Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Morphine Sulfate 20mg/ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml dose contains 20mg of Morphine Sulfate.

Excipients with known effect: Amaranth (E123) 0.003%w/v Sodium Benzoate 0.10% w/v

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Oral solution.

A clear red solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the relief of severe pain.

4.2 Posology and method of administration

Posology
Adults: Usual dose 10-20 mg (0.5 - 1.0 ml) every 4 hours.

Paediatric population:
Children 13 – 18 years: Maximum single dose 5-20 mg (0.25 – 1.0 ml) every 4 hours

Children 6-12 years: Maximum dose 5-10 mg (0.25 - 0.5 ml) every 4 hours.

Children 1-5 years: Maximum dose 5 mg (0.25 ml) every 4 hours.

Children under 1 year: Not recommended.

Dosage can be increased under medical supervision according to the severity of the pain and the patient's previous history of analgesic requirements. Reductions in dosage may be appropriate in the elderly, patients with moderate-severe renal or hepatic impairment, or where sedation is undesirable.

When patients are transferred from other morphine preparations to morphine sulfate 20mg/ml oral solution dosage titration may be appropriate.

A calibrated oral dosing pipette is supplied with this dosage form for accurate and convenient dose adjustment. The required dose may be added to a soft drink immediately prior to administration.

Morphine sulfate is readily absorbed from the gastro-intestinal tract following oral administration. However, when morphine sulfate oral solution is used in place of parenteral morphine, a 50 % to 100 % increase in dosage is usually required in order to achieve the same level of analgesia.

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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Respiratory depression, obstructive airways disease, known morphine sensitivity, acute hepatic disease, acute alcoholism, head injuries, coma, convulsive disorders and where the intracranial pressure is raised, paralytic ileus. Concurrent administration of monoamine-oxidase inhibitors or within two weeks of discontinuation of their use.

Morphine sulfate oral solution is contraindicated in patients known to be hypersensitive to morphine sulfate or to any other component of the product

Morphine and some other opioids can induce the release of endogenous histamine and thereby stimulate catecholamine release making them unsuitable for use in patients with phaeochromocytoma.

Opioids are contra-indicated in acute asthma exacerbations, see section 4.4 for information relating to use in controlled asthma.

4.4 Special warnings and precautions for use

Care should be exercised if morphine sulfate is given in the first 24 hours post-operatively, in hypothyroidism, and where there is reduced respiratory reserve, such as kyphoscoliosis, emphysema and severe obesity. Opioids are contra-indicated in acute asthma exacerbations. However, it has been suggested that they can be used with caution in controlled asthma.

Morphine sulfate should not be given if paralytic ileus is likely to occur (see section 4.3) or where there is an obstructive bowel disorder, or prostatic hyperplasia. If constipation occurs, this may be treated with the appropriate laxatives.

It is wise to reduce dosage in chronic hepatic and renal disease, myxoedema, adrenocortical insufficiency, prostatic hypertrophy or shock.

The administration of morphine may result in severe hypotension in individuals whose ability to maintain homeostatic blood pressure has already been compromised by depleted blood volume or the concurrent administration of drugs such as phenothiazine or certain anaesthetics.

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. Withdrawal symptoms may occur on abrupt discontinuation or on the administration of a narcotic antagonist e.g. naloxone.

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. Withdrawal symptoms may occur on abrupt discontinuation or on the administration of a narcotic antagonist e.g. naloxone.

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Hypersensitivity and anaphylactic reaction have both occurred with the use of morphine sulfate oral solution. Care should be taken to elicit any history of allergic reactions to opiates.

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.

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

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 20 mg/ml oral solution contains the following excipients:
Amaranth: Morphine sulfate oral solution contains the excipient Amaranth (E123), which may cause allergic reactions.

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

Sodium Benzoate: This medicine contains 1mg sodium benzoate in each ml.

4.5 Interaction with other medicinal products and other forms of interactions

Phenothiazine anti-emetics may be given with morphine, but it should be noted that morphine potentiates the effects of tranquillisers, anaesthetics, hypnotics, sedatives, antipsychotics, tricyclic antidepressants and alcohol. Morphine may possibly increase plasma concentrations of esmolol

Cimetidine inhibits the metabolism of morphine. Opioid analgesics including morphine may antagonise the actions of domperidone and metoclopramide on gastro-intestinal activity. Concomitant use of ritonavir should be avoided as the plasma concentration of morphine may be increased. The absorption of mexiletine may be delayed by concurrent use of morphine.

Monoamine oxidise inhibitors are known to interact with narcotic analgesics producing CNS excitation or depression with hyper- or hypotensive crisis, please see section 4.3.

Interactions have been reported in those subjects taking morphine sulfate oral solution and voriconazole. Interactions have been reported in those taking morphine sulfate oral solution and gabapentin. Both interactions suggest an increase in opioid adverse events when co-prescribed, the mechanism of which is not known. Caution should be taken where these medicines are co-prescribed.

In a study involving healthy volunteers (N=12), when a 60 mg controlled-release morphine capsule was administered 2 hours prior to a 600 mg gabapentin capsule, mean gabapentin AUC increased by 44% compared to gabapentin administered without

morphine. Therefore, patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of gabapentin or morphine should be reduced appropriately.

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
In humans, there are no adequate data available to allow an evaluation of any potential teratogenic risk. There have been reports of a possible link to an increased incident of inguinal hernias. Morphine crosses the placental barrier. Animal studies showed a potential for damage in offspring throughout the entire duration of gestation (see section 5.3). For this reason, morphine must only be used during pregnancy in cases where the maternal benefit clearly outweighs the risk for the child.

Due to the mutagenic properties of morphine, it should not be administered to men and women of child-producing/child bearing potential unless effective contraception is assured.
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.

Parturition
Morphine can prolong or shorten the duration of labour. Neonates, whose mothers are given opioid analgesics during childbirth, should be monitored for signs of respiratory depression or withdrawal syndrome and (if necessary), treated with a specific opioid antagonist.

Breast-feeding
Morphine is excreted into breast milk, where it reaches higher concentrations than in maternal plasma. As clinically relevant concentrations may be reached in nursing infants, breast-feeding is not advised.

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

4.7 Effects on ability to drive and use machines

Morphine sulfate is likely to impair ability to drive or use machinery. This effect is even more enhanced, when used in combination with alcohol or CNS depressants.

4.8 Undesirable effects

In routine clinical practice, the commonest side effects of morphine sulfate are nausea, vomiting, constipation, drowsiness and confusion. If constipation occurs, this may be treated with appropriate laxatives.

A full list of currently known adverse reactions is presented below:

SOC Category	Side effect
Immune system disorders	Hypersensitivity reactions including anaphylaxis Unknown: Anaphylactoid reactions
Psychiatric disorders	Confusion Restlessness Mood changes Hallucinations Dependence
Nervous system disorders	Drowsiness Headache

	Unknown: Allodynia, Hyperalgesia, hyperhidrosis
Eye Disorders	Miosis
Ear and labyrinth disorders	Vertigo
Cardiac disorders	Bradycardia Tachycardia Palpitations
Vascular disorders	Orthostatic hypotension Hypothermia Facial flushing Raised intracranial pressure occurs in some patients.
Gastrointestinal disorders	Nausea Vomiting Constipation Dry mouth
Hepatobiliary Disorders	Biliary spasm
Skin and subcutaneous tissue disorders	Urticaria Pruritis Sweating
Musculoskeletal and connective tissue disorders	Muscle rigidity
Renal and urinary disorders	Micturition may be difficult Ureteric spasm Antidiuretic effect
Reproductive system and breast disorders	Decreased libido/potency
General disorders and administration site conditions	Unknown: drug withdrawal (abstinence syndrome)

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: http://www.hpra.ie/; e-mail: medsafety@hpra.ie

4.9 Overdose

Signs of morphine toxicity and overdosage: These are likely to consist of pin-point pupils, respiratory depression and sedation. Circulatory failure, deepening coma and aspiration pneumonia may occur in more severe cases. Convulsions may occur in infants and children. Death may occur from respiratory failure.

Treatment of morphine overdosage*:* In unconscious patients with respiratory depression maintenance of the airway and administration of naloxone intravenously. Repeat as necessary according to the dose recommendations. Care should always be taken that the airway is maintained. Assist respiration if necessary. Maintain fluid and electrolyte levels, oxygen, i.v. fluids, vasopressors and other supportive measures should be employed as indicated.

Caution: the duration of the effect of naloxone may be shorter than the duration of the effect of the morphine overdose. It is recommended that a patient who has regained consciousness after naloxone treatment should be observed for at least 24 hours.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Opioid analgesic.
ATC Code: N02AA01

Morphine binds to opiate receptors located on the cell surfaces of the brain and nervous tissue. This action results in alteration of neurotransmitter release and calcium uptake. It has been postulated that this is the basis of the modulation of sensory input from afferent nerves sensitive to pain.

5.2 Pharmacokinetic properties

Morphine-N-methyl ^{14}C sulfate administered orally to humans reaches peak plasma level after around 15 minutes; levels of plasma-conjugated morphine peak at about 3 hours, and slowly decrease over the following 24 hours. After the first hour no significant differences in total plasma levels of radioactivity are seen whether administration is by intravenous, intramuscular subcutaneous or oral route. Morphine is a basic amine, and rapidly leaves the plasma, concentrating in the tissues. In animals it has been shown that a relatively small amount of morphine crosses the blood-brain barrier.

Morphine is metabolised in the liver and probably also in the mucosal cells of the small intestine. The metabolites recovered in the urine, in addition to free morphine, are morphine-3-glucuronide and morphine ethereal sulfate. These account for over 65% of administered radioactivity; further radioactivity can be recovered as exhaled $^{14}CO_2$.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity. Effects in non-clinical studies were observed for genotoxicity, and toxicity to reproduction and development.

Mutagenic and tumorigenic potential
There are clearly positive findings available with regards to mutagenicity, which indicate that morphine has a clastogenic effect and that, furthermore, this effect exerts an influence on gametes. Thus, morphine is to be regarded as a mutagenic substance and such an effect may also be assumed in humans.

There have been no long-term animal studies on the tumorigenic potential of morphine.

Reporoductive toxicity
Animal studies showed a potential for damage in offspring throughout the entire duration of gestation (CNS malformations, growth retardation, testicular atrophy, changes in neurotransmitter systems and behavioural patterns, dependence). In addition, morphine had an effect on male sexual behaviour and fertility in various animal species.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate
Citric acid anhydrous
Sodium benzoate (E211)
Amaranth (E123)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

After opening: 4 months

6.4 Special precautions for storage

Do not store above 25°C. Store in the original container in order to protect from light.

6.5 Nature and contents of container

The finished product is packed in 125ml (120ml fill volume), 60ml (50ml fill volume) and 30ml (30ml fill volume) conventional amber soda glass (Type III) bottles fitted with a 28mm white polypropylene push and turn, tamper evident caps with expanded polyethylene (EPE) liner.

In addition the product is supplied with a 1ml dispensing oral syringe and bottle adaptor.

Pack size:
Single pack containing 1 bottle (120 ml/ 50 ml and 30 ml)
Single pack containing 2 bottles (50 ml)
Bundle pack: 2 single pack (2 x 50ml)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Wockhardt UK Limited
Ash Road North
Wrexham
LL13 9UF
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA1339/051/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th November 2014
Date of last renewal: 14th September 2019

10 DATE OF REVISION OF THE TEXT

May 2020