

Summary of Product Characteristics

for

**Morphine Sulphate Injection BP
1mg in 5ml**

PA 73/20/3

**Antigen Pharmaceuticals Ltd.
Roscrea
Co. Tipperary**

Summary of Product Characteristics

Product Name : **Morphine Sulphate Injection BP 1mg in 5ml**

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Summary of Product Characteristics

1. TRADE NAME OF THE MEDICINAL PRODUCT

Morphine Sulphate Injection BP 1mg/5ml.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml of sterile solution for injection contains Morphine Sulphate 0.2mg (1mg in 5ml).

For a full list of excipients see section 6.1

3. PHARMACEUTICAL FORM

Solution for 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 1mg in 5ml is for epidural or intrathecal administration.

Adults only :

Epidural Administration : An initial dose of 5mg may be administered in the lumbar region or 2 to 4mg over 24 hours to start an epidural infusion which may be increased by up to 2mg daily. The incidence of early and late respiratory depression is greatly increased if morphine is administered in the thoracic region.

Intrathecal Administration : A single injection of 0.2 to 1mg in the lumbar area is recommended. The injection should not be repeated.

4.3 Contra-indications

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 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, pheochromocytoma.

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4. CLINICAL PARTICULARS

4.3 Contra-indications cont/d.

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.

Administration of morphine by the epidural or intrathecal route is contraindicated in the presence of infection at the injection site, anticoagulant therapy, bleeding diathesis, or other concomitant drug therapy or medical condition which would contraindicate the technique of epidural or intrathecal analgesia.

Use in children.

4.4 Special Warnings and Special Precautions for Use

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

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.

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

Epidural and intrathecal administration of morphine should be carried out by clinicians with the necessary knowledge and experience. When the epidural or intrathecal routes of administration are employed, patients must be carefully observed for at least 24 hours, as respiratory depression can occur any time during this period. Oxygen, resuscitative equipment, naloxone and other resuscitative drugs should be available.

Clinical experience with repeated intrathecal injections is limited. Therefore, repeated administration by this route is not recommended. Alternative routes of administration should be considered for treating recurrent or chronic pain.

Use of this product is restricted to experienced personnel in a hospital or hospice, where complications of therapy can be properly managed.

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

Each ampoule of this injection contains 88.55 mg of sodium. This should be taken into consideration for patients who are on restricted sodium diet.

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4. CLINICAL PARTICULARS cont/d.

4.5 Interactions with other medicaments and other forms of interaction

The depressant effects of morphine may be exaggerated and prolonged by phenothiazines, tricyclic antidepressants, anaesthetics, hypnotics, sedatives and alcohol

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.

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

With normal therapeutic doses, the commonest side effects of morphine are nausea, vomiting, constipation and drowsiness. There may be difficulty in micturition or biliary spasm. Dry mouth, sweating, hypothermia, facial flushing, palpitations, bradycardia, orthostatic hypotension, mood change and miosis may occur. An anti-diuretic effect may occur and intracranial pressure may be raised in some patients. Anaphylactic reactions following intravenous injection have been reported, but such reactions are quite rare. Larger doses may cause respiratory depression and hypotension, with circulatory failure and deepening coma. Convulsions may occur with high doses of opioids, especially in infants and children.

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.

Bolus administration by the epidural or intrathecal route may result in early respiratory depression due to direct venous distribution of morphine to the respiratory centres in the

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4. CLINICAL PARTICULARS cont/d.

4.8 Undesirable effects cont/d

brain; respiratory depression may also emerge later, when analgesia may no longer be present, due to rostral spread of the drug.

4.9 Overdose

Overdosage is characterised by pin-point pupils hypotension and respiratory depression, progressing to circulatory failure and coma. Naloxone is the specific antidote and should be administered intravenously at a dose of 0.4mg repeated as required or 0.004 mg/ml of infusion.

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Morphine is the principal alkaloid of opium and is the phenanthrene derivative.

Morphine produces its major effects on the central nervous system and organs containing smooth muscle by acting as an agonist, particularly at μ receptors. Pharmacologic effects include analgesia, drowsiness, alteration in mood, respiratory depression, decreased gastrointestinal motility, nausea, vomiting and changes within the endocrine and autonomic nervous systems.

The analgesic effect of morphine is due to actions at both spinal and supraspinal sites within the CNS, particularly at μ receptors. However, morphine also has an affinity for δ and κ receptors. Although the mechanism by which morphine produces euphoria and other mood changes is not clear, it is likely that activation of dopaminergic neurones, as well as some nondopaminergic mechanisms, are involved.

5.2 Pharmacokinetic properties

Following epidural or intrathecal administration of small amounts of morphine, the analgesic effect may last up to 24 hours. The delay in the onset of analgesia following epidural or intrathecal injection may be attributed to the relatively poor lipid solubility of morphine and its slow access to the receptor sites. The hydrophilic character of morphine may also explain its retention in the CNS and its slow release into the systemic circulation, resulting in a prolonged effect.

Morphine diffuses across the placenta and traces also appear in milk and sweat.

The major metabolic pathway for morphine is conjugation with glucuronic acid to form both active and inactive products. In normal healthy adults, the plasma 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.

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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride
Sodium Hydroxide or
Dilute Hydrochloric Acid
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

3 years

6.4 Special precautions for storage

Do not store above 25°C
Keep the container in the outer carton

6.5 Nature and contents of container

Clear glass ampoules, glass type 1, Ph Eur.
Pack size : 10 x 5ml 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

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

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7. MARKETING AUTHORIZATION HOLDER

Antigen Pharmaceuticals Ltd.,
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8. MARKETING AUTHORIZATION NUMBER

PA 73/20/3

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

Date of first authorisation: 18th May 1995
Date of last renewal: 18th May 2005

10. DATE OF (PARTIAL) REVISION OF THE TEXT

April 2007