

**MORPHINE SULPHATE INJECTION 2 MG/ML**

**PL 13079/0006**

**UKPAR**

**TABLE OF CONTENTS**

Lay summary	Page 2
Scientific discussion	Page 3
Steps taken for assessment	Page 14
Summary of product characteristics	Page 15
Product information leaflet	Page 22
Labelling	Page 25

## **MORPHINE SULPHATE INJECTION 2 MG/ML**

**PL 13079/0006**

### **LAY SUMMARY**

The Medicines and Healthcare products Regulatory Agency granted South Devon Healthcare NHS Trust a Marketing Authorisation (licence) for the medicinal product Morphine Sulphate Injection 2mg/ml (PL 13079/0006) on 23 May 2006. This product has been granted prescription only status.

Natural opium alkaloids similar to this product have been available in the European Union, including the UK, for much more than ten years. Their use is well established with recognised efficacy and acceptable safety.

Morphine Sulphate Injection 2mg/ml raised no clinically significant safety concerns and it was therefore judged that the benefits of using this product outweigh the risks; hence Marketing Authorisation has been granted.

# MORPHINE SULPHATE INJECTION 2 MG/ML

PL 13079/0006

## SCIENTIFIC DISCUSSION

### TABLE OF CONTENTS

Introduction	Page 4
Pharmaceutical assessment	Page 5
Preclinical assessment	Page 10
Clinical assessment (including statistical assessment)	Page 11
Overall conclusions and risk benefit assessment	Page 13

## **INTRODUCTION**

Based on the review of the data on quality, safety and efficacy, the UK granted a Marketing Authorisation for the medicinal product Morphine Sulphate Injection 2mg/ml (PL 13079/0006) to South Devon Healthcare NHS Trust on 23 May 2006. This natural opium alkaloid is a prescription only product.

This is a stand-alone, national application for Morphine Sulphate Injection 2mg/ml submitted under EC, Article 10.1 of Directive 2001/83/EC, cross-referring to Morphine Sulphate Injection BP Minijet 2 mg/ml presented in 2ml, 10ml and 50ml vials (PL 03265/0038), granted to the International Medication System (UK) Ltd in March 1978.

Morphine Sulphate Injection 2mg/ml contains the active ingredient morphine sulphate and is indicated for the relief of moderate to severe pain. Morphine 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.

## **PHARMACEUTICAL ASSESSMENT REPORT**

### **1. INTRODUCTION**

This is a national standard abridged application for Marketing Authorisation in the UK submitted under Article 10.1 of Directive 2001/83/EC, for Morphine Sulphate Injection 2 mg per ml presented in clear glass vials. The proposed product is a line extension of the applicant's Morphine Sulphate Injection 1 mg/ml preparation, marketed in the UK.

Essential similarity has been claimed to PL 03265/0038, Morphine Sulphate Injection BP Minijet 2 mg/ml presented in 2ml, 10ml and 50ml vials, granted to International Medication System (UK) Ltd in March 1978.

Morphine Sulphate Injection is indicated for the relief of moderate to severe pain, especially pain associated with cancer, myocardial infarction and surgery. The proposed preparation is specifically formulated for administration undiluted in devices designed for patient-controlled analgesia.

### **2. DRUG SUBSTANCE**

Morphine Sulphate is sourced from a suitable manufacturer, in accordance with details provided in the DMF, submitted in December 1994 and most recently updated in May 2000. Morphine Sulphate from this source has previously been authorised for use in UK licensed products for parenteral administration. A letter of access from the active ingredient manufacturer, dated 16 June 2000, has been provided, permitting use of their drug master file to support this application. Confirmation has been provided that the information submitted for the bulk drug material is the current edition of the applicant's 'open' part of the DMF.

#### **SPECIFICATIONS**

The active ingredient manufacturer's specification complies with the Ph Eur monograph for Morphine Sulphate, with some additional tests. The pharmacopoeial reference standard stated for Morphine Sulphate has been updated to Ph Eur. Tests routinely carried out on incoming batches of bulk drug material by the proposed finished product manufacturer have been confirmed.

#### **BATCH ANALYSES**

Satisfactory batch analytical data were reported for 10 batches, manufactured in July/August 1996 and December 1999, in the applicant's part of the DMF.

#### STABILITY

Stability data reported in the applicant's part of the DMF support the proposed 3 year retest date for material stored in the appropriate containers in the specified conditions.

### 3. DOSAGE FORM

#### COMPOSITION

Morphine Sulphate Injection 2 mg per ml is described as a clear, colourless, sterile, aqueous solution for injection, containing 2 mg Morphine Sulphate in 1 ml. The proposed product is presented in Type II clear glass vials sealed with rubber stoppers and aluminium tamper-evident caps. Three fill volumes are proposed: 30 ml, 50 ml and 60 ml. The proposed product is identical to the claimed essentially similar preparation, PL 03265/0038 - Morphine Sulphate Injection BP Miniject 2 mg/ml, with respect to the qualitative and quantitative composition of the active ingredient. The qualitative composition of the proposed product is summarised in Table 1.

Table 1 – Qualitative composition of Morphine Sulphate Injection 2 mg/ml

<b>Ingredient</b>		<b>Function</b>
Morphine Sulphate BP		Active Ingredient
Sodium Chloride Ph Eur		Isotonic agent
Bulk Water for Injections Ph Eur		Diluent
Helium gas BP		Degassing agent
Oxygen-free nitrogen gas		Inert head space filler

#### CLINICAL TRIAL FORMULATION

Not applicable.

#### PHARMACEUTICAL DEVELOPMENT

The proposed product is presented as an aqueous solution containing morphine sulphate 2 mg per ml, made isotonic with sodium chloride. The product is primarily intended for use in patient controlled analgesia, hence the requirement for a low strength preparation. Since the formulation is so well established the applicant did not consider it necessary to carry out a full scale development exercise, however, the pharmaceutical development issues that have been detailed have been well presented.

Since morphine sulphate injections are so well established and this product is merely a line extension of the existing 0.1% product marketed by the applicant in the UK, clinical testing was not considered necessary. Comparative bioequivalence and bioavailability studies are not normally required for parenteral solutions.

Formal studies on pack/product compatibility, including migration of additives and metals from the rubber stopper into the product, have not been carried out since the grade of glass used has been employed for many years for the higher strength products and for the 0.1% solution. Reported real-time and accelerated stability data do not suggest adverse interaction between the container/closure and the proposed preparation.

#### MANUFACTURE/PROCESS VALIDATION

##### GMP Statement

The proposed site of manufacture, assembly and batch release is South Devon Healthcare, NHS Trust, Torbay Pharmacy Manufacturing Unit, Long Road, Paignton, Devon TQ4 7TW, UK. A satisfactory current manufacturer's authorisation for this site (ML 13079/1) has been presented. The proposed finished product manufacturer has been approved for the manufacture of other parenteral products marketed in the UK.

#### Manufacturing Process

The manufacture of the product is relatively simple and uses conventional pharmaceutical methods. The account of the process is generally satisfactory.

#### In-process controls

The in-process controls applied are generally appropriate and appear to give a reproducible product.

Batch analytical data presented for five consecutive production scale batches of Morphine Sulphate Injection 2 mg per ml demonstrated full compliance with the proposed finished product release specifications and indicated a consistent manufacturing process. Process validation is simple and straightforward. Process parameters have been investigated and a total of 63 production scale batches manufactured under a Special Licence to date. All key processing steps, in-process controls and testing protocols have reportedly been in use for considerable time without problems arising. An assurance has been given that all production batches following licence grant will be made in full compliance with the methods and testing information already submitted.

#### Validation of the autoclave cycle

The filled vials are autoclaved using the standard pharmacopoeial cycle (121° C for 15 mins). The proposed autoclave cycle for the finished product in its final containers has been fully validated to demonstrate that a satisfactory level of sterility is achieved.

#### **EXCIPIENTS**

Sodium Chloride and Water for Injections in bulk are specified as complying with the respective corresponding Ph Eur monographs. Sodium Chloride is supplied with Certificates of Analysis and no further testing is carried out by the finished product manufacturer. Satisfactory results have been reported for chemical, microbiological and endotoxin testing of water for injections used. Confirmation has been provided that helium and nitrogen used comply with the BP 1988 monograph and Ph Eur monograph, respectively.

#### TSE Status

An assurance has been provided that there are no starting materials of animal origin used in the production of Morphine Sulphate Injection 2 mg per ml. Confirmation of full compliance with current CPMP-CVMP guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products has been provided.

#### **PACKAGING**

Primary containers are 50ml and 100ml Type II clear glass vials sealed with bromobutyl rubber stoppers and aluminium tamper-proof flip-top caps. The vials are packed into cardboard boxes, each containing 10 vials.

The containers are specified as 20 mm clear DIN vials made from Type II clear glass which complies with the USP, DIN 52339 and Ph Eur (3.2.1) requirements. Satisfactory specifications, test methods and technical drawings have been presented. Data provided by both proposed suppliers of the glass vials confirm compliance with Ph Eur requirements for glass containers for aqueous parenterals.

The 20 mm DIN bromobutyl rubber stoppers used comply with the Ph Eur requirements (3.2.9) for Type I rubber closures for containers for aqueous preparations for parenteral use. The tamper-proof flip-top seals made from 0.20 mm aluminium with a polypropylene non-protruding button are supplied by Schubert Seals. Packaging components are received with certificates of conformity. Dimension and visual checks are routinely performed by the finished product manufacturer on receipt of containers and packaging components.

#### **CONTROL TESTS ON THE FINISHED PRODUCT**

Proposed specifications are generally in line with requirements included in the BP monograph for Morphine Sulphate Injection. The tests applied in the Finished Product Specification are considered appropriate for this type of product.

Batch analytical data provided for 5 batches (B/No: 911101, 911121, 911111, 003281 and 006225), each of 100 litres, indicated compliance with proposed finished product specifications.

#### **ANALYTICAL METHODS**

Analytical methods have been validated by submission of a comprehensive validation package.

#### **STABILITY**

Stability data have been provided for 3 production batches (B/No: 911101, 911111 & 911121), each of 100 litres (1500 units), manufactured in November 1999 and stored at 25° C, 40° C and 60° C for up to 6 months. The fill volume tested was 65ml and the sterilised sealed vials were kept upright during the stability studies. Supplementary stability data for 3 batches of Morphine Sulphate Injection 1 mg/ ml, in amber glass vials, autoclaved, and stored at 25° C, 40° C and 60° C for up to 24 months, and 3 batches in clear glass vials stored at 25° C for 24 months, were provided.

Appropriate tests were carried out on the samples. Reported data indicated a slight increase in the concentration of Morphine Sulphate after 6 months storage at 25° C and 40° C. At 60° C, morphine levels decreased slightly. However, there were no corresponding changes in levels of pseudomorphine reported after storage at all temperatures for the same 6 month period. A slight increase in pH values was recorded on storage at 25° C and 40° C. At 60° C, pH values decreased slightly.

Appropriate tests were carried out on the drug product from vials stored upright and inverted at 25° C for 8 weeks, analysed in-house using test methods included in Ph Eur. These results combined with a report from the suppliers of the rubber stopper demonstrated that there are no differences between vials stored upright and inverted and that the levels of extractables from rubber subjected to 121° C for one hour are very low. The proposed outer carton for the vials includes a warning statement that this product should be stored in an upright position.

Stability studies for the 30ml and 50ml fill volumes (both in 50 ml vials) is currently ongoing to support the proposed shelf life. South Devon Healthcare have confirmed that stability studies performed on the 30ml and 50ml fill volumes will be expanded so that the first 3 production batches of each will be placed on long term stability throughout the proposed 24 months shelf life and on accelerated studies for 6 months. The applicant has confirmed that the Licensing Authority will be immediately informed of any anomalous results. The additional stability data is generated in full accordance with CPMP guidance on stability testing of finished products data includes actual numerical results for extractable volumes, individual (including morphine-n-oxide) and total related substances of morphine, extractables/leachables, sub-visible and visible particulate contamination.

No light stability studies have been performed but photostability of the finished product has been addressed by the storage recommendation to protect from light, in line with the BP storage requirement for Morphine Sulphate Injection.

#### **BIOEQUIVALENCE AND BIOAVAILABILITY**

Bioequivalence data not available. This has been justified by reference to CPMP guidance on bioequivalence exemption for parenteral solutions intended solely for administration by injection.

#### **ESSENTIAL SIMILARITY**

The Applicant has not addressed the issue of essential similarity. However, in view of the fact that the active ingredient is not only a well established drug but also a natural product nothing of value will be gained on this issue from the Applicant. The degradation products of morphine are well known and autoclaving of injectables of this active is standard practice. There is no scientific reason to doubt that this product will not be essentially similar to the cross-referral product.

### **4. ADMINISTRATIVE DETAILS**

#### **PRODUCT LABELLING**

All labelling is satisfactory.

#### **PATIENT INFORMATION LEAFLET**

The Patient Information leaflet is satisfactory.

#### **MAA FORM**

The MAA for this product is satisfactory.

#### **SUMMARY OF PRODUCT CHARACTERISTICS**

The SPC is satisfactory.

#### **Expert Report**

A comprehensive Pharmaceutical Expert Report has been prepared by a suitably qualified expert.

### **5. PHARMACEUTICAL RECOMMENDATION**

Granting of a Marketing Authorisation is recommended.

## **PRECLINICAL ASSESSMENT**

No new preclinical data have been supplied with this application and none are required for an application of this type.

## **CLINICAL ASSESSMENT**

### **1. INTRODUCTION**

This is a national abridged application for variation of an existing marketing authorisation to provide a new strength of authorised medicinal product, marketed by the same supplier (PL 13079, Morphine Sulphate 1mg/ml). The product is a dilute solution containing morphine sulphate 2mg/ml in vials of 30ml, 50ml or 60 ml for single use. The product is formulated specifically for infusion via a PCA device.

### **2. BACKGROUND**

Morphine is a potent analgesic.

### **3. INDICATIONS**

Satisfactory. Consistent with originator.

### **4. DOSE & DOSE SCHEDULE**

Satisfactory. Consistent with the originator.

### **5. TOXICOLOGY**

No new data have been submitted and none are required for this application.

### **6. CLINICAL PHARMACOLOGY**

No new data submitted and none are required for this application.

### **7. EFFICACY**

No new data submitted and none are required for this application.

### **8. SAFETY**

No new data submitted.

### **9. EXPERT REPORTS**

A comprehensive clinical expert report by an appropriately qualified physician has been submitted.

#### **10. PATIENT INFORMATION LEAFLET (PIL)**

Satisfactory.

#### **11. LABELLING**

Satisfactory.

#### **12. APPLICATION FORM (MAA)**

Satisfactory.

#### **13. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**

Satisfactory. Identical to originator product.

#### **14. DISCUSSION**

This product is a 'line extension' of a morphine sulphate 1mg/ml product already manufactured by South Devon Healthcare Trust originally under a 'specials' licence. A specials licence was also granted for the 2mg/ml solution for injection at the same time. The applicants now wish to produce this line extension commercially in order to facilitate administration of parenteral morphine via an infusion pump without having to increase the volume required. In essence this may be considered equivalent to using 2x1mg/ml. The dose response relationship of morphine's analgesic activity is well described, together with the adverse events profile. The use of the 1mg/ml solution via PCA is well documented and there are no reasons to suppose that the 2mg/ml solution would pose additional risks.

The SPC, labelling and leaflets are identical to the originator product.

#### **15. MEDICAL CONCLUSION**

Marketing authorisation is recommended.

## **OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT**

### **QUALITY**

The important quality characteristics of Morphine Sulphate Injection 2mg/ml are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

### **PRECLINICAL**

No new preclinical data were submitted and none are required for applications of this type.

### **EFFICACY**

The indication is for relief of moderate to severe pain.

The efficacy of Morphine Sulphate Injection 2mg/ml in pain relief is well established. Natural opium alkaloids similar to this product have been available in the European Union, including the UK, for much more than ten years. Their use is well established with recognised efficacy and acceptable safety.

### **RISK BENEFIT ASSESSMENT**

The quality of the product is acceptable and no significant preclinical or clinical safety concerns were identified. When used as indicated, Morphine Sulphate Injection 2mg/ml has a favourable benefit-to-risk ratio. The hazard associated with Morphine Sulphate Injection 2mg/ml appears to be low and acceptable when considered in relation to its therapeutic benefits.

## MORPHINE SULPHATE INJECTION 2 MG PER ML

PL 13079/0006

### STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 30 January 2001
2	Following assessment of the application the MHRA requested further information relating to the quality dossier on 23 May 2001.
3	The applicant responded to the MHRA's requests, providing further information on 12 February 2002.
4	Following assessment of the response the MHRA requested further information relating to the quality dossier on 13 March 2002.
5	The applicant responded, providing further information on 14 March 2002 and 12 June 2003.
6	Following assessment of the response the MHRA requested further information relating to the quality dossier on 23 December 2003.
7	The applicant responded, providing further information on 13 August 2004.
8	The application was determined on 23 May 2006.

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. Name of the Medicinal Product

Morphine Sulphate Injection 2mg/ml.

### 2. Qualitative and Quantitative Composition

Each ml of sterile solution for injection contains 2 mg Morphine Sulphate.

For excipients, see 6.1

### 3. Pharmaceutical Form

Solution for injection.

The solution is clear, colourless and visibly free from particles.

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic indications

Morphine Sulphate Injection is indicated for the relief of moderate to severe pain. Morphine 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

*Adults and children over 12 years:*

Morphine Sulphate Injection is formulated for use by intravenous injection 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 1mg and 10mg (maximum 15mg) of morphine sulphate 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 1mg Morphine Sulphate 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 sulphate 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.

#### *Use in children:*

Not recommended for children under 12 years.

#### *Use in the elderly:*

Morphine doses need to be reduced in elderly patients.

### **4.3. Contraindications**

Morphine Sulphate Injection should not be given to patients with known hypersensitivity to morphine or other opioid preparations. Use of Morphine Sulphate Injection is also contra-indicated in patients with 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; in presence of a risk of paralytic ileus; biliary and renal tract spasm and acute alcoholism; phaeochromocytoma.

Morphine Sulphate Injection should not be given to patients with moderate to severe renal impairment (glomerular filtration rate <20ml/min) or with severe or acute liver failure.

Morphine Sulphate Injection is contra-indicated in patients receiving monoamine oxidase inhibitors or within two weeks of discontinuing such treatment. Use of Morphine Sulphate 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 Sulphate Injection should be used with caution in debilitated patients and those with adrenocortical insufficiency; 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 postoperatively following total joint arthroplasty (colonic pseudo-obstruction).

Although the dependence potential is low when morphine is used legitimately for pain relief, physical and psychological dependence and tolerance may occur in susceptible individuals. Abrupt cessation of therapy after prolonged use may result in withdrawal symptoms.

#### **4.5. Interactions with other medicaments and other forms of interaction**

Concomitant or recent use of monoamine oxidase inhibitors with morphine is contra-indicated since interactions have been reported, resulting in CNS excitation or depression with hyper- or hypotensive crises.

The CNS depressant effects of morphine are increased by the co-administration of CNS depressants including alcohol, anaesthetics, muscle relaxants, hypnotics sedatives, tricyclics, neuroleptics and phenothiazines. Hyperpyrexia and CNS toxicity may result from an opiate selegiline combination. Such combinations should, therefore, be used with extreme caution.

Combined with alcohol, antidepressants and antipsychotics the hypotensive effect of morphine may be enhanced.

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). Morphine may reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. The combination of morphine with anticholinergics may enhance the constipatory effect and urinary retention.

Cimetidine and ranitidine appear to interfere with the metabolism of morphine and the metabolism and excretion of morphine may be inhibited by disulfiram. Increased morphine levels may result from the co-administration of cisapride. Metoclopramide and domperidone may antagonise morphine's gastrointestinal effects and metoclopramide enhances its sedative effect. Ciprofloxacin concentration may be reduced

and mexiletine absorption delayed by co-administered opiate. Animal data suggest that propranolol may increase the toxicity of opioids.

#### **4.6. Pregnancy and lactation**

There is inadequate evidence on the safety of morphine in human pregnancy nor is there evidence from animal work that morphine is free from hazard. Morphine Sulphate Injection is not, therefore, recommended for use in pregnancy.

Morphine has been shown to suppress lactation, although morphine is secreted in breast milk and may cause respiratory depression in the infant.

#### **4.7. Effects on ability to drive and to use machines**

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

#### **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.

Difficult micturition, ureteric or biliary spasm, dry mouth, sweating, facial flushing, headache, vertigo, bradycardia, palpitations, orthostatic hypotension, hypothermia, restlessness, mood changes, hallucinations, bronchospasm (in association with anaphylaxis), miosis, decreased libido or potency and regression of secondary sexual characteristics (males) and disruption of ovulation and amenorrhoea (females) on long term treatment may also occur. Raised intracranial pressure and muscle rigidity have also been reported.

Pain and irritation at the injection site may occur, as well as generalised histamine-mediated reactions such as urticaria and pruritus. Anaphylactic reactions to morphine injections have been reported rarely.

Tolerance and psychological and physical dependence may occur.

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

#### **4.9. Overdose**

*Signs:*

The signs of morphine overdose consist of pin-point pupils, respiratory depression, 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 overdose.

*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 10mg.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1. Pharmacodynamic properties**

Pharmacotherapeutic group: Natural opium alkaloids, ATC Code: N02AA

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**

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

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

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**

The toxicological profile of morphine in animals has not been systematically identified as a result of its established widespread clinical use. Recent animal studies have confirmed some targets for morphine toxicity. A nephrotoxic action has been reported in rats following subcutaneous administration of relatively high levels (up to 96mg/kg) of morphine. Adverse effects of morphine on development of the foetus and newborn have been confirmed in rats and mice. Morphine has been shown to reduce the release of LH from the pituitary causing reductions in serum testosterone levels, reduction in the weight of secondary sex organs and reductions in spermatogenic cell populations. The adverse effects of morphine sulphate in both males and females are consistent with recent findings that morphine exhibits significant genotoxic actions in several in vivo test systems. Immunotoxicity associated with morphine treatment has been reported in animal tests for several parameters which provide possible mechanisms for decreased resistance to a range of infections. Evidence suggests that part of this effect may be mediated via release of endogenous corticosterone.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1. List of excipients**

Sodium chloride  
Water for Injections

### **6.2. Incompatibilities**

Morphine Sulphate Injection should not be mixed with other preparations.

Morphine salts are incompatible with aminophylline, sodium salts of barbiturates and phenytoin, aciclovir sodium, furosemide, heparin sodium, pethidine HCl, prochlorperazine edisylate and promethazine HCl.

### **6.3. Shelf-life**

*As packaged for sale:*  
2 years

*After first opening the container:*  
For single dose use only. Discard any unused solution immediately after initial use.

**6.4. Special precautions for storage**

Do not store above 25°C. Keep the container in the outer carton. Store vials in an upright position.

**6.5. Nature and contents of container**

Type II clear glass vials containing 30ml, 50ml or 60ml volume, with bromobutyl rubber stoppers and tamper-evident aluminium caps.

**6.6. Instructions for use/handling**

For Single Dose Use Only. Discard any unused solution immediately and safely after initial use.

**7. MARKETING AUTHORISATION HOLDER**

South Devon Healthcare  
Torbay PMU  
Long Road  
Paignton  
Devon  
TQ4 7TW

**8. Marketing Authorisation Number**

PL 13079/0006

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

23/05/2006

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

23/05/2006

## PATIENT INFORMATION LEAFLET

immediately. Further side effects can occur during long-term treatment with morphine. These side-effects include difficulty in urinating; spasm of the bile duct (colic) or ureter; dry mouth; sweating; facial flushing; headache; palpitations; slowed heartbeat; reduced blood pressure; restlessness; hallucinations; spasm of the airways; contractions of the pupils; mood changes; decreased libido or potency; disruption of the menstrual cycle; regression of secondary sexual characteristics. Increased intracranial pressure and muscle rigidity have also been reported. Tolerance and dependence are likely to occur and you may experience withdrawal symptoms after long-term treatment if you stop taking morphine suddenly.

### Signs of overdose

Overdosage with morphine causes slow shallow breathing, reduced blood pressure, and pin-point pupils. In cases of severe overdose circulatory failure and coma can develop which may lead to death. Less severe overdoses of morphine cause nausea, vomiting, restlessness, anxiety, confusion, tremor, hyperthermia and drowsiness. Skeletal muscle disease progressing to kidney failure can also be a consequence of overdose.

If you think that an overdose may have occurred seek medical assistance immediately.

### Action following overdose

It is vital that circulation and respiration are maintained and supported. 400-micrograms of naloxone should be administered intravenously, repeated at 2-3 minute intervals as necessary up to a maximum dose of 10mg.

### STORING MORPHINE SULPHATE INJECTION

For Single Dose Use Only. Any unused solution should be discarded immediately after initial use. Morphine Sulphate Injection must not be used after the expiry date printed on the label. After the expiry date, return any unused product to a pharmacy. Do not store above 25°C. Keep the container in the outer carton.

Morphine Sulphate Injection should be clear, colourless and particle free. Any change in colour or clarity indicates deterioration of the solution. In this instance return any unused product to a pharmacy.

This medicine should be kept in a safe place where children cannot see or reach it.

Date of leaflet preparation: January 2004

PL 13079/0006

PIL/6/1

**SOUTH DEVON  
HEALTHCARE**

### PATIENT INFORMATION LEAFLET MORPHINE SULPHATE INJECTION

**2MG/1 ML**

**PLEASE READ THIS LEAFLET CAREFULLY. IF YOU HAVE ANY QUESTIONS OR ARE NOT SURE ABOUT ANYTHING, ASK YOUR DOCTOR OR PHARMACIST. KEEP THIS LEAFLET IN A SAFE PLACE, YOU MAY WISH TO READ IT AGAIN.**

### ABOUT MORPHINE SULPHATE INJECTION

Each ml of sterile solution for injection contains 2mg Morphine Sulphate as the active ingredient. It is presented in 30ml, 50ml and 60ml single use vials. The product is packed into boxes which contain 10 vials. Morphine Sulphate Injection also contains the following inactive substances:

Sodium chloride;

Water for Injection.

Morphine Sulphate Injection is a solution of morphine that has been prepared in water so that it can be used with specially designed pumps which provide a continuous injection into the body. It is one of a group of strong painkilling drugs called opioids which must be used only under a doctor's instruction.

The manufacturer and marketing authorisation holder is:

South Devon Healthcare  
Torbay PMU  
Long Road  
Plymouth  
Devon  
TQ4 7TW

### WHAT IS MORPHINE SULPHATE INJECTION USED FOR?

Morphine Sulphate Injection is intended for the long term relief of moderate to severe pain, such as the pain caused by surgery, heart attacks and cancer. Morphine also helps to reduce the anxiety and sleeplessness which may be caused by the pain.

**DO NOT USE MORPHINE SULPHATE INJECTION**

if you have ever been told that you are allergic to morphine sulphate or any other strong painkilling drugs.

Please tell your doctor if:-

- you suffer from asthma, chronic bronchitis or have any other illness which causes breathing difficulties;
- you suffer from kidney or liver problems;
- you suffer from stomach or bowel problems;
- you have difficulty in passing urine due to an enlarged prostate;
- you suffer from bad headaches, feel sick, or have suffered a head injury;
- you suffer from epilepsy or other fits;
- you suffer from poor blood supply to the heart or other heart problems;
- you suffer from malfunctioning of the adrenal gland;
- if you have a tumor of the adrenal gland;
- you suffer from myasthenia gravis;
- you have taken one of a group of drugs called monoamine oxidase inhibitors within the last two weeks;
- you suffer from biliary colic (pain from gallstones);
- you suffer from thyroid problems;
- you have a history of alcohol abuse.

Morphine Sulphate Injection is only suitable for long lasting pain and is not intended for pain which only lasts for short periods. NEVER give your medication to other people even if their symptoms are the same as yours.

#### **BEFORE USING MORPHINE SULPHATE INJECTION**

If any of the following apply to you please tell your doctor before using Morphine Sulphate Injection because he/she may need to check you more closely:

- You are pregnant or breast feeding.
- You are taking medicines to treat depression.
- You are taking medicines for sickness (phenothiazines), for drying secretions (anticholinergics) or other pain killers.
- You are taking medicines to make you sleep, such as hypnotics or sedatives.
- You have taken this medicine in the last two weeks.

#### **USING MORPHINE SULPHATE INJECTION**

Morphine Sulphate Injection will need to be administered by a nurse or doctor using a syringe and needle to draw up the injection for administration. The syringe may be put into a small machine which allows a slow continuous intravenous injection of morphine sulphate to be given.

There is also a procedure called Patient Controlled Analgesia (PCA) in which you would be provided with a button to press when you are in pain and the machine would then give you a small amount of Morphine Sulphate Injection. There will be a safety device on the machine so that you cannot exceed the maximum number of doses.

Requirements for morphine can vary considerably between patients. You may be given a higher or "loading" dose initially. If you are an adult or child over 12 years this will typically be 1mg-10mg (up to 15mg) by intravenous infusion over four to five minutes. When the PCA procedure is used the system will typically be set to give you 1mg of morphine when you press the button. The machine will then allow no more doses for 5-10 minutes.

If you are an elderly patient reduced doses may be required. Morphine Sulphate Injection is not recommended for children under 12 years old.

Let your doctor or nurse know if your pain gets worse while you are using Morphine Sulphate Injection. Your doctor may want to increase your dose of the drug and/or give you some extra medicine for the pain. You must not drive or use machinery whilst using morphine.

#### **SIDE EFFECTS OF MORPHINE SULPHATE INJECTION**

Most people will have constipation when they are receiving Morphine Sulphate Injection. Your doctor can prescribe a laxative to overcome this problem.

You may feel sick or be sick when you take this injection. Your doctor can prescribe medicine to prevent vomiting if it causes problems.

You may find that you cannot concentrate, feel confused or feel more sleepy than normal either while receiving Morphine Sulphate Injection or when the dose is increased. This feeling should wear off after a few days. Some people have experienced pain or irritation where the injection was given and others have reported general itchiness.

If any of these effects are particularly troublesome or if you have any other side effects, tell your doctor

## **LABELLING**

### 30ml carton label

MHRA PAR MORPHINE SULPHATE INJECTION 2MG/ML PL 13079/0006

**SOUTH DEVON HEALTHCARE** **10 x 30ml Vials**

**Morphine Sulphate Injection**  
**2mg/ml**

**( Morphine Sulphate 60mg in 30ml )**

**POM** **CD**

Sterile Solution for Injection  
Each ml of sterile solution for injection contains 2mg Morphine Sulphate.  
Also contains; Sodium Chloride and Water for Injections

Batch no **000000**  
Expiry date **MMYYYY**

TORBAY P.A.U.  
LONG ROAD PAIGNTON,  
DEVON TQ4 7TW

PL **13079/0006**

**10 x 30ml Vials**

**Morphine Sulphate Injection**  
**2mg/ml**

**( Morphine Sulphate 60mg in 30ml )**

**POM** **CD**

Sterile Solution for Injection  
Each ml of sterile solution for injection contains 2mg Morphine Sulphate. Also contains; Sodium Chloride and Water for Injections

Each vial is for single dose use only.  
Discard any unused solution immediately after initial use.  
This product is for intravenous injection. It has been formulated specifically for use with Patient Controlled Analgesic (PCA) devices.  
Use as directed by a medical practitioner.  
Please read the Patient Information Leaflet before you are given this injection.

Keep this product out of the reach and sight of children.  
Do not store above 25°C.

Keep containers in the outer carton. Store vials in an upright position.  
After the expiry date, return any unused product to a pharmacy.

Batch no **000000**  
Expiry date **MMYYYY**

PL **13079/0006** MOR16030B4

SOUTH DEVON HEALTHCARE 10 x 30ml Vials

**Morphine Sulphate  
Injection  
2mg/ml**

( Morphine Sulphate 60mg in 30ml )  
Sterile Solution for Injection

Each ml of sterile solution for injection contains 2mg  
Morphine Sulphate. Also contains: Sodium Chloride  
and Water for Injections



Each vial is for single dose use only.  
Discard any unused solution immediately after initial use.  
This product is for intravenous injection. It has been formulated specifically for  
use with Patient Controlled Analgesic (PCA) devices.  
Use as directed by a medical practitioner.  
Please read the Patient Information Leaflet before you are  
given this injection.  
Keep this product out of the reach and sight of children.  
Do not store above 25°C.  
Keep containers in the outer carton. Store vials in an upright position.  
After the expiry date, return any unused product to a pharmacy.

MOR16030BT/-

Batch no 000000  
Expiry date MMMYYYY

PL 13079/0006

TORBAY P.M.U.  
LONG ROAD, PAIGNTON,  
DEVON TQ4 7TW

**30ml vial label**

**SOUTH DEVON HEALTHCARE**

**10 x 50ml Vials**

**Morphine Sulphate Injection**  
**2mg/ml**

**( Morphine Sulphate 100mg in 50ml )**

**POM**

**CD**

Sterile Solution for Injection  
Each ml of sterile solution for Injection contains 2mg Morphine Sulphate.  
Also contains: Sodium Chloride and Water for Injections

Batch no **000000**  
Expiry date **MMMMYYYY**

PL 13079/0006

TORBAY HALL  
LONG ROAD, BARNSTON,  
DEVON, TQ4 7TW

**10 x 50ml Vials**

**Morphine Sulphate Injection**  
**2mg/ml**

**( Morphine Sulphate 100mg in 50ml )**

**POM**

**CD**

Sterile Solution for Injection  
Each ml of sterile solution for Injection contains 2mg Morphine Sulphate. Also contains: Sodium Chloride and Water for Injections

Batch no **000000**  
Expiry date **MMMMYYYY**

PL 13079/0006

MOR110050B/-

Each vial is for single dose use only.

Discard any unused solution immediately after initial use.

This product is for intravenous injection. It has been formulated specifically for use with Patient Controlled Analgesic (PCA) devices.

Use as directed by a medical practitioner.

Please read the Patient Information Leaflet before you are given this injection.

Keep this product out of the reach and sight of children.

**Do not store above 25°C.**

Keep containers in the outer carton. Store vials in an upright position. After the expiry date, return any unused product to a pharmacy.

50ml carton label

SOUTH DEVON  
HEALTHCARE

50ml

**Morphine Sulphate  
Injection  
2mg/ml**

(Morphine Sulphate 100mg in 50ml)

Each ml of sterile solution for injection contains  
2mg Morphine Sulphate. Also contains: Sodium  
Chloride and Water for Injections.

POM

CD

**Sterile Solution for Injection**  
This product is for single use intravenous  
administration as directed by a physician.  
Discard any unused solution immediately  
after initial use.

Keep this product out of the reach  
and sight of children.

Do not store above 25°C  
Keep container in the outer carton.  
Store vials in an upright position.

Batch no 000000

Expiry date MMMYYYY

PL 13079/0006

TORBAY P.M.U.  
LONG ROAD, PAIGNTON,  
DEVON TQ4 7TW

MORI10050VI/-

50ml vial label

10 x 60ml Vials

# Morphine Sulphate Injection

2mg/ml

( Morphine Sulphate 120mg in 60ml )

Sterile Solution for Injection

Each ml of sterile solution for injection contains 2mg  
Morphine Sulphate. Also contains: Sodium Chloride and  
Water for Injections

POM



Each vial is for single dose use only.

This product is for intravenous injection. It has been formulated specifically for use with Patient Controlled Analgesic (PCA) devices.

Use as directed by a medical practitioner.  
Please read the Patient Information Leaflet before you are given this injection.

Keep this product out of the reach and sight of children.

Do not store above 25°C.

Keep containers in the outer carton. Store vials in an upright position.  
After the expiry date, return any unused product to a pharmacy.

Batch no 000000

Expiry date MMMYYYY

PL 13079/0006

TORBAY P.M.U.  
LONG ROAD, PAIGANTON,  
DEVON TQ4 7TW

MORI12060BT/-

60ml carton label

SOUTH DEVON  
HEALTHCARE

60ml

**Morphine Sulphate  
Injection**  
**2mg/ml**

(Morphine Sulphate 120mg in 60ml)

Each ml of sterile solution for injection contains  
2mg Morphine Sulphate. Also contains:  
Sodium Chloride and Water for Injections.

**Sterile Solution for Injection**  
This product is for single use intravenous  
administration as directed by a physician.  
Discard any unused solution immediately  
after initial use.

Keep this product out of the  
reach and sight of children.

**Do not store above 25 °C**  
Keep container in the outer carton.  
Store vials in an upright position.

MOR112060V/-

POM

CD

PL 13079/0006

Batch no 000000  
Expiry date MMMYYYY

TORBAY P.M.U.  
LONG ROAD, PAIGNTON,  
DEVON TQ4 7TW

**60ml vial label**