SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Morphine Sulfate 10mg in 1ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution contains 10 mg of Morphine Sulfate

Excipients with known effect:
Also, contains 3.26 mg of sodium per ml and sodium metabisulphite (E223).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection
A clear**,** colourless or almost colourless, particle free solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Morphine is used for the symptomatic relief of severe pain; relief of dyspnoea

of left ventricular failure and pulmonary oedema; pre-operative use.

4.2 Posology and method of administration

Posology
Adults
The dosage should be based on the severity of the pain and the response and tolerance of the patient. The usual adult subcutaneous or intramuscular dose is 10 mg every 4 hours if necessary, but may range from 5 mg to 20 mg.
The usual adult intravenous dose is 2.5 mg to 15 mg not more than 4 hourly, where necessary, but dosage and dosing interval must be titrated against the patient's response and adjustments made until analgesia is achieved.

Elderly
Because of the depressant effect on respiration, caution is necessary when giving morphine to the elderly. A reduction of dose is advisable.

Paediatric Population

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	1 year	10	1 - 2 mg	0.1 - 0.2 ml

micrograms/kg	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.

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.

Method of administration

By intramuscular, subcutaneous or intravenous injection.
The subcutaneous route is not suitable for oedematous patients.
The epidural or intrathecal routes must not be used as the product contains a preservative.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Acute respiratory depression
- Asthma attack or Chronic Obstructive Airways Disease
- Acute alcoholism
- Biliary colic (see section 4.4)
- Head injuries, comatose patients or increased intracranial pressure. The sedation and pupillary changes produced may interfere with accurate monitoring of the patient.
- Heart failure secondary to lung disease
- Monoamine oxidase inhibitors (including moclobemide), or within two weeks of their withdrawal
- Risk of paralytic ileus
- Phaeochromocytoma (due to the risk of pressor response to histamine release).
- Acute diarrhoeal conditions associated with antibiotic-induced pseudomembranous colitis or diarrhoea caused by poisoning (until the toxic material has been eliminated)

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
- Asthma (avoid during attack)
- Adrenocortical insufficiency
- Urethral stricture
- Inflammatory or obstructive bowel disorders

Opioids such as morphine should either be avoided in patients with biliary disorders or they should be given with an antispasmodic.

Morphine can cause an increase in intrabiliary pressure as a result of effects on the sphincter of Oddi. Therefore, in patients with biliary tract disorders morphine may exacerbate pain (use in biliary colic is a contraindication, see 4.3).

In patients given morphine after cholecystectomy, biliary pain has been induced.

Abrupt withdrawal from persons physically dependent on them precipitates a withdrawal syndrome, the severity of which depends on the individual, the drug used, the size and frequency of the dose and the duration of drug use. Great caution should be exercised in patients with a known tendency or history of drug abuse

Palliative care - in the control of pain in terminal illness, these conditions should not necessarily be a deterrent to use.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:
Concomitant use of Morphine Sulfate 1mg/ml Solution for Injection 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 Sulfate 1mg/ml Solution for Injection 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).

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.

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.
Morphine has an abuse potential similar to other strong agonist opioids and should be used with particular caution in patients with a history of alcohol or drug abuse.

Dependence and withdrawal (abstinence) syndrome
Use of opioid analgesics may be associated with the development of physical and/or psychological dependence or tolerance. The risk increases with the time the drug is used, and with higher doses. Symptoms can be minimised with adjustments of dose or dosage form, and gradual withdrawal of morphine. For individual symptoms, see section 4.8.
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

Morphine Sulfate Solution for Injection contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

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).

4.5 Interaction with other medicinal products and other forms of interaction

Alcohol: Enhanced sedative and hypertensive effects.

Anti-arrhythmics**:** There may be delayed absorption of mexiletine.

Antibacterials**:** The opioid analgesic papaveretum has been shown to reduce plasma ciprofloxacin concentration. The manufacturer of ciprofloxacin advises that premedication with opioid analgesics be avoided.

Antidepressants, anxiolytics, hypnotics: Severe CNS excitation or depression (hypertension or hypotension) has been reported with the concurrent use of pethidine and monoamine oxidase inhibitors (MAOIs) including selegiline, moclobemide and linezolid. As it is possible that a similar interaction may occur with other opioid analgesics, morphine should be used with caution and consideration given to a reduction in dosage in patients receiving MAOIs.

The sedative effects of morphine (opioid analgesics) are enhanced when used with depressants of the central nervous system such as hypnotics, anxiolytics, tricyclic antidepressants and sedating antihistamines.

Antipsychotics**:** possible enhanced sedative and hypotensive effect.

Antidiarrhoeal and antiperistaltic agents (such as loperamide and kaolin): concurrent use may increase the risk of severe constipation.

Antimuscarinics**:** agents such as atropine antagonise morphine-induced respiratory depression and can partially reverse biliary spasm but are additive to the gastrointestinal and urinary tract effects. Consequently, severe constipation and urinary retention may occur during intensive antimuscarinic analgesic therapy.

Metoclopramide and domperidone**:** There may be antagonism of the gastrointestinal effects of metoclopramide and domperidone.

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.

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:
Morphine sulfate should only be used when benefit is known to outweigh risk. As with all drugs it is not advisable to administer morphine during pregnancy. Morphine crosses the placental barrier. Administration during labour may

cause respiratory depression in the new born infant and gastric stasis during labour, increasing the risk of inhalation pneumonia. Therefore, it is not advisable to administer morphine during labour.

Babies born to opioid-dependent mothers may suffer withdrawal symptoms including CNS hyperirritability, gastrointestinal dysfunction, respiratory distress and vague autonomic symptoms including yawning, sneezing, mottling and fever.

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:
While morphine can suppress lactation, the quantity from therapeutic doses that may reach the neonate via breast milk is probably insufficient to cause major problems of dependence or adverse effects.

Fertility
Animal studies have shown that morphine may reduce fertility (see section 5.3.)

4.7 Effects on ability to drive and use machines

Morphine causes drowsiness so patients should avoid driving or operating 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

The most serious hazard of therapy is respiratory depression (see section 4.9).
The commonest side-effects of morphine are

- Nausea
- Vomiting
- Constipation
- Drowsiness

- Dizziness

Tolerance generally develops with long term use, but not to constipation.
Other side effects include the following:

Psychiatric disorders

- Dependence.

Immune system disorders:

- Anaphylactic reactions following intravenous injection have been reported rarely, anaphylactoid reactions.

Cardiac disorders:

- Bradycardia
- Palpitations
- Tachycardia
- Orthostatic hypotension.

Nervous system disorders:

- Myoclonus
- Mental clouding
- Confusion (with large doses)
- Hallucinations
- Headache
- Vertigo
- Mood changes including dysphoria
- Euphoria
- Allodynia
- Hyperalgesia (see section 4.4)
- Hyperhidrosis

Gastrointestinal disorders:

- Dry mouth
- Biliary spasm

Eye disorders:

- Blurred or double vision or other changes in vision
- Miosis

Reproductive system and breast disorders:

- Long term use may lead to a reversible decrease in libido or potency.

Skin and subcutaneous tissue disorders:

- Pruritus
- Urticaria
- Rash
- Sweating.
- Contact dermatitis has been reported and pain and irritation may occur on injection.

- Facial flushing

Musculoskeletal and connective tissue disorders

- Muscle rigidity

Renal and urinary disorders:

- Difficulty with micturition
- Ureteric spasm
- Urinary retention
- Antidiuretic effect.

General disorders and administration site conditions :

- Drug withdrawal (abstinence) syndrome

Tolerance develops to the effects of opioids on the bladder.
The euphoric activity of morphine has led to its abuse and physical and psychological dependence may occur (see section 4.4).

Description of selected adverse reactions

Drug dependence and withdrawal (abstinence) syndrome

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: 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 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

Toxic doses vary considerably with the individual, and regular users may tolerate large doses.

The triad of respiratory depression, coma and constricted pupils is considered indicative of opioid overdosage with dilatation of the pupils occurring as hypoxia develops. Death may occur from respiratory failure

Other opioid overdose symptoms include hypothermia, confusion, severe dizziness, severe drowsiness, hypotension, bradycardia, circulatory failure

pulmonary oedema, severe nervousness or restlessness, hallucinations, pneumonia aspiration, convulsions (especially in infants and children). Rhabdomyolysis, progressing to renal failure, has been reported in overdosage.

Death may occur from respiratory failure.
Treatment: The medical management of overdose involves prompt administration of the specific opioid antagonist naloxone if coma or bradypnoea are present using one of the recommended dosage regimens. Both respiratory and cardiovascular support should be given where necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids,

ATC Code: N02AA01

Morphine is a narcotic analgesic obtained from opium, which acts mainly on the central nervous system and smooth muscle.

Morphine is a potent analgesic with competitive agonist actions at the μ-receptor, which is thought to mediate many of its other actions of respiratory depression, euphoria, inhibition of gut motility and physical dependence. It is possible that analgesia, euphoria and dependence may be due to the effects of morphine on a μ-1 receptor subtype, while respiratory depression and inhibition of gut motility may be due to actions on a μ-2 receptor subtype.

Morphine is also a competitive agonist at the κ-receptor that mediates spinal analgesia, miosis and sedation. Morphine has no significant actions at the other two major opioid receptors, the δ- and the σ-receptors.
Morphine directly suppresses cough by an effect on the cough centre in the medulla. Morphine also produces nausea and vomiting by directly stimulating the chemoreceptor trigger zone in the area postrema of the medulla. Morphine provokes the release of histamine.

5.2 Pharmacokinetic properties

Absorption:
Variably absorbed after oral administration; rapidly absorbed after subcutaneous or intramuscular administration.

Blood concentration: After an oral dose of 10mg as the sulfate, peak serum concentrations of free morphine of about 10ng/ml are attained in 15 to 60 minutes; after an intramuscular does of 10mg, peak serum concentrations of 70 to 80ng/ml are attained in 10 to 20 minutes; after an intravenous does of 10mg, serum concentrations of about 60ng/ml are obtained in 15 minutes falling to 30ng/ml after 30 minutes and to 10ng/ml after 3 hours; subcutaneous

doses give similar concentrations to intramuscular doses at 15 minutes but remain slightly higher during the following 3 hours; serum concentrations measured soon after administration correlate closely with the ages of the subjects studied and are increased in the aged.

Half-life:
Serum half-life in the period 10 minutes to 6 hours following intravenous administration, 2 to 3 hours; serum half-life in the period 6 hours onwards, 10 to 44 hours.

Distribution:
Widely distributed throughout the body, mainly in the kidneys, liver, lungs and spleen; lower concentrations appear in the brain and muscles; morphine crosses the placenta and traces are secreted in sweat and milk; protein binding, about 35% bound to albumin and to immunoglobulins at concentrations within the therapeutic range.

Biotransformation:
Mainly glucuronic acid conjugation to form morphine-3 and 6-glucuronides, with sulfate conjugation. N-demethylation, 0-methylation and N-oxide glucuronide formation occurs in the intestinal mucosa and liver; N-demethylation
occurs to a greater extent after oral than parenteral administration; the 0-methylation pathway to form codeine has been challenged and codeine and norcodeine metabolites in urine may be formed from codeine impurities in the morphine sample studied.

Elimination:
After an oral dose, about 60% is excreted in the urine in 24 hours, with about 3% excreted as free morphine in 48 hours; after parenteral dose, about 90% is excreted in 24 hours, with about 10% as free morphine, 65 to 70% as conjugated morphine, 1% as normorphine and 3% as normorphine glucuronide; after administration of large doses to addicts about 0.1% of a dose is excreted as norcodeine; urinary excretion of morphine appears to be pH dependent to some extent: as the urine becomes more acid more free morphine is excreted and as the urine becomes more alkaline more of the glucuronide conjugate is excreted; up to 10% of a dose may be excreted in the bile.

5.3 Preclinical safety data
In male rats, reduced fertility and chromosomal damage in gametes have been reported.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride,
Sodium Metabisulfite(E223)
Water for Injection.
The pH may be adjusted with Sodium Hydroxide or Sulfuric Acid Solution.

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. Compounds incompatible with morphine salts include aminophylline and sodium salts of barbiturates and phenytoin. Other incompatibilities (sometimes attributed to particular formulations) have included aciclovir sodium, doxorubicin, fluorouracil, frusemide, heparin sodium, pethidine hydrochloride, promethazine hydrochloride and tetracyclines. Specialised references should be consulted for specific compatibility information.
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 30°C.
Keep the ampoules in the outer carton in order to protect from light.
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6.5 Nature and contents of container

Clear, colourless 1ml Ph.Eur type1 glass ampoules containing sufficient solution to permit the removal of 1ml. 10 ampoules are packed into a cardboard carton.

6.6. Special precautions for disposal and other handling

Any solution remaining should be discarded or returned to the pharmacy.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

03892/5632/NMR/2017

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