SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Morphine Sulfate 1 mg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 ml ampoule contains 10 mg morphine sulfate pentahydrate

Excipient with known effect:

This medicinal product contains 35 mg sodium per each 10 ml ampoule, equivalent to 2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Morphine Sulfate 1 mg/ml solution for injection is indicated for the relief of moderate to severe pain. Morphine sulfate 1 mg/ml solution for injection is used especially in pain associated with cancer, myocardial infarction and surgery. Morphine also helps to relieve the anxiety and insomnia which may be associated with severe pain.

4.2 Posology and method of administration

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with morphine in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4).

Posology

Adults and children over 12 years:

Morphine Sulfate 1 mg/ml solution for injection is formulated for use by the intravenous route in Patient Controlled Analgesia (PCA) systems. PCA, which

permits adjustment of dosage according to the patient's individual needs, must only be carried out in departments and by staff who are trained and have experience of the system. Patient selection for the use of PCA must ensure that the patient is capable of understanding and following the instructions of the medical/nursing staff. The specific department or unit protocols must be covered to ensure aseptic transfer of the contents of the vial to the PCA system.

There is a considerable variation in analgesic requirements among patients and therefore individualised treatment strategies are required. Dosage should be based on the severity of the pain and the response and opiate tolerance of the patient.

Loading dose

Loading doses of typically between 1 mg and 10 mg (maximum 15 mg) of morphine sulfate may be given by intravenous infusion over four or five minutes. The loading dose used will depend upon the patient's diagnosis and condition.

PCA demand dose

An initial demand dose of 1 mg Morphine Sulfate 1 mg/ml solution for injection with a lockout period of 5 to 10 minutes is recommended. Dosages may vary depending on the loading dose, the tolerance and condition of the patient, and whether a background infusion of morphine is being given.

The patient should be specifically monitored for pain, sedation and respiratory rate during the first few hours of treatment to ensure that the dosage regimen is suitable.

The duration of treatment should be kept to a minimum, although dependence and tolerance are not generally a problem when morphine is used legitimately in patients with opioid-sensitive pain.

Discontinuation of therapy:

An abstinence syndrome may be precipitated if opioid administration is suddenly discontinued. Therefore the dose should be gradually reduced prior to discontinuation.

Use in children:

Not recommended for children under 12 years.

Use in the elderly:

Morphine doses need to be reduced in elderly patients.

Method of administration

For intravenous injection.

The product should not be diluted before use.

The medicinal product is to be visually inspected prior to use. Only clear solutions practically free from particles should be used.

Treatment goals and discontinuation

Before initiating treatment with Morphine Sulfate 1 mg/ml solution for 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 Sulfate 1 mg/ml solution for 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 Sulfate 1 mg/ml solution for injection should not be used longer than necessary.

4.3 Contraindications

Morphine Sulfate 1 mg/ml solution for injection is contraindicated in:

- hypersensitivity to the active substance, to other opioid preparations or to any of the excipients listed in section 6.1
- respiratory depression; obstructive airways disease; excessive bronchial secretions; during a bronchial asthma attack or in heart failure secondary to chronic lung disease
- head injury; raised intra-cranial pressure
- coma
- convulsion disorders
- ulcerative colitis
- presence of a risk of paralytic ileus
- biliary and renal tract spasm
- acute alcoholism
- phaeochromocytoma
- moderate to severe renal impairment (glomerular filtration rate <20ml/min)
- severe or acute liver failure
- patients receiving monoamine oxidase inhibitors or within two weeks of discontinuing such treatment

Use of Morphine Sulfate 1 mg/ml solution for injection during pregnancy or lactation is not recommended.

4.4 Special warnings and precautions for use

As with other narcotics, a dose reduction may be appropriate in elderly patients, in patients with hypothyroidism, renal and chronic hepatic disease.

Morphine Sulfate 1 mg/ml solution for injection should be used with caution in debilitated patients and those with adrenocortical insufficiency (see below); hypopituitarism; prostatic hypertrophy; shock; diabetes mellitus; diseases of the biliary tract; myasthenia gravis; cardiac arrhythmias; excessive obesity; hypotension and severe cardiac failure. It should also be used with caution post-operatively following total joint arthroplasty (colonic pseudo-obstruction).

Concomitant use of other opioid analgesics such as codeine, administered orally or by some other route of administration, increases the CNS depressant effect of morphine (see Section 4.5 – Interaction with other medicinal products and other forms of interaction).

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).

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.

Opioid Use Disorder (abuse and dependence)

Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as Morphine Sulfate 1 mg/ml solution for injection. Repeated use of Morphine Sulfate 1 mg/ml solution for 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 Sulfate 1 mg/ml solution for 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 (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with Morphine Sulfate 1 mg/ml solution for 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.

Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse.

Patients will require monitoring for signs of drug-seeking behaviour (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.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance.
The risks of developing tolerance should be explained to the patient.

It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction. The clinical need for analgesic treatment should be reviewed regularly.

Drug withdrawal syndrome

Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with morphine.

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

However, when doses of morphine are carefully titrated against pain, clinically significant respiratory depression, dependence, rapid tolerance and euphoria rarely develop. Clinically significant tolerance to morphine is unusual in cancer patients with severe pain.

If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

Acute chest syndrome (ACS) in patients with sickle cell disease (SCD)
Due to possible association between ACS and morphine use in SCD patients treated with morphine during a vaso-occlusive crisis, close monitoring for ACS is warranted.

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
Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

Rifampicin
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 (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).

Sodium content
This medicinal product contains 35 mg sodium per each 10 ml ampoule, equivalent to 2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Monoamine oxidase inhibitors (MAOIs)
Concomitant or recent use of monoamine oxidase inhibitors with morphine is contraindicated since interactions have been reported, resulting in CNS excitation or depression with hyper- or hypotensive crises (see section 4.3).

Hyperpyrexia and CNS toxicity may result from an opiate selegiline combination. Such combinations should, therefore, be used with extreme caution.

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).

Other CNS depressants
The CNS depressant effects of morphine are increased by the co-administration of CNS depressants including alcohol, anaesthetics, muscle relaxants, hypnotics, sedatives, tricyclics, neuroleptics, gabapentin or pregabalin and phenothiazines as well as other opioid analgesics.

The analgesic effects of opioids tend to be enhanced by the concomitant administration of dexamphetamine, hydroxyzine and some phenothiazines (although the latter may also cause respiratory depression).

Diuretics
Morphine may reduce the efficacy of diuretics by inducing the release of the antidiuretic hormone.

Anticholinergics
The combination of morphine with anticholinergics may enhance the constipatory effect and urinary retention.

Antihistamines
Cimetidine and ranitidine appear to interfere with the metabolism of morphine.

Disulfiram
The metabolism and excretion of morphine may be inhibited by disulfiram.

Prokinetics
Increased morphine levels may result from the co-administration of cisapride.

Metoclopramide and domperidone may antagonise morphine's gastrointestinal effects and metoclopramide enhances it sedative effect.

Antibiotics
Ciprofloxacin concentration may be reduced.

Anti-arrhythmics
Mexiletine absorption may be delayed by co-administered opiate. Co-administration of morphine with esmolol results in a slight increase in the esmolol levels, but the clinical implications of this increase are not considered very significant.

Enzyme modulating agents
Animal data suggest that propranolol may increase the toxicity of opioids. Ritonavir can induce the formation of metabolising enzymes made in the liver and can cause increased metabolism of morphine which can reduce the clinical efficacy of the analgesic.

Rifampicin
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 (see section 4.4).

Oral P2Y12 inhibitor antiplatelet therapy
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.

4.6 Fertility, pregnancy and lactation

Pregnancy
Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.

If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

There are no adequate data from the use of morphine in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Morphine Sulfate 1 mg/ml solution for injection is not, therefore, recommended for use in pregnancy.

Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Newborns 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

Administration to nursing women is not recommended as morphine may be secreted in breast milk and may cause respiratory depression in the infant.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from morphine therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

Non-clinical data based on conventional studies reveal no special hazard additional to the known safety profile of morphine in humans (see Section 5.3 – Preclinical safety data). Animal studies have shown that morphine may reduce fertility (see section 5.3 – Preclinical safety data).

4.7 Effects on ability to drive and use machines

Morphine has major influence on the ability to drive and use machines. It may modify the patient's reactions to a varying extent depending on the dosage and individual susceptibility. Ambulatory patients should be warned not to use machines.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
    - The medicine has been prescribed to treat a medical or dental problem and
    - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
    - It was not affecting your ability to drive safely

4.8 Undesirable effects

The side-effects most commonly seen with morphine and other opioids are respiratory depression, nausea, vomiting, constipation, drowsiness and confusion. With long term use these symptoms generally lessen, although constipation frequently persists.

The following adverse events are from published literature and frequencies are not known.

Immune system disorders

Anaphylactic reactions and anaphylactoid reactions to morphine have been reported rarely.

Endocrine disorders

Long term use of opioid analgesics can cause adrenal insufficiency. Exacerbation of pancreatitis.

Psychiatric disorders

Drug dependence (see section 4.4), restlessness, mood changes, hallucinations, delirium, disorientation, excitation, agitation, sleep disturbance.

Nervous system disorders

Headache, vertigo, euphoria, dysphoria, dizziness, taste disturbances, seizures, paraesthesia, raised intracranial pressure, hyperhidrosis. Allodynia and hyperalgesia have been reported (see section 4.4)..

Eye disorders
Visual disturbances, nystagmus, miosis.

Ear and labyrinth disorders
Vertigo.

Cardiac disorders
Bradycardia, tachycardia, palpitations, syncope.

Vascular disorders
Orthostatic hypotension, hypotension, hypertension, facial flushing, oedema.

Respiratory, thoracic and mediastinal disorders
Bronchospasm (in association with anaphylaxis), inhibition of cough reflex.

Central sleep apnoea syndrome.

Gastrointestinal disorders
Dyspepsia, paralytic ileus, abdominal pain, anorexia, dry mouth, pancreatitis.

Hepatobiliary disorders
Biliary spasm, spasm of sphincter of Oddi.

Skin and subcutaneous tissue disorders
Rashes, urticaria, pruritus.

Acute generalised exanthematous pustulosis (AGEP).

Musculoskeletal and connective tissue disorders
Muscle fasciculation, myoclonus, rhabdomyolysis, muscle rigidity.

Renal and urinary disorders
Difficult micturition, ureteric spasm, urinary retention.

Reproductive system and breast disorders
Long term use of opioid analgesics can cause hypogonadism in both men and women.

This can lead to amenorrhoea, reduced libido, infertility, depression and erectile dysfunction.

General disorders and administration site conditions
Hypothermia, malaise, asthenia, pain and irritation at the injection site.

The side effect uncommonly seen with morphine and other opioids is drug withdrawal syndrome – see Drug dependence and withdrawal syndrome below for further information.

Long Term Use
Long term use of opioid analgesics has been associated with a state of abnormal pain sensitivity (hyperalgesia).

Tolerance and psychological and physical dependence may occur (see below). Decreased potency may be experienced.

High doses may produce respiratory depression and hypotension, with deepening coma. Convulsions may occur particularly in infants.

Drug dependence and withdrawal syndrome
Repeated use of Morphine Sulfate 1 mg/ml solution for 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).

Use of opioid analgesics may be associated with the development of physical and/or psychological dependence or tolerance. 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 restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

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 via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Signs:
The signs of morphine overdosage consist of pin-point pupils, respiratory depression (potentially leading to fatal respiratory failure), pneumonia aspiration, and hypotension. Circulatory failure and deepening coma may develop in severe cases and death may ensue. Less severe cases may be manifest by nausea, vomiting, tremor, dysphoria, hypothermia, hypotension, confusion and sedation. Rhabdomyolysis progressing to renal failure can also be a consequence of overdosage.

Treatment:
It is vital to maintain and support respiration and circulation. The specific opioid antagonist naloxone should be employed for the reversal of coma and restoration of spontaneous respiration. 400 micrograms of naloxone should be administered intravenously, repeated at 2-3 minute intervals as necessary up to a maximum dose of 10 mg.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Opioids, natural opium alkaloids, ATC code: N02AA01

Morphine acts as a competitive agonist at opiate receptors in the CNS, particularly mu and to a lesser extent kappa receptors. Activity at the mu-1 subtype receptor is thought to mediate analgesia, euphoria and dependence whilst activity at the mu-2 receptor is thought to be responsible for respiratory depression and inhibition of gut motility. Action at the kappa receptor may mediate spinal analgesia. The analgesic action of morphine is effective at several spinal and supraspinal sites.

5.2 Pharmacokinetic properties

Absorption
Onset of action is rapid following parenteral administration of morphine with peak analgesic effect occurring within 20 minutes via the intravenous route.

Distribution
Morphine is widely distributed in the body, with an apparent volume of distribution of 2-3 lkg^{-1}. Due to its relatively hydrophilic nature, morphine does not readily cross the blood-brain barrier although it is detectable in the cerebrospinal fluid.

Biotransformation
Morphine is extensively metabolised by the liver. Renal glucuronidation also takes place. The major metabolite, quantitatively, is morphine-3-glucuronide although morphine-6-glucuronide is significant in terms of potency. The metabolites are excreted mainly via the renal route.

5.3 Preclinical safety data

Non-clinical data based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development reveal no special hazard additional to the known safety profile of morphine in humans.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Hydrochloric acid

Water for injections

6.2 Incompatibilities

Morphine Sulfate 1 mg/ml solution for injection is physically incompatible with aciclovir sodium, aminophylline, amobarbital sodium, cefepime hydrochloride, chlorothiazide sodium, floxacillin sodium, furosemide, gallium nitrate, heparin sodium, meperidine hydrochloride, meperidine sodium, methicillin sodium, minocycline hydrochloride, pentobarbital sodium, phenobarbital sodium, phenytoin sodium, sargramostim, sodium bicarbonate, thiopental sodium.

Physicochemical incompatibility (formation of precipitates) has been demonstrated between solutions of morphine sulfate and 5- fluorouracil.

6.3 Shelf life

36 months

6.4 Special precautions for storage

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

6.5 Nature and contents of container

10 ml colourless glass ampoules (type I) in packs of 10 ampoules.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

hameln pharma ltd
Nexus, Gloucester Business Park
Gloucester, GL3 4AG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 01502/0098

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/10/2015

10 DATE OF REVISION OF THE TEXT

12/10/2023