

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Morphine Sulphate 10mg/ml Solution for Injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml of sterile solution for injection contains 10mg Morphine Sulphate.

Excipients: Each 1ml also contains 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:

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

Slow intravenous injection:

For intravenous use, 4 to 10mg, diluted in 4 to 5ml of Water for Injections BP should be administered slowly over four to five minutes.

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.

Elderly and debilitated patients: The dose should be reduced because of the depressant effect on respiration. Caution is required.

Hepatic impairment:

A reduction in dosage should be considered in hepatic impairment.

Renal impairment:

The dosage should be reduced in moderate to severe renal impairment.

For concomitant illnesses/conditions where dose reduction may be appropriate see 4.4 Special Warnings and Precautions for Use.

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.

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.

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.

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

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 0.81mg of sodium.

4.5 Interaction 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 are excreted in the milk. This should be borne in mind when considering their use in patients during pregnancy and lactation. Morphine may cause respiratory depression in neonates particularly if premature. Morphine is not recommended for use during lactation in nursing mothers.

4.7 Effects on ability to drive and use machines

Morphine will induce drowsiness and 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:

Body System	Common ($\geq 1/100$ to $<1/10$)	Uncommon ($\geq 1/1000$ to $\leq 1/100$)
Immune system disorders		Allergic reaction Anaphylactic reactions Anaphylactoid reaction
Psychiatric disorders	Confusion Insomnia Thinking disturbances	Agitation Drug dependence Dysphoria Euphoria Hallucinations

		Mood altered
Nervous system disorders	Dizziness Headache Involuntary muscle contractions Myoclonus Somnolence	Convulsions Hypertonia Paraesthesia Syncope Vertigo
Eye disorders		Miosis Visual disturbance
Cardiac disorders		Bradycardia, palpitations Tachycardia
Vascular disorders		Facial flushing Hypertension Hypotension
Respiratory, thoracic and mediastinal disorders	Bronchospasm Cough decreased	Respiratory depression Pulmonary oedema
Gastrointestinal disorders	Dry mouth Nausea, vomiting, constipation Abdominal pain Anorexia Dyspepsia	Gastrointestinal disorders Ileus Taste perversion Toxic megacolon
Hepatobiliary disorders	Exacerbation of pancreatitis	Biliary pain Increased hepatic enzymes
Skin and subcutaneous tissue disorders	Hyperhidrosis Rash	Urticaria
Renal and urinary disorders		Ureteric spasm Urinary retention
Reproductive system and breast disorders	-	Amenorrhoea Decreased libido

		Erectile dysfunction
General disorders and administration site conditions	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. Rhabdomyolosis 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

Natural Opium alkaloids

ATC CODE: N02AA01

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. Pharmacological 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.

6.3 Shelf Life

Unopened: 4 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

1ml clear glass ampoules, glass type I Ph. Eur. Borosilicate glass packed in cardboard cartons to contain 10 x 1ml ampoules.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and 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 AUTHORISATION HOLDER

Antigen Pharmaceuticals Ltd

Roscrea

County Tipperary

8. MARKETING AUTHORISATION NUMBER

PA 73/20/1

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 1978

Date of last renewal: 01 April 2003

10. DATE OF REVISION OF THE TEXT

20 December 2011