SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Morphine Sulfate Injection BP 10mg in 1ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Morphine Sulfate BP 1.0 % w/v

3. PHARMACEUTICAL FORM

Solution for Injection

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

For the relief of severe pain.

4.2. Posology and Method of Administration

By intramuscular, subcutaneous or intravenous injection.

Adults

Initially 10 - 20mg, the dose may be repeated every 4-6 hours.

In cases of terminal pain higher doses may be required.

The Elderly

Caution is advised. A reduction of dose is advisable.

Children

Not recommended for children under 1 year old.

i) Children 1 – 5 years

- *For acute/post-operative pain*

By intramuscular or subcutaneous injection: 2.5 – 5mg. The dose may be repeated every 4 hours if necessary.

By intravenous injection over at least 5 minutes: 100 – 200micrograms/kg repeated every 4 hours if necessary. (see table 1)

By intravenous injection and infusion: initially by intravenous injection (over at least 5 minutes) 100-200 micrograms/kg (see table 1) then by continuous intravenous infusion 20 micrograms/kg/hour adjusted according to response.

- *For chronic pain*

By intramuscular or subcutaneous injection: initially 150 – 200 micrograms/kg every 4 hours, adjusted according to response. (see table 2)

ii) Children 6 - 12 years

- *For acute/post-operative pain*

By intramuscular or subcutaneous injection: 5 – 10mg, repeated every 4 hours if necessary.

By intravenous injection over at least 5 minutes: 100 – 200 micrograms/kg repeated every 4 hours if necessary. (see table 1)

By intravenous injection and infusion: initially by intravenous injection (over at least 5 minutes) 100-200 micrograms /kg (see table 1) then by continuous intravenous infusion 20 micrograms/kg/hour adjusted according to response.

- *Chronic pain*

By intramuscular or subcutaneous injection: initially 200 micrograms/kg every 4 hours, adjusted according to response. (see table 2)

iii) Children 13 - 17 years

- *For acute/post-operative pain*

By intramuscular or subcutaneous injection: 10mg, repeated every 4 hours if necessary.

By intravenous injection over at least 5 minutes: 2.5 – 10mg

By intravenous injection and infusion: initially by intravenous injection (over at least 5 minutes) 2.5–10 mg then by continuous intravenous infusion 20 micrograms/kg/hour adjusted according to response.

- *Chronic pain*

By intramuscular or subcutaneous injection: initially 5 – 20mg every 4 hours, adjusted according to response.

Hepatic Impairment:

Morphine may precipitate coma in hepatic impairment – avoid or reduce dose.

Renal Impairment

A reduced maintenance dose may be necessary in moderate to severe impairment. In children, use 75% of the dose if creatinine clearance is 10 - 50ml/min/1.73m^2 and 50% if it is <10ml/min/1.73m^2.

Because the dose given to a child under 12 years is often based on their weight the following tables are provided to enable the calculated dose to be checked. These tables used age related data based on mean values of weight.

Table 1:

Dose (micrograms/Kg)	Age (Approx.)	Patients weight (kg)	Dose in mg	Dose volume in ml
100-200 micrograms/kg	1 year	10	1 - 2 mg	0.1 - 0.2 ml
	3 years	15	1.5 - 3 mg	0.15 - 0.3 ml
	5 years	18	1.8 - 3.6 mg	0.18 - 0.36 ml
	7 years	23	2.3 - 4.6 mg	0.23 - 0.46 ml
	10 years	30	3 - 6 mg	0.3 - 0.6 ml
	12 years	39	3.9 - 7.8 mg	0.39 - 0.78 ml

Table 2:

Dose (micrograms/Kg)	Age (Approx.)	Patients weight (kg)	Dose in mg	Dose volume in ml
150-200 micrograms/kg	1 year	10	1.5 - 2 mg	0.15 - 0.2 ml
	3 year	15	2.25 - 3 mg	0.23 - 0.3 ml
	5 years	18	2.7 - 3.6 mg	0.27 - 0.36 ml

Doses and volumes for children must be calculated, measured and checked carefully by competent healthcare professionals to avoid error. Particular care must be taken when measuring very small volumes.

After calculation the information in these tables should be used to check that the dose and volume are appropriate for the specific age and weight of the child.

4.3. Contra-indications

- Hypersensitivity to any of the product's ingredients
- Acute respiratory depression or Chronic Obstructive Airways Disease
- Asthma attack
- Acute alcoholism
- Biliary colic

- Head injuries or increased intracranial pressure
- Heart failure secondary to lung disease
- Monoamine oxidase inhibitors (including moclobemide), or within two weeks of their withdrawal
- Risk of paralytic ileus
- Phaeochromocytoma
- Liver failure in children may precipitate coma

4.4. Special Warnings and Precautions for Use

Repeated use can cause tolerance and dependence. Caution in use should be exercised and a reduction in dose may be advisable in the elderly and in the following cases:

- Hypotension
- Hypothyroidism
- Depressed respiratory reserve
- Prostatic hypertrophy
- Hepatic or renal impairment (avoid or reduce dose)
- Convulsive disorders
- Administration of morphine to children with hepatic impairment may precipitate coma
- The subcutaneous route is not suitable if tissue perfusion impaired or if oedema is present
- Consideration should be given to prescribing prophylactic laxatives when initiating treatment with major opioids to children
- Asthma (avoid during attack)
- Prophylactic laxatives should always be prescribed when commencing major opioids to children.
- Respiratory support should be available for non-ventilated neonates and children < 1 year as such patients show an increased susceptibility to respiratory depression.

4.5. Interactions with other Medicinal Products and other Forms of Interaction

Alcohol : Enhanced sedative and hypertensive effects.

Antidepressants: The use of morphine should be avoided or used with caution in patients receiving monoamine oxidase inhibitors (including moclobemide), or within two weeks of their withdrawal.

Anxiolytics, Hypnotics and other CNS Depressants: Sedative effects may be enhanced by simultaneous use of morphine.

Ciprofloxacin: Morphine Sulfate should not be used as a premedication when ciprofloxacin is used for surgical prophylaxis as serum levels of ciprofloxacin are reduced and adequate cover may not be obtained during surgery.

4.6. Pregnancy and Lactation

Morphine should not be used during pregnancy or lactation as it crosses the placenta and is secreted in breast milk and can cause respiratory depression in the neonate.

4.7 Effects on ability to drive and use machines

May cause drowsiness, if affected patients should not drive or operate machinery.

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

Cardiac disorders

- Bradycardia
- Tachycardia
- Palpitations

Vascular disorders

- Postural hypotension
- Hypotension due to large doses

Nervous system disorders

- Headache
- Vertigo
- Dizziness
- Drowsiness
- Restlessness
- Seizure, particularly with infants and children
- Raised intracranial pressure

Eye disorders

- Miosis

Respiratory, thoracic and mediastinal disorders

- Respiratory depression especially with large doses. Neonates and children < 1 year show an increased susceptibility to respiratory depression
- Bronchospasm

Gastrointestinal disorders

- Constipation
- Ileus
- Nausea
- Vomiting
- Dry mouth

Renal and urinary disorders

- Ureteric spasm
- Difficulty in micturition
- Urinary retention

Skin and subcutaneous disorders

- Sweating
- Facial flushing
- Rashes and pruritis
- Contact dermatitis
- Urticaria
- Angioedema

Musculoskeletal and connective tissue disorders

- Muscle rigidity
- Myoclonus with higher doses

Hepatobiliary disorders

- Increase in liver enzymes as a result of spasm of the sphincter of Oddi
- Biliary spasm

Immune system disorders

- Allergic reactions (including anaphylaxis)

Reproductive system and breast disorders

- Decrease in libido or potency

Psychiatric disorders

- Hallucination
- Confusion
- Mood change
- Dysphoria
- Dependence

General disorders and administration site conditions

- Hypothermia
- Pain and irritation at the site of injection has been reported
- Syndrome of inappropriate anti diuretic hormones (SIADH)

4.9. Overdose

Symptoms: Progressive depression of the central nervous system leading to deep coma, cyanosis and marked reduction of the respiratory rate before respiratory arrest occurs. The pupils are usually pin-point in size. Hypotension, tachycardia, hallucinations and rhabdomyolysis have been reported.

Treatment: Maintain fluid and electrolyte levels and provide assisted respiration if necessary.

Naloxone is indicated if coma or respiratory depression is present. Patients should be carefully observed for recurrence of CNS and respiratory depression. The plasma half-life

of naloxone is shorter than that of all opioid analgesics-repeated doses of naloxone may be required.

In children, the usual initial dose of naloxone is 10 micrograms per kg body-weight intravenously followed, if necessary, by a larger dose of 100 micrograms per kg.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Morphine is a powerful analgesic and narcotic and has central stimulant action. It depresses the thalamus, sensory cortex , respiratory and cough centres but stimulates the vomiting centre. Morphine increases the tone of involuntary muscles especially the sphincters of the gastro-intestinal tract.

5.2. Pharmacokinetic Properties

Morphine is distributed throughout the body but mainly in the kidneys, liver, lungs and spleen. Morphine is conjugated with glucuronic acid in the liver and gut into the active metabolites morphine-3-glucuronide and morphine-6-glucuronide. Up to 10% of a dose may be excreted through the bile into the faeces; the remainder is excreted in the kidneys.

It crosses the placenta and traces are found in sweat and milk. It is about 35% plasma protein bound. The plasma half life is 2 - 3 hours and about 60% of the dose is excreted in the urine after 24 hours. A small proportion of this is free morphine (higher in alkaline urine) and about 60 - 70% is conjugated. A small amount may be excreted in the bile.

The pharmacokinetics of morphine in children aged >1 year are similar to adults, with an elimination half-life of about 2 hours following IV administration.

5.3. Pre-clinical Safety Data

No additional pre-clinical data of relevence to the prescriber.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Sodium Chloride, Sodium Metabisulphite and Water for Injection.

The pH may be adjusted with Sodium Hydroxide or Sulphuric Acid Solution.

6.2. Incompatibilities

None stated.

6.3. Shelf Life

36 months.

6.4. Special Precautions for Storage

Do not store above 25°C and protect from light.

6.5. Nature and Content of Container

Clear, colourless 1ml glass ampoules containing sufficient solution to permit the removal of 1ml. 10 ampoules are packed into a cardboard carton.

6.6. Instructions for Use, Handling and Disposal

None stated.

ADMINISTRATIVE DATA

7. MARKETING AUTHORISATION HOLDER

Macarthys Laboratories Ltd t/a Martindale Pharmaceuticals,

Bampton Road,

Harold Hill,

Romford RM3 8UG

8. MARKETING AUTHORISATION NUMBER

PL 1883/6138R

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

First authorised: 19th January, 1982

Last renewal: 19th August 2002

10 DATE OF REVISION OF THE TEXT

24/07/2014