MODULE 1 ADMINISTRATIVE INFORMATION AND PRESCRIBING INFORMATION

1.6 Product Information

1.6.1 Summary of Product Characteristics

- Package Insert

Refer attached

1.6.1 PACKAGE INSERT

SCHEDULING STATUS
S6

PROPRIETARY NAMES AND DOSAGE FORM
Morphine Sulphate Fresenius PF 10 mg/1 ml
Morphine Sulphate Fresenius PF 15 mg/1 ml
Injection

COMPOSITION
Each 1 ml ampoule contains 10 or 15 mg morphine sulphate.
The inactive ingredients are: Sodium chloride, water for injection, sulphuric acid (for pH-adjustment)
Contains no sugar or preservatives

PHARMACOLOGICAL CLASSIFICATION
A 2.9 Other analgesics

PHARMACOLOGICAL ACTION
Pharmacodynamic properties:
Morphine acts as an agonist particularly at μ receptors, and also d and K-receptors. Its effects are diverse and include analgesia, drowsiness, changes in mood, respiratory depression, decreased gastrointestinal motility, nausea, vomiting and alterations of the endocrine and autonomic nervous systems. The development of tolerance and physical dependence is a characteristic feature.

Pharmacokinetic properties:
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 readily absorbed into the blood. 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. 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.
Morphine is distributed throughout the body but mainly in the kidneys, liver, lungs and spleen, with lower concentrations 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 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. 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. Up to 10 % of a dose of morphine may eventually be

excreted, as conjugates, through the bile into the faeces. The remainder is excreted in the urine, mainly as conjugates. About 90 % of total morphine is excreted in 24 hours with traces in urine, for 48 hours or more. The latter is due to the occurrence of enterohepatic circulation of morphine and its glucuronides.

INDICATIONS

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

CONTRA-INDICATIONS

Morphine Sulphate Fresenius PF is not usually administered to children under the age of one year.
It is contra-indicated in:

- patients taking monoamine oxidase inhibitors or within 10 days of stopping such treatment;
- 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 and conditions in which intracranial pressure is raised;
- during an attack of bronchial asthma or in heart failure secondary to chronic lung disease.

WARNINGS AND SPECIAL PRECAUTIONS

The euphoric activity of morphine may lead to abuse. Dependence and tolerance to morphine may occur.
Morphine Sulphate Fresenius PF should be used with extreme caution in patients with decreased respiratory reserve.
In the case of geriatric patients, and in patients with hypothyroidism, adrenocortical insufficiency, impaired kidney or liver function, prostatic hypertrophy, shock or inflammatory or obstructive bowel disorders, it should be used with caution and the dosage reduced.
It should be used with caution in patients with myasthenia gravis and in patients taking monoamine oxidase inhibitors.
The administration of opioid analgesics during labour may cause respiratory depression in the newborn infant.
The dosage should be reduced in elderly and debilitated patients.

Driving and using machinery

Drowsiness may affect the ability to perform skilled tasks; those affected should not drive or operate machinery.

INTERACTIONS

The depressant effects of Morphine Sulphate Fresenius PF are enhanced by central nervous system depressants such as alcohol, anaesthetics, hypnotics, sedatives, tricyclic antidepressants and phenothiazines.

PREGNANCY AND LACTATION

The safety of this preparation during pregnancy and lactation has not been established.
Morphine Sulphate Fresenius PF crosses the placenta and is distributed into breast milk, hence risk-benefit must be considered before use during pregnancy or lactation. Regular use during pregnancy may cause physical dependence in the foetus, leading to withdrawal symptoms in the neonate. Use during labour may cause respiratory depression in the neonate.

1.6.1 Summary of Product Characteristics (Morphine sulphate Fresenius PF 10 mg/1 ml, Morphine sulphate Fresenius PF 15 mg/1 ml, Solution for injection / infusion)

DOSAGE AND DIRECTIONS FOR USE

Doses should generally be reduced in the elderly or debilitated 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.

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.

SIDE 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 PF:

Cardiac disorders:

Less frequent: Bradycardia, tachycardia, pounding heartbeat

Gastrointestinal disorders:

Frequent: Nausea and vomiting, constipation
Less frequent: Dry mouth, gastrointestinal irritation (stomach cramps or pain), paralytic ileus or toxic megacolon

General disorders and administration site conditions:

Frequent: Unusual tiredness or weakness
Less frequent: Redness, swelling, pain or burning at the site of injection

Hepatobiliary disorders:

Less frequent: Biliary spasm
The following side effect has been reported but the frequency is unknown: Hepatotoxicity

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

Musculoskeletal and connective tissue disorders:
Less frequent: Muscle rigidity (especially in muscles of respiration), trembling or uncontrolled muscle movements

Nervous system disorders:
Frequent: Drowsiness
Less frequent: Headache, paradoxical CNS stimulation (unusual excitement or restlessness, especially in children), blurred or double vision or other changes in vision
The following side effects have been reported but frequencies are unknown: Convulsions, tinnitus (ringing or buzzing in the ears)

Psychiatric disorders:
Less frequent: False sense of wellbeing, general feeling of discomfort or illness, nervousness or restlessness, insomnia, confusion, hallucinations, mental depression
The following side effects have been reported but frequencies are unknown:
Nightmares or unusual dreams

Renal and urinary disorders:
Less frequent: Ureteral spasm (difficult or painful urination, frequent urge to urinate), antidiuretic effect

Respiratory, thoracic and mediastinal disorders:
Less frequent: Atelectasis; bronchospastic allergic reaction; laryngeal oedema; allergic laryngospasm; respiratory depression

Vascular disorders:
Less frequent: Dizziness, feeling faint or light-headedness, hypotension
The following side effect has been reported but frequency is unknown: Increased blood pressure

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
Signs and symptoms of overdose indicating need for medical attention: cold, 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 “Side effects”.
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 drugs may induce withdrawal symptoms.

IDENTIFICATION
A sealed, amber, glass ampoule containing a colourless or almost colourless solution; or a light straw to

yellow coloured solution

PRESENTATION
Containers with 10 x 1 ml amber ampoules
Morphine Sulphate Fresenius PF 10 mg: packed in an amber glass ampoule with a red ring above the neck
Morphine Sulphate Fresenius PF 15 mg: packed in an amber glass ampoule with a yellow ring above the neck

STORAGE INSTRUCTIONS
Protect from light. Store at or below 25 ºC.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS
Morphine Sulphate Fresenius PF 10 mg/1 ml: B930 (Act 101/1965)
Morphine Sulphate Fresenius PF 15 mg/1 ml: B931 (Act 101/1965)

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION
Fresenius Kabi Manufacturing SA (Pty) Ltd
6 Gibaud Road, Korsten, 6020, Port Elizabeth
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Botswana	15 mg	BOT0801158 S1A
Kenya	10 mg	H2014/CTD1217/053, POM
Namibia	10 mg	NS4 02 1001523 (Act 13/2003)
Namibia	15 mg	NS4 02 1001524 (Act 13/2003)
Tanzania	10 mg	TAN06, 364 V03A BOD, POM
Tanzania	15 mg	TAN06, 363 V03A BOD, POM
Uganda	10 mg	9431/02/16, POM
Uganda	15 mg	9432/02/16, POM
Zambia	10 mg	254/017, POM
Zambia	10 mg	254/018, POM
Zimbabwe	15 mg	2006/4.1/4434, 4.1 Narcotic analgesics