PROFESSIONAL INFORMATION

SCHEDULING STATUS

S6

1 NAME OF THE MEDICINE

Pharma-Q Morphine 10 mg Injection solution for injection

Pharma-Q Morphine 15 mg Injection solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Pharma-Q Morphine 10 mg Injection: Each 1 ml ampoule contains 10 mg morphine sulphate.

Pharma-Q Morphine 15 mg Injection: Each 1 ml ampoule contains 15 mg morphine sulphate.

Contains no sugar or preservative.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

A clear colourless to slightly 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 a loading dose for continuous or patient-controlled infusion:

Adults: Doses of up to 15 mg have been given.

Maintenance dose for continuous intravenous administration and continuous subcutaneous infusion:

Doses have generally ranged from 0,8 mg to 80 mg per hour.

Intrathecal dose~~s~~ range from 0,2 mg to 1 mg and should only involve the administration of a single dose.

Method of administration

Doses should generally be reduced in the elderly or 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

- Patients with a hypersensitivity to morphine sulphate or to any of the excipients of Pharma-Q Morphine Injection listed in section 6.1.
- 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 in 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).

- Phaeochromocytoma.
- Paralytic ileus.
- Acute diarrhoea caused by poisoning or invasive pathogens.
- Patients taking monoamine oxidase inhibitors or within 10 days of stopping such treatment.

4.4 Special warnings and precautions for use

The euphoric activity of morphine sulphate may lead to abuse. Dependence and tolerance to Pharma-Q Morphine Injection may occur.

Pharma-Q Morphine Injection 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.

Biliary disorders

Opioids such as Pharma-Q Morphine Injection should either be avoided in patients with biliary disorders, or they should be given with an antispasmodic.

Pharma-Q Morphine Injection can cause an increase in intrabiliary pressure as a result of effects on the sphincter of Oddi. Therefore, in patients with biliary tract disorders morphine may exacerbate pain (use in biliary colic is contraindicated, see section 4.3).

In patients given Pharma-Q Morphine Injection after cholecystectomy, biliary pain has been induced.

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

Concomitant use of Pharma-Q Morphine Injection 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 a Pharma-Q Morphine Injection 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 Pharma-Q Morphine Injection, 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.

Dependence and withdrawal (abstinence) syndrome

Use of opioid analgesics may be associated with the development of physical and/or psychological dependence or tolerance. The risk increases with the time the medicine 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 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.

Morphine Sulphate Fresenius contains sodium

Pharma-Q Morphine Injection contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially sodium free.

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: The sedative effects of Pharma-Q Morphine Injection are enhanced when used with central nervous system depressants such as alcohol, anaesthetics, hypnotics, sedatives, tricyclic antidepressants and phenothiazines.

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. 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.

4.5 Fertility, pregnancy and lactation

Pregnancy

The safety and efficacy of Pharma-Q Morphine Injection has not been established 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.

Breastfeeding

The safety of Pharma-Q Morphine Injection has not been established in breastfeeding women.

Fertility

Animal studies have shown that morphine may reduce fertility.

4.6 Effects on ability to drive and use machines

Patients should be advised not to drive or use machines until they know how they are affected by the administration of Pharma-Q Morphine Injection, as drowsiness and dizziness may occur with the use of Pharma-Q Morphine Injection and may affect the ability to perform skilled tasks. Patients who experience such effects should be advised not drive or operate machinery.

4.7 Undesirable effects

Adverse effects are listed below according to system organ class and their frequency of occurrence: frequent, less frequent and frequency unknown.

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). Anaphylactic reaction, hypersensitivity.
	Frequency unknown	Anaphylactoid reactions.
Metabolism and nutritional disorders	Less frequent	Loss of appetite.
Psychiatric disorders	Frequent	Physical and psychological dependence.
	Less frequent	False sense of wellbeing, general feeling of discomfort or illness, nervousness or restlessness, insomnia, confusion,

MedDRA system organ class	**Frequency**	**Adverse reactions**
		hallucinations, mental depression, decreased libido, mood swings, restlessness.
	Frequency unknown	Nightmares or unusual dreams.
Nervous system disorders	Frequent	Drowsiness, hyperhidrosis, dizziness, increased intracranial pressure, myoclonus; opioid-induced hyperalgesia (or hyperaesthesia), vertigo.
	Less frequent	Headache, paradoxical CNS stimulation (unusual excitement or restlessness, especially in children).
	Frequency unknown	Allodynia, coma, convulsions.
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, circulatory failure, tachycardia.
	Frequency unknown	Palpitations.

MedDRA system organ class	**Frequency**	**Adverse reactions**
Vascular disorders	Less frequent	Dizziness, feeling faint or light-headedness, hypotension, orthostatic hypotension.
	Frequency unknown	Increased blood pressure.
Respiratory, thoracic and mediastinal disorders	Frequent	Bronchospasm, pulmonary oedema, which can lead to death.
	Less frequent	Atelectasis, bronchospastic allergic reaction, laryngeal oedema, allergic laryngospasm, respiratory depression.
	Frequency unknown	Respiratory failure, which also can lead to death.
Gastrointestinal disorders	Frequent	Nausea, vomiting, constipation.
	Less frequent	Dry mouth, paralytic ileus, gastrointestinal irritation (stomach cramps or pain), toxic megacolon, increased risk of abdominal pain, including pancreatitis.
	Frequency unknown	Anorexia, intestinal functional disorder, narcotic bowel syndrome.
Hepato-biliary disorders	Less frequent	Biliary spasm, hepatic enzyme increase.
	Frequency	Hepatotoxicity, spasm of the

MedDRA system organ class	**Frequency**	**Adverse reactions**
	unknown	sphincter of Oddi.
Skin and subcutaneous tissue disorders	Frequent	Pruritus
		Urticaria, rash, angioedema, contact dermatitis.
Musculoskeletal and connective tissue disorders	Less frequent	Muscle rigidity (especially in muscles of respiration), trembling or uncontrolled muscle movements.
	Frequency unknown	Rhabdomyolysis.
Renal and urinary disorders	Frequent	Urinary retention.
	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, fatigue, facial flushing, hypothermia.
	Less frequent	Redness, swelling, pain or burning at the site of injection, medicine withdrawal (abstinence) syndrome (babies born to opioid-

MedDRA system organ class	Frequency	Adverse reactions
		dependent mothers also at risk of present withdrawal syndrome).

c. Description of selected adverse reactions

Histamine release

- Due to the histamine-releasing effect, urticarial, pruritus and contact dermatitis as well as hypotension and flushing may occur.
- Anaphylactic reactions following intravenous injection may occur as well as muscle rigidity.
- Toxic doses vary considerably with the individual and regular users may tolerate large doses.

Drug dependence and withdrawal (abstinence) syndrome

Use of opioid analgesics may be associated with the development of physical and/or psychological dependence or tolerance. 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 medicine is

important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.8 Overdose

Signs and symptoms of overdose which indicate a need for medical attention:

Cold and clammy skin, confusion, convulsions, severe dizziness, severe drowsiness, low blood pressure, severe nervousness or restlessness, pinpoint pupils of eyes, slow heartbeat, slow or troubled breathing, unconsciousness and 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 mg to 2 mg is given intravenously, repeated at an interval of 2 to 3 minutes if necessary, administering up to 10 mg. For children, the initial dose is 0,01 mg/kg.

Naloxone may also be given by subcutaneous or intramuscular injection.

Additional doses may be required to prevent relapses.

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

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 readily absorbed into the blood.

Distribution

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 breastmilk 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. The latter is considered to contribute to the analgesic effect of morphine. 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Nitrogen

Sodium chloride

Water for injections

6.2 Incompatibilities

Morphine salts, such as in Pharma-Q Morphine Injection, 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

24 months

6.4 Special precautions for storage

Store at or below 25 ºC.

Protect from light.

6.5 Nature and contents of container

1 ml amber ampoules in containers of 10 or 100.

6.6 Special precautions for disposal and other handling

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

PHARMA-Q HOLDINGS (PTY) LTD

50 Commando Road

Industria West, 2093

Johannesburg

South Africa

8 REGISTRATION NUMBERS

Pharma-Q Morphine 10 mg Injection: 29/2.7/0475

Pharma-Q Morphine 15 mg Injection: 29/2.7/0476

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Original date of registration: February 2011

10 DATE OF REVISION OF THE TEXT

1 May 2024