphine ethereal sulphate.

Enterohepatic circulation probably occurs. *N*-demethylation, *O*-methylation and *N*-oxide glucuronide formation occur in the intestinal mucosa and liver; *N*-demethylation occurs to a greater extent after oral than parenteral 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

Mean plasma elimination half lives of about 2 hours for morphine and 2,4 to 6,7 hours for morphine-3-glucuronide have been reported.

Morphine is eliminated by glomerular filtration. 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 acid 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

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Sulphuric acid (for pH adjustment)

Water for injection.

6.2 Incompatibilities

Morphine salts, such as **Morphine Sulphate Fresenius**, are sensitive to changes in pH and morphine is liable to be precipitated out of solution in an alkaline environment. Morphine sulphate is incompatible with oxidizing agents. Physicochemical incompatibility has been demonstrated between solutions of morphine sulphate and 5-fluorouracil.

6.3 Shelf life

Morphine Sulphate Fresenius 10 mg/1 ml: 36 months.

Morphine Sulphate Fresenius 15 mg/1 ml: 60 months.

6.4 Special precautions for storage

Protect from light. Store at or below 25 °C.

6.5 Nature and contents of container

Containers with 10 x 1 ml amber ampoules.

Morphine Sulphate 10 mg/1 ml Fresenius: packed in 1 ml amber OPC glass ampoule (Type I) with a red ring above the neck.

Morphine Sulphate 15 mg/1 ml Fresenius: packed in 1 ml amber OPC glass ampoule (Type I) with a yellow ring above the neck.

6.6 Special precautions for disposal and other handling

Any unused medicine should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBERS

Morphine Sulphate 10 mg/1 ml Fresenius: B930 (Act 101/1965)

Morphine Sulphate 15 mg/1 ml Fresenius: B931 (Act 101/1965)

9 DATE OF FIRST AUTHORISATION

Not applicable.

10 DATE OF REVISION OF THE TEXT

03 March 2025.