Professional Information (PI)

for Medicines for Human Use

MORPHINE 10 mg UNIMED (Injection)

MORPHINE 15 mg UNIMED (Injection)

SCHEDULING STATUS:

S6

1. NAME OF THE MEDICINE

MORPHINE 10 mg UNIMED (Injection)

MORPHINE 15 mg UNIMED (Injection)

2. QUALTITATIVE AND QUANTITATIVE COMPOSITION

MORPHINE 10 mg UNIMED

Each 1 ml ampoule contains 10 mg morphine sulphate

MORPHINE 15 mg UNIMED

Each 1 ml ampoule contains 15 mg morphine sulphate

Antioxidant: Sodium metabisulphate 0,1 % *m/v*.

Contains no sugar or preservatives

For full list of excipients, see section 6.1

Antioxidant: Sodium metabisulphate 0,1 % *m/v*.

Contains no sugar or preservatives

3. PHARMACEUTICAL FORM

MORPHINE 10 mg UNIMED: 1 ml amber glass ampoules containing a colourless to almost colourless solution.

MORPHINE 15 mg UNIMED: 1 ml amber glass ampoules containing a colourless to almost colourless solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MORPHINE UNIMED is an analgesic for the symptomatic relief of severe pain especially that associated with neoplastic disease, myocardial infarction and surgery.

4.2 Posology and method of administration

The usual dose by subcutaneous or intramuscular injection is 5 to 20 mg every 4 hours.

Paediatric population

Children up to 1 month of age may be given 150 µg per kg body mass every 4 hours; those aged 1 to 12 months: 200 µg per kg; 1 to 5 years: 2,5 to 5 mg; 6 to 12 years: 5 to 10 mg.

Elderly or debilitated patients

The dosage should be reduced in elderly and debilitated patients.

Doses of up to 15 mg have been given by slow intravenous injection sometimes as a loading dose for continuous or patient-controlled infusion. For continuous intravenous administration,

maintenance doses have generally ranged from 0,8 to 80 mg per hour although some patients have required and been given much higher doses.

Method of administration

By subcutaneous, instramuscular or slow intravenous administration.

4.3 Contraindications

MORPHINE UNIMED is contraindicated in:

- Hypersensitivity to morphine sulphate or to any of the excipients of MORPHINE UNIMED (see section 6.1)
- Patients taking monoamine oxidase inhibitors or within 14 days of stopping such treatment.
- Morphine Unimed is contra-indicated in respiratory depression, 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

MORPHINE UNIMED is liable to be subject to abuse, the euphoric activity of morphine has led to its abuse. Dependance and tolerance to Morphine Unimed may occur.
MORPHINE UNIMED should be used with extreme caution in patients with decreased respiratory reserve.
It should be given with extreme care to newborn or premature infants for other conditions. It should be given with caution or in reduced doses to patients with hypotension hypothyroidism, convulsive disorders, adrenocortical insufficiency, myasthenia gravis, urethral stricture, impaired kidney or liver function, prostatic hypertrophy, or shock or inflammatory or obstructive bowl disorders. Larger doses produce respiratory depression and hypotension, with circulatory failure and deepening coma. Convulsions may occur in infants and children. Death may occur from respiratory failure. Toxic doses vary considerably with the individual.

Biliary Disorders

Opioids such as MORPHINE UNIMED should either be avoided in patients with biliary disorders or they should be given with an antispasmodic.
MORPHINE UNIMED 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 MORPHINE UNIMED after cholecystectomy, biliary pain has been induced.

Risk from concomitant use of sedative medicines such as benzodiazepines or medicines*:*

Concomitant use of MORPHINE UNIMED 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 UNIMED 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.

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.

Mental health disorders or Psychological dependence (addiction)

MORPHINE UNIMED should be used with particular care in patients with a personal or family history of substance abuse or mental health disorders including, but not limited to major depression, anxiety and alcohol and drug abuse.

MORPHINE UNIMED contains sodium

MORPHINE UNIMED contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially sodium-free.

Note: Facilities for administration of oxygen and assisted respiration should be available if morphine is given intravenously.

4.5 Interaction with other medicines and other forms of interaction

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 depressant effects of MORPHINE UNIMED are enhanced by depressants of the central nervous system such as alcohol, anaesthetics, hypnotics and sedatives, tricyclic antidepressants and phenothiazines

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

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 UNIMED during pregnancy has not been established. Regular use during pregnancy may cause physical dependence in the foetus, leading to withdrawal symptoms in the neonate. The administration of opioid analgesics during labour may cause respiratory depression in the newborn infant.

Lactation

The safety of MORPHINE UNIMED 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

Table 1: Tabulated list of adverse reactions

System Organ Class	Frequency	Adverse effect
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 disorder	*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 not known	Nightmares or unusual dreams
Nervous system disorders	*Frequent*	Drowsiness, hyperhidrosis
	Less Frequent	Headache, paradoxical CNS stimulation (unusual excitement or restlessness, especially in children), vertigo
	Frequency not known	Convulsions, allodynia
Eye disorders	*Less Frequent*	Miosis, nystagmus
	Frequency not known	Blurred or double vision or other changes in vision

Ear and labyrinth	*Frequency not known*	Tinnitus (ringing or buzzing in the ears).
Cardiac Disorders	*Less Frequent*	Bradycardia, tachycardia, pounding heartbeat
	Frequency not known	Palpitations
Vascular Disorders	*Less Frequent*	Dizziness, feeling faint or light-headedness, hypotension, orthostatic hypotension
	Frequency not known	Increased Blood Pressure
Respiratory, thoracic and mediastinal disorders	*Less Frequent*	Atelectasis, bronchospastic allergic reaction, laryngeal oedema, allergic laryngospasm, respiratory depression
Gastrointestinal disorders	*Frequent*	Nausea and vomiting, constipation.
	Less Frequent	Dry mouth, gastrointestinal irritation (stomach cramps or pain), paralytic ileus or toxic megacolon.
	Frequency Unknown	Intestinal functional disorder, narcotic bowel syndrome
Hepato-billary disorders	*Less Frequent*	Biliary spasm, hepatic enzyme increase.
	Frequency not known	Hepatotoxicity, spasm of the sphincter of Oddi
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
Skin and subcutaneous tissue disorders	*Frequent*	pruritus, sweating, facial flushing
	Less Frequent	Urticaria, rash, angioedema, contact dermatitis
Reproductive system and breast disorders	*Frequent*	Erectile dysfunction
General disorders and administrative site conditions	*Frequent*	Unusual tiredness or weakness, medicine tolerance
	Less Frequent	Redness, swelling, pain 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:

Dependance and withdrawal (abstinence) syndrome.

Use of opioid analgesics may be associated with the development of physical and/or psychological dependance 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. Pychological symtoms 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 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 the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc-org) found on SAHPRA website

4.9 Overdose

Symptoms and signs

Signs and symptoms of overdose indicating need for medical attention: cold clammy skin; confusion; convulsions; serve dizziness; serve drowsiness; low blood pressure; nervousness or serve restlessness; pinpoint pupils of eyes; slow heartbeat; slow or troubled breathing; unconsciousness; severe weakness (see section 4.8).

Management of overdose

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, repeated at intervals of 2 to 3 minutes if necessary, up to 10 mg. For children, the initial dose is 0,01 mg/kg. Naloxone may also be given by subcutaneous or intramuscular injection. The effect of naloxone may be of shorter duration than that of the opioid analgesic and additional doses may be required to prevent relapses.

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

A 2.9 Other analgesics

ATC Code: N02AA01

Morphine Unimed is an opioid analgesic. The major effects are produced on the central nervous system and the bowel.

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, the onset of action is 10 - 30 minutes. The duration of action is 4 - 5 hours.

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, 0-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 UNIMED is eliminated by glomerular filtration. 90% of total excretion takes place during the first day, 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.

Enterohepatic circulation of morphine and its glucuronides occurs, which accounts for small amounts of morphine in the faeces and in the urine for several days after the last dose.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride

Sodium Metabisulphate

Nitrogen

Water for Injection

6.2 Incompatibilities

Morphine salts are sensitive to changes in pH and morphine is liable to be precipitated out of solution in an alkaline environment. Incompatibilities with other ~~drugs~~ medicines in solution have been reported. 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 10 mg UNIMED: 24 months

MORPHINE 15 mg UNIMED: 24 months

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light.

KEEP OUT OF THE REACH OF CHILDREN.

6.5 Nature and contents of container

Polystyrene containers or cartons with 10 x 1 ml amber glass ampoules.

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

Unimed Healthcare (Pty) Ltd

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8 REGISTRATION NUMBER(S)

MORPHINE 10 mg UNIMED: 30/2.9/0181

MORPHINE 15 mg UNIMED: 28/2.9/0587

9 DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORIZATION

Date of registration: 12 September1996 – MORPHINE 10 mg UNIMED

Date of registration: 13 December 1994 – MORPHINE 15 mg UNIMED

10 DATE OF REVISION OF THE TEXT

17 June 2025