

## Part II

### Summary of Product Characteristics

#### 1. NAME OF THE MEDICINAL PRODUCT

Morphine Sulphate Injection BP 60mg/1ml.

#### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml of sterile solution for injection contains Morphine Sulphate 60mg.  
Excipients: Sodium Metabisulphite (E223) 1mg

For a full list of excipients see section 6.1

#### 3. PHARMACEUTICAL FORM

Solution for injection (Injection)

A clear colourless or almost colourless sterile solution.

#### 4. CLINICAL PARTICULARS

##### 4.1 Therapeutic indications

In the management of moderate to severe pain.

##### 4.2 Posology and method of administration

Morphine Sulphate Injection BP is for subcutaneous, intramuscular or intravenous administration.

Adults:

10 to 15 mg by subcutaneous or intramuscular injection, repeated every four hours, if required. Dosage should be adjusted according to the severity of pain and the response of the patient.

For intravenous use, 4 to 10 mg, diluted in 4 to 5 ml of water for injection BP should be administered slowly over four to five minutes. Caution must be exercised while diluting with water for injection to avoid potential for accidental over dosage.

Elderly:

Morphine doses should be reduced in elderly patients and titrated to provide optimal pain relief with minimal side effects since:

- Increased duration of pain relief from a standard dose of morphine has been reported in elderly patients.

- A review of pharmacokinetic studies has suggested that morphine clearance decreases and half-life increases in older patients.

- The elderly may be particularly sensitive to the adverse effects of morphine.

Paediatric patients:

Children from age one year: 0.1 to 0.2mg/kg body weight by subcutaneous or intramuscular injection every four hours as required, not to exceed 15mg per dose.

Hepatic and renal impairment:

Morphine Injection should not be administered to patients with severe hepatic impairment and to patients with moderate or severe renal impairment (see Section 4.3)

#### 4.3 Contraindications

Use in patients with hypersensitivity or idiosyncratic response to the active ingredient or to any of the other ingredients listed in section 6.1 (List of excipients)

Use in patients with ulcerative colitis because of the risk of toxic megacolon.

Use in patients with respiratory depression, cyanosis, excessive bronchial exudation, bronchoconstriction (reversible or irreversible), or chronic pulmonary disease.

Use in patients immediately after operative interventions in the biliary tract, biliary colic, head injury, paralytic ileus, acute abdomen of unknown origin, delayed gastric emptying and phaeochromocytoma.

Severe and prolonged respiratory depression may occur in patients with renal impairment given morphine; this is attributed to the accumulation of the active metabolite morphine-6-glucuronide. Therefore Morphine Injection should not be administered to patients with moderate or severe renal impairment (glomerular filtration rate <20 ml/min).

As with other opioid analgesic containing preparations Morphine Injection should not be administered to patients with severe hepatic impairment as it may precipitate coma.

Use in patients with acute alcoholism, increased intracranial pressure, or in coma, or with convulsive disorders.

Use in patients who are receiving, or have within two weeks received, monoamine oxidase inhibitors.

#### 4.4 Special Warnings and Precautions for use

Use with caution in patients with impaired respiratory function, severe bronchial asthma, convulsive disorders, acute alcoholism, delirium tremens, hypotension with hypovolaemia, severe cor pulmonale, opioid dependent patients, patients with a history of substance abuse, inflammatory bowel disorders,

Morphine should not be used where there is a possibility of paralytic ileus occurring.

Should paralytic ileus be suspected or occur during use, Morphine sulphate should be discontinued immediately.

Morphine Sulphate should only be used with extreme caution and in reduced dosage in neonates, premature infants, the elderly, the debilitated, or in patients with hypothyroidism, adrenocortical insufficiency, shock, liver dysfunction, prostatic hypertrophy, hepatic or renal insufficiency.

Patients about to undergo additional pain relieving procedures (e.g. surgery, plexus blockade) should not receive Morphine for 4 hours prior to the intervention. If further treatment with Morphine is indicated then the dosage should be adjusted to the new post-operative requirement. Morphine should be used with caution pre-operatively and within the first 24 hours post-operatively. Morphine should also be used with caution following abdominal surgery.

Repeated use will result in the development of tolerance requiring an increase in dosage to achieve the required effect.

Drug dependence may occur after treatment for one or two weeks with therapeutic doses.

The product should be used with particular care in patients with a history of alcohol and drug abuse.

Patient may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain control. Prolonged use of this product may lead to physical dependence and a withdrawal syndrome may occur upon abrupt cessation of therapy. When a patient no longer requires therapy with morphine, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

Morphine has an abuse profile similar to other strong agonist opioids. Morphine may be sought and abused by people with latent or manifest addiction disorders. There is potential for development of psychological dependence (addiction) to opioid analgesics, including morphine. The product should be used with particular care in patients with a history of alcohol and drug abuse.

Morphine can induce severe respiratory depression, particularly in neonates, for which reason it should not be used in obstetric delivery.

Morphine may lower the seizure threshold in patients with a history of epilepsy.

Use with caution in disorders of the biliary tract including acute pancreatitis.

Sodium Metabisulphite in this injection may rarely cause hypersensitivity reactions and bronchospasm.

Each ampoule of this injection contains 0.81 mg of sodium.

#### 4.5 Interactions with other medicinal products 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 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.

It is recommended that opiate premedicants, (e.g. morphine) are not used concomitantly with ciprofloxacin, as the serum levels of ciprofloxacin are reduced.

Mixed agonist/antagonist opioid analgesics (e.g. buprenorphine, nalbuphine, pentazocine) should not be administered to a patient who has received a course of therapy with a pure opioid agonist analgesic.

Cimetidine inhibits the metabolism of morphine.

Monoamine oxidase inhibitors are known to interact with narcotic analgesics producing CNS excitation or depression with hyper- or hypotensive crisis.

Morphine should not be co-administered with monoamine oxidase inhibitors or within two weeks of such therapy.

Plasma concentrations of morphine may be reduced by rifampicin.

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.

#### 4.6 Pregnancy and Lactation

Animal reproduction studies have not been conducted with morphine sulphate. There is inadequate evidence of safety in human pregnancy and administration of morphine during pregnancy should only be considered if the expected benefit to the mother clearly outweighs any possible risk to the foetus.

Withdrawal symptoms may be observed in the new born of mothers undergoing chronic treatment

All the narcotic analgesics are able to traverse the placenta and administration during labour, may result in respiratory depression in the neonate. Naloxone and resuscitative equipment should be available for reversal of narcotic-induced respiratory depression in the newborn. Morphine is excreted in breast milk and its use is not recommended in nursing mothers.

#### 4.7 Effects on Ability to Drive and Use Machines

Morphine will induce drowsiness. Patients receiving it should not drive or operate machinery unless its effects on physical and mental activity have gone.

#### 4.8 Undesirable Effects

Common (incidence of  $\geq 1/100$  to  $<1/10$ ) and Uncommon (incidence of  $\geq 1/1000$  to  $\leq 1/100$ ) adverse drug reactions are listed in the table below:

<b>Body System</b>	<b>Common (<math>\geq 1/100</math> to <math>&lt;1/10</math>)</b>	<b>Uncommon (<math>\geq 1/1000</math> to <math>\leq 1/100</math>)</b>
<b>Immune system disorders</b>		Allergic reaction Anaphylactic reaction Anaphylactoid reaction
<b>Psychiatric disorders</b>	Confusion Insomnia Thinking disturbances	Agitation Drug dependence Dysphoria Euphoria Hallucinations Mood altered
<b>Nervous system disorders</b>	Dizziness Headache Involuntary muscle contractions Myoclonus Somnolence	Convulsions Hypertonia Paraesthesia Syncope Vertigo
<b>Eye disorders</b>		Miosis Visual disturbance
<b>Cardiac disorders</b>		Bradycardia Palpitations Tachycardia
<b>Vascular disorders</b>		Facial flushing Hypertension

		Hypotension
<b>Respiratory, thoracic and mediastinal disorders</b>	Bronchospasm Cough decreased	Pulmonary oedema Respiratory depression
<b>Gastrointestinal disorders</b>	Abdominal pain Anorexia Constipation Dry mouth Dyspepsia Nausea Vomiting	Gastrointestinal disorders Ileus Toxic megacolon Taste perversion
<b>Hepatobiliary disorders</b>	Exacerbation of pancreatitis	Biliary pain Increased hepatic enzymes
<b>Skin and subcutaneous tissue disorders</b>	Hyperhidrosis Rash	Urticaria
<b>Renal and urinary disorders</b>		Ureteric spasm Urinary retention
<b>Reproductive system and breast disorders</b>		Amenorrhoea Decreased libido Erectile dysfunction
<b>General disorders and administration site conditions</b>	Asthenia Pruritus	Drug tolerance Drug withdrawal syndrome Malaise Peripheral oedema

The most serious side effect of morphine is respiratory depression. Maximal respiratory depression occurs within 5 to 10 minutes after intravenous administration of morphine, within 30 minutes following intramuscular injection, and within 90 minutes after subcutaneous administration.

#### 4.9 Overdose

Signs of morphine toxicity and overdosage are pin-point pupils, skeletal muscle flaccidity, bradycardia, respiratory depression and hypotension. Circulatory failure and deepening coma may occur in more severe cases. Overdosage can result in death. Rhabdomyolysis progressing to renal failure has been reported in opioid overdosage.

Treatment of morphine overdosage:

Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation.

The pure opioid antagonists are specific antidotes against the effects of opioid overdose. Other supportive measures should be employed as needed.

In the case of massive overdosage, administer naloxone 0.8 mg intravenously. Repeat at 2-3 minute intervals as necessary, or by an infusion of 2 mg in 500 ml of normal saline or 5% dextrose (0.004 mg/ml).

The infusion should be run at a rate related to the previous bolus doses administered and should be in accordance with the patient's response. However, because the duration of action of naloxone is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established.

For less severe overdosage, administer naloxone 0.2 mg intravenously followed by increments of 0.1 mg every 2 minutes if required.

Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdosage. Naloxone should be administered cautiously to persons who are known, or suspected, to be physically dependent on morphine. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Natural opium alkaloid

ATC code: N02A A01

Morphine is a narcotic analgesic. The drug exerts its major effects on the central nervous system and organs containing smooth muscle, apparently by acting as an agonist on opioid receptors. Pharmacologic effects include analgesia, drowsiness and dose-related respiratory depression.

## 5.2 Pharmacokinetic properties

Following subcutaneous or intramuscular injection, morphine is readily absorbed into the blood. About one-third of the drug is protein bound.

Morphine is distributed throughout the body but mainly in the kidneys, liver, lungs and spleen. Although the CNS is the primary site of action of morphine, only small quantities cross the blood-brain barrier in adults. Morphine diffuses across the placenta and traces also appear in milk and sweat. In the liver, morphine is conjugated with glucuronic acid to form both active and inactive metabolites. In normal healthy adults, the half-life of morphine is about two hours. Little morphine is excreted unchanged. About 90% of total morphine is excreted in 24 hours, mainly by glomerular filtration and the remainder via bile into faeces.

## 5.3 Preclinical Safety Data

No further relevant information other than that which is included in the other sections of the Summary of Product Characteristics.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of Excipients

Sodium Metabisulphite (E223)  
Sodium Hydroxide or  
Dilute Hydrochloric Acid (for pH-adjustment)  
Water for Injections

## 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.

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

## 6.3 Shelf life

Unopened: 2.5 years  
Once opened: Use immediately.

## 6.4 Special precautions for storage

Do not store above 25°C  
Keep the ampoule in the outer carton in order to protect from light.

6.5 Nature and contents of container

Clear glass ampoules, glass type 1, Ph Eur.  
Pack size: 10 x 1ml ampoules

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product or other handling of the product

For single use only.  
If only part of the contents of an ampoule is used, the remaining solution should be discarded.

**7.     MARKETING AUTHORIZATION HOLDER**

Antigen Pharmaceuticals Ltd.  
Chandler House  
Castle Street  
Roscrea  
County Tipperary.  
Ireland

**8.     MARKETING AUTHORIZATION NUMBER**

PA 73/20/8

**9.     DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION**

Date of first Authorisation: 26<sup>th</sup> June 1995  
Date of last renewal:         26<sup>th</sup> June 2005

**10.    DATE OF REVISION OF THE TEXT**

25 August 2010