

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Morphine Sulphate 15mg/ml Solution for Injection

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of Morphine Sulphate solution for injection contains 15 mg morphine sulphate.

Also contains 1.1 mg of sodium metabisulphite (E223) and 0.24mg Sodium in each ml of Morphine Sulphate solution for injection.

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Solution for injection.

A clear colourless solution.

## 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; pre-operative use.

### 4.2 Posology and method of administration

The injection may be given by the intravenous, intramuscular or subcutaneous route.

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 10mg every 4 hours if necessary, but may range from 5mg to 20mg.

The usual adult intravenous dose is 2.5mg to 15mg 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.

Children: Use in children is not recommended.

### 4.3 Contraindications

Respiratory depression, obstructive airways disease, concurrent treatment with monoamine oxidase inhibitors or within two weeks of their discontinuation of treatment with them.

Known morphine sensitivity, or sensitivity to any of the ingredients. Cerebral oedema, head injuries, coma, convulsive disorders and raised intracranial pressure, biliary colic and acute alcoholism.

Administration of morphine is contra-indicated in patients with phaeochromocytoma, those at risk of paralytic ileus and in patients with 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. It should be used with special caution in patients with a history of drug abuse. Dependence may occur after 1-2 weeks of treatment.

Morphine should be given with caution where there is a reduced respiratory reserve as in emphysema and asthma, chronic cor pulmonale, kyphoscoliosis and excessive obesity. Opiates should also be used cautiously in patients with cardiac arrhythmias, myasthenia gravis or inflammatory or obstructive bowel disorders.

Morphine 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 or shock.

Morphine should be given with great care to infants, especially neonates. Dosage should be reduced in elderly and debilitated patients.

Disappearance of opioid analgesic effects, particularly when associated with an unexplained increase in pain, may indicate the development of tolerance or opioid-induced hyperalgesia. 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 sulphate, 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.

Morphine Sulphate Injection contains sodium metabisulphite (E223). This may rarely cause severe hypersensitivity reactions and bronchospasm.

Morphine Sulphate Injection contains 0.24 mg of sodium per ml. This should be taken into consideration for patients on a controlled sodium diet.

#### 4.5 Interaction with other medicinal products and other forms of interaction

Concurrent administration of other CNS depressants, including hypnotics and anxiolytics, may potentiate the sedative effects.

Morphine should not be administered to patients receiving monoamine oxidase inhibitors (see section 4.3).

Anticholinergic agents such as atropine antagonise morphine-induced respiratory depression and can partially reverse biliary spasm but are additive to the gastro-intestinal and urinary tract effects. Consequently, severe constipation and urinary retention may occur during intensive anticholinergic-analgesic therapy.

Morphine sulphate should not be used for premedication when ciprofloxacin is given for surgical prophylaxis as serum levels of ciprofloxacin are reduced and adequate cover may not be obtained during surgery.

Taking alcohol with morphine sulphate can cause enhanced sedative and hypertensive effects.

#### 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.

Lactation: 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.

#### 4.7 Effects on ability to drive and use machines

Morphine may cause drowsiness. If this occurs the patient should not be allowed to drive or operate machinery.

#### 4.8 Undesirable effects

In routine clinical practice, the commonest side effects of morphine sulphate are nausea, vomiting, constipation, drowsiness and confusion. If constipation occurs, this may be treated with appropriate laxatives.

Adverse effects can be listed in terms of their frequency of occurrence:

- Very common ( $\geq 1/10$ )
- Common ( $\geq 1/100$  to  $< 1/10$ )
- Uncommon ( $\geq 1/1,000$  to  $< 1/100$ )
- Not known (cannot be estimated from the available data)

Morphine may cause the following adverse events:

Nervous system disorders	<p>Very Common: Drowsiness</p> <p>Common: Convulsion, headache, increased intracranial pressure, myoclonus, opioid-induced hyperalgesia (or hyperaesthesia), vertigo</p> <p>Not Known: Allodynia, coma</p>
Psychiatric disorders	<p>Very Common: Confusional state, hallucinations, physical and psychological dependence</p> <p>Common: Decreased libido, mood swings, restlessness</p>
Eye disorders	<p>Common: Blurred vision, miosis, nystagmus</p>
Respiratory, thoracic and mediastinal disorders	<p>Very Common: Respiratory depression</p> <p>Common: Bronchospasm, pulmonary oedema, which can lead to death</p> <p>Not Known: Respiratory failure, which also can lead to death</p>
Cardiac disorders	<p>Common: Bradycardia, circulatory failure, tachycardia</p> <p>Uncommon: Palpitations</p>

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
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
Musculoskeletal and connective tissue disorders	Not Known: Muscle rigidity, rhabdomyolysis
Skin and subcutaneous tissue disorders	Very Common: Pruritis Common: Angioedema, contact dermatitis, rash, urticaria
General disorders and administration site conditions	Very Common: Drug tolerance, hyperhidrosis Common: Fatigue, facial flushing, hypothermia, injection site pain, injection site irritation, withdrawal syndrome (babies born to opioid-dependent mothers are also at risk to present withdrawal syndrome).

#### 4.9 Overdose

Symptoms: respiratory depression, pin-point pupils 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 and death may occur.

Treatment: the patient must be given respiratory support and the specific antagonist, naloxone, should be administered at a dose of 0.4-2.0 mg intravenously. This dose should be repeated at 2-3 minute intervals if improvement is not achieved, up to a total of 10 mg. Fluid and electrolyte levels should be maintained.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Natural opium alkaloids ATC Code: N02 AA01

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 10mg as the sulphate, peak serum concentrations of free morphine of about 10ng/ml are attained in 15 to 60 minutes; after an intramuscular dose of 10mg, peak serum concentrations of 70 to 80ng/ml are attained in 10 to 20 minutes; after an intravenous dose of 10mg, serum concentrations of about 60ng/ml are obtained in 15 minutes falling to 30ng/ml after 30 minutes and to 10ng/ml after 3 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 aged.

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.

Metabolic reactions: Mainly glucuronic acid conjugation to form morphine-3 and 6-glucuronides, with sulphate 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 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.

Excretion: 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 parenteral 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 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

There are no pre-clinical data of relevance to the prescriber, which are additional to those included in other sections.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Sodium metabisulphite (E223)  
Water for injections  
Sodium hydroxide (for pH adjustment)  
Sulphuric acid (for pH adjustment)

### **6.2 Incompatibilities**

Morphine salts may be precipitated in alkaline solution.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

### **6.3 Shelf life**

20 months

### **6.4 Special precautions for storage**

Keep the ampoule in its outer carton to protect from light. Do not refrigerate or freeze.

### **6.5 Nature and contents of container**

Type I Ph Eur clear glass ampoules containing 1 ml.  
5 or 10 ampoules per carton.

### **6.6 Special precautions for disposal and other handling**

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

## **7 MARKETING AUTHORISATION HOLDER**

Auden Mckenzie (Pharma Division) Ltd  
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## **8 MARKETING AUTHORISATION NUMBER**

PA 1352/8/2

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 10th June 2011

## **10 DATE OF REVISION OF THE TEXT**