Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Morphine Sulphate 1mg/5ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml of sterile solution for injection contains morphine sulphate 0.2mg (1mg/5ml).

Excipient(s) with known effect:
None

For the 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

Morphine Sulphate Injection is indicated in adults for the management of moderate to severe pain.

4.2 Posology and method of administration

Posology
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.

Morphine Sulphate Injection should not be used in children

Method of administration

Morphine Sulphate Injection 1mg/5ml is for epidural or intrathecal administration.

Treatment goals and discontinuation

Before initiating treatment with Morphine Sulphate Injection, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with Morphine Sulphate Injection, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

Duration of treatment
Morphine Sulphate Injection should not be used longer than necessary.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients 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, 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 Sulphate 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 Sulphate 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.

Administration of Morphine Sulphate Injection 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 precautions for use

Use with caution in patients with impaired respiratory function, severe bronchial asthma, convulsive disorders, acute alcoholism, delirium tremens, raised intracranial pressure, hypotension with hypovolemia, severe cor pulmonale, opioid dependent patients, patients with a history of substance abuse, inflammatory bowel disorders.
Morphine Sulphate Injection should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, Morphine Sulphate Injection should be discontinued immediately.

Morphine Sulphate Injection 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, mild and moderate hepatic and mild 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.
Morphine has an abuse potential similar to other strong agonist opioids, and should be used with particular care in patients with a history of alcohol and drug abuse.

Opioid Use Disorder (abuse and dependence) and withdrawal (abstinence) syndrome
Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as Morphine Sulphate Injection.

Repeated use of Morphine Sulphate Injection can lead to Opioid Use Disorder (OUD). A higher dose and longer duration of opioid treatment, can increase the risk of developing OUD. Abuse or intentional misuse of Morphine Sulphate Injection may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents

or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (eg. major depression, anxiety and personality disorders).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. For individual symptoms, see section 4.8.

Before initiating treatment with Morphine Sulphate Injection and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician.

Patients will require monitoring for signs of drug-seeking behavior (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

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.

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.

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.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:
Concomitant use of morphine and sedative medicines such as benzodiazepines or related drugs 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 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).

Sleep-related breathing disorders

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Severe cutaneous adverse reactions (SCARs)
Acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, has been reported in association with morphine treatment. Most of these reactions occurred within the first 10 days of treatment. Patients should be informed about the signs and symptoms of AGEP and advised to seek medical care if they experience such symptoms.
If signs and symptoms suggestive of these skin reactions appear, morphine should be withdrawn and an alternative treatment considered.

Hepatobiliary disorders
Morphine may cause dysfunction and spasm of the sphincter of Oddi, thus raising intrabiliary pressure and increasing the risk of biliary tract symptoms and pancreatitis.

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.

Hyperalgesia that does not respond to a further dose increase of morphine may occur in particular in high doses. A morphine dose reduction or change in opioid may be required.

Plasma concentrations of morphine may be reduced by rifampicin. The analgesic effect of morphine should be monitored and doses of morphine adjusted during and after treatment with rifampicin.

This medicine contains less than 1 mmol sodium (23 mg) per ampoule, that is to say essentially 'sodium-free'.

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 or pregabalin 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.

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.

A delayed and decreased exposure to oral P2Y12 inhibitor antiplatelet therapy has been observed in patients with acute coronary syndrome treated with morphine. This interaction may be related to reduced gastrointestinal motility and apply to other opioids. The clinical relevance is unknown, but data indicate the potential for reduced P2Y12 inhibitor efficacy in patients co-administered morphine and a P2Y12 inhibitor (see section 4.4). In patients with acute coronary syndrome, in whom morphine cannot be withheld and fast P2Y12 inhibition is deemed crucial, the use of a parenteral P2Y12 inhibitor may be considered.

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

Sedative medicines such as benzodiazepines or related drugs:
The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs 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).

4.6 Fertility, pregnancy and lactation

Pregnancy
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.
New-born's whose mothers received opioid analgesics during pregnancy should be monitored for signs of neonatal withdrawal (abstinence) syndrome. Treatment may include an opioid and supportive care.

Breast-feeding
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.

Fertility
Animal studies have shown that morphine may reduce fertility (see 5.3. preclinical safety data).

4.7 Effects on ability to drive and use machines

Morphine Sulphate Injection 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

Side effects grouped by frequency of occurrence Common (*≥1/100 to <1/10*) Uncommon (*≥1/1,000 to< 1/100*) and Not known: frequency cannot be estimated from the available data adverse drug reactions are listed in the table below:

Body System	Common	Uncommon	Not known
Immune system disorders		Allergic reaction Anaphylactic reaction Anaphylactoid reactions	
Psychiatric disorders	Confusion Insomnia Thinking disturbances	Agitation Drug dependence Dysphoria Euphoria Hallucinations Mood altered	
Nervous system disorders	Dizziness Headache Involuntary	Convulsions Hypertonia Paraesthesia	Allodynia** Hyperaesthes ***

	muscle contractions Myoclonus Somnolence	Syncope Vertigo	Hyperalgesia(see section 4.4), Hyperhidrosis
Eye disorders		Miosis Visual disturbance	
Cardiac disorders		Bradycardia Palpitations Tachycardia	
Vascular disorders		Facial flushing Hypertension Hypotension	
Respiratory, thoracic and mediastinal disorders	Bronchospasm Cough decreased	Pulmonary oedema Respiratory depression	Central sleep apnoea syndrome
Gastrointestinal disorders	Abdominal pain Anorexia Constipation Dry mouth Dyspepsia Nausea Vomiting	Ileus paralytic Toxic megacolon Taste perversion	Narcotic bowel syndrome* Pancreatitis
Hepatobiliary disorders	Exacerbation of pancreatitis	Biliary pain Increased hepatic enzymes	Spasm of sphincter of Oddi
Skin and subcutaneous tissue disorders	Hyperhidrosis Rash	Urticaria	Acute generalised exanthematous pustulosis (AGEP)
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	Hypothermia, Drug withdrawal (abstinence) syndrome

		oedema			

*Long term narcotics use may cause Narcotic bowel Syndrome (NBS).By the time, narcotics can slow the bowel and lead to symptoms of constipation, bloating, or nausea, and abdominal distension
**Allodynia (Pain due to stimulus which does not normally provoke pain)
***Hyperaesthesia (is a condition that involves an abnormal increase in sensitivity to stimuli of the sense i.e increased response to a painful stimulus)

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

Drug dependence and withdrawal (abstinence) syndrome:
Repeated use of Morphine Sulphate Injection can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).. 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 4.4.
Physiological withdrawal symptoms include: Body aches, tremors, restless legs syndrome, diarrhoea, abdominal colic, nausea, flu-like symptoms, tachycardia and mydriasis. Psychological symptoms include dysphoric mood, anxiety and irritability. In drug dependence, "drug craving" is often involved

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 viaHPRA Pharmacovigilance
Website: www.hpra.ie

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 from respiratory failure. Rhabdomyolysis progressing to renal failure and Pneumonia aspiration 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 the principal alkaloid of opium and is the phenanthrene derivative.

Mechanism of action
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 k 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

Absorption
Following epidural or intrathecal administration of small amounts of morphine, the analgesic effect may last up to 24 hours.

Distribution
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.

Biotransformation
The major metabolic pathway for morphine is conjugation with glucuronic acid to form both active and inactive products.

Elimination
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

Fertility
In male rats, reduced fertility and chromosomal damage in gametes have been reported.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride
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 compatability studies, this medicinal product must not be mixed with other medicinal products.
Physicochemical incompatibility (formation of precipitates) has been demonstrated between solutions of morphine sulphate and 5- fluorouracil.

6.3 Shelf life

Unopened: 3 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 I, Ph. Eur.
Pack size: 10 x 5 ml 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.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.6 Special precautions for disposal

For single use only.
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Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Mercury Pharmaceuticals (Ireland) Ltd
4045 Kingswood Road
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8 MARKETING AUTHORISATION NUMBER

PA0073/020/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 May 1995

Date of latest renewal: 18 May 2010

10 DATE OF REVISION OF THE TEXT

December 2023