Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Morphine Sulfate 10mg/5ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml dose contains 10mg of Morphine Sulfate.

Excipient(s) with known effect:
Methyl parahydroxybenzoate (E218) – 9.00mg/5ml
Propyl parahydroxybenzoate (E216) – 1.00mg/5ml
Sucrose – 1500.00mg/5ml
Glucose, liquid – 500.00mg/5ml

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Oral solution.

A clear colourless to pale yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the relief of severe pain in adults, adolescents (aged 13-18 years) and children (ages 1-12 years).

4.2 Posology and method of administration

Posology
Adults: Usual dose 10-20 mg (5 - 10ml) every 4 hours.
Maximum daily dose: 120 mg per day
Paediatric population:

Children 13-18 years:	Recommended dose 5-20 mg (2.5 – 10 ml) every 4 hours
	Maximum daily dose: 120 mg per day
Children 6-12 years:	Recommended dose 5-10 mg (2.5 – 5 ml) every 4 hours
	Maximum daily dose: 60 mg per day
Children 1-5 years:	Recommended dose 5 mg (2.5 ml) every 4 hours
	Maximum daily dose: 30 mg per day
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.

Special populations:
Reduction in dosage may be appropriate in the elderly and in patients with chronic hepatic disease (for acute hepatic disease see section 4.3), renal impairment, severe hypothyroidism, adrenocortical insufficiency, prostatic hypertrophy, shock or where sedation is undesirable.

Method of Administration

For oral use.

When patients are transferred from other morphine preparations oral preparations dosage titration may be appropriate.

Morphine **s**ulfate 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(s) or any of excipients listed in section 6.1

Morphine Sulfate Oral Solution is contraindicated in:

- respiratory depression
- obstructive airways disease
- paralytic ileus (see section 4.4)
- acute hepatic disease
- acute alcoholism
- head injuries (see section 4.4)
- coma (see section 4.4)
- increased intracranial pressure (see section 4.4)
- convulsive disorders
- patients with known morphine sensitivity
- concurrent administration with monoamine oxidase inhibitors or within two weeks of discontinuation of their use (see section 4.5)
- patients with phaeochromocytoma. Morphine and some other opioids can induce the release of endogenous histamine and thereby stimulate catecholamine release
- 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 (see section 4.2),
- and where there is reduced respiratory reserve, such as kyphoscoliosis, emphysema, cor pulmonale and severe obesity.

Asthma
It has been suggested that opioids can be used with caution in controlled asthma. However, opioids are contraindicated in acute asthma exacerbations (see section 4.3).

Head injury and increased intracranial pressure
Morphine Sulfate Oral Solution is contraindicated in patients with increased intracranial pressure, head injuries and coma (see section 4.3). The capacity of morphine to elevate cerebrospinal fluid pressure may be greatly increased in the presence of already elevated intracranial pressure produced by trauma. Also, morphine may produce confusion, miosis, vomiting and other adverse reactions which may obscure the clinical course of patients with head injury.

Abdominal conditions
Morphine sulfate must not be given if paralytic ileus is likely to occur (see section 4.3), or if the patient has bowel or obstructive biliary disease. Should paralytic ileus be suspected or occurring during these, Morphine Sulfate Oral Solution should be discontinued immediately.

Caution should be exercised where there is an obstructive bowel disorder, biliary colic, operations on the biliary tract, acute pancreatitis or prostatic hyperplasia.

If constipation occurs, this may be treated with the appropriate laxatives.

Care should be exercised in patients with inflammatory bowel disease.

Morphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions and complications following abdominal surgery.

Hypotensive effect
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 (see section 4.5).

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 sulfate is an opioid agonist and controlled drug. Such drugs are sought by drug abusers and people with addiction disorders. Morphine sulfate can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing morphine in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. 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.

Morphine sulfate may be abused by inhaling or injecting the product. These practices pose a significant risk to the abuser that could result in overdose and death.

Hypersensitivity
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. Morphine Sulfate Oral Solution is contraindicated in patients known to be hypersensitive to morphine sulphate (see section 4.3).

Risk in special populations
Morphine is metabolised by the liver and should be used with caution in patients with hepatic disease as oral bioavailability may be increased. It is wise to reduce dosage in chronic hepatic and renal disease, severe hypothyroidism, adrenocortical insufficiency, prostatic hypertrophy or shock (see section 4.2).

The active metabolite Morphine-6-glucuronide may accumulate in patients with renal failure, leading to CNS and respiratory depression.

Excipients
Morphine Sulfate Oral Solution contains the excipients methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) which may cause allergic reactions (possibly delayed).

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine. Contains 1g glucose and 3g sucrose per 10ml dose. May be harmful to teeth.

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 Oral Solution 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 Oral Solution 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.

4.5 Interaction with other medicinal products and other forms of interactions

Monoamine oxidase inhibitors
Monoamine oxidase inhibitors are known to interact with narcotic analgesics producing CNS excitation or depression with hyper- or hypotensive crisis, therefore their concomitant use with Morphine Sulfate Oral Solution is contraindicated (see section 4.3).

Gabapentin
Interactions have been reported in those taking morphine and gabapentin. Reported 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 mggabapentin 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.

Ritonavir
Although there are no pharmacokinetic data available for concomitant use of ritonavir with morphine, ritonavir may increase the activity of glucuronyl transferases. Consequently, co-administration of ritonavir and morphine may result in decreased serum concentrations of morphine with possible loss of analgesic effectiveness.

Rifampicin
Rifampicin can reduce the serum concentration of morphine and decrease its analgesic effect, the mechanism of which is not known.

Cimetidine
Cimetidine inhibits the metabolism of morphine.

CNS depressants
It should be noted that morphine potentiates the effects of CNS depressants such as tranquillisers, anaesthetics (see section 4.4), hypnotics, sedatives, antipsychotics, tricyclic antidepressants and alcohol.

Esmolol
Morphine may increase plasma concentrations of esmolol.

Domperidone/metoclopramide
Opioid analgesics including morphine may antagonise the actions of domperidone and metoclopramide on gastro-intestinal activity.

Mexiletine
The absorption of mexiletine may be delayed by concurrent use of morphine.

Phenothiazine antiemetics
Phenothiazine antiemetics may be given with morphine. However, hypotensive effects have to be considered (see section 4.4).

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
Although morphine sulfate has been in general use for many years, there is inadequate evidence of safety in human pregnancy.

Morphine is known to cross the placenta. Therefore, Morphine Sulfate Oral Solution should not be used in pregnancy, especially the first trimester unless the expected benefit is thought to outweigh any possible risk to the foetus.

Newborns whose mothers received opioid analgesics during pregnancy should be monitored for signs of neonatal withdrawal (abstinence) syndrome. This should be borne in mind when considering the use of Morphine Sulfate Oral Solution in patients during pregnancy. Treatment may include an opioid and supportive care.

The risk of gastric stasis and inhalation pneumonia is increased in the mother during labour. Since morphine rapidly crosses the placental barrier it should not be used during the second stage of labour or in premature delivery because of the risk of secondary respiratory depression in the newborn infant

Breast feeding
Although morphine sulfate has been in general use for many years, there is inadequate evidence of safety during lactation.

Morphine is not recommended for nursing mothers. Morphine is excreted in breast milk, and may thus cause respiratory depression in the newborn infant.

Fertility
Long term use of opioid analgesics can cause hypogonadism and adrenal insufficiency in both men and women. This is thought to be dose related and can lead to amenorrhoea, reduced libido, infertility and erectile dysfunction.

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. Patients should be warned not to drive or operate dangerous machinery after taking Morphine Sulfate Oral Solution.

4.8 Undesirable effects

In normal doses, the commonest side effects of morphine sulfate are nausea, vomiting, constipation, drowsiness and confusion. If constipation occurs, this may be treated with appropriate laxatives. The effects of morphine have led to its abuse and misuse. Dependence and addiction may develop with regular, inappropriate use.

Data from clinical trials are not available. Therefore it is not possible to provide information on the frequencies of undesirable effects. A full list of currently known adverse reactions is presented below:

SOC Category	Side effect
Immune system disorders	Hypersensitivity Unknown: Anaphylactic reactions (see section 4.4)
Psychiatric disorders	Confusional state Restlessness Altered mood Hallucination Dependence (see section 4.4)
Nervous system disorders	Somnolence Headache Increased intracranial pressure (see section 4.4) Unknown: allodynia, hyperhidrosis, hyperalgesia (see section 4.4)
Eye disorders	Miosis
Ear and labyrinth disorders	Vertigo
Respiratory, thoracic and mediastinal disorders	Respiratory depression (see section 4.4 and section 4.6)
Cardiac disorders	Bradycardia Tachycardia Palpitations
Vascular disorders	Hypotension Flushing
Gastrointestinal disorders	Nausea Vomiting Constipation (see section 4.4) Dry mouth

Hepatobiliary disorders	Biliary colic
Skin and subcutaneous tissue disorders	Urticaria Pruritis Hyperhidrosis
Musculoskeletal and connective tissue disorders	Muscle rigidity
Renal and urinary disorders	Dysuria Ureteral spasm Oliguria
Reproductive system and breast disorders	Decreased libido Erectile dysfunction
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 drug 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: www.hpra.ie: e-mail: medsafety@hpra.ie

4.9 Overdose

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

Treatment
Adults: Administer 0.4-2 mg ofnaloxone intravenously. Repeat at 2-3 minute intervals as necessary to a maximum of 10 mg, or by 2 mg in 500 ml of normal saline or 5 % dextrose (4 micrograms/ml). Children: 5-10 micrograms per kilogram body weight intravenously. If this does not result in the desired degree of clinical improvement, a subsequent dose of 100 mcg/kg body weight may be administered.

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. Peak plasma concentrations of morphine are expected to occur within 15 minutes of oral ingestion. Therefore gastric lavage and activated charcoal are unlikely to be beneficial.

Caution: the duration of the effect of naloxone (2-3 hours) 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 6 hours after the last dose of naloxone.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Opioid analgesic.

ATC Code: N02AA01

Morphine binds to specific receptors which are located at various levels of the central nervous system and also in various peripheral organs. The pain sensation and the affective reaction to pain is relieved by interaction with the receptors in the central nervous system.

5.2 Pharmacokinetic properties

Absorption
Morphine is modestly absorbed from the gastrointestinal tract following oral administration. Following oral administration of radiolabelled morphine to humans, peak plasma levels were reached after approximately 15 minutes. Morphine undergoes significant first pass metabolism in the liver resulting in a systemic bioavailability of approximately 25%.

Distribution
Approximately one third of morphine in the plasma is protein bound after a therapeutic dose.

Biotransformation
Metabolism of morphine principally involves conjugation to morphine 3- and 6- glucuronides. Small amounts are also metabolised by N-demethylation and N-dealkylation. Morphine-6-glucuronide has pharmacological effects indistinguishable from those of morphine. The half-life of morphine is approximately 2 hours. The t1/2 of morphine-6-glucuronide is somewhat longer.

Elimination
A small amount of a dose of morphine is excreted through the bowel into the faeces. The remainder is excreted in the urine, mainly in the form of conjugates. Approximately 90 % of a single dose of morphine is excreted in the first 24 hours. Enterohepatic circulation of morphine and its metabolites can occur, and may result in small quantities of morphine to be present in the urine or faeces for several days after the last dose.

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

Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Sucrose
Glucose, liquid
Sodium hydroxide solution (for p.H. adjustment)
Hydrochloric acid solution (for p.H. adjustment)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

After opening: 3 months

6.4 Special precautions for storage

Store below 25^{o}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 either 100ml, 250ml, 300ml and 500ml conventional amber soda glass (Type III) bottles fitted with a 28mm white, polypropylene, push and turn caps with expanded polyethylene (EPE) liner.

In addition the product is supplied with a 5ml dispensing oral syringe and bottle adaptor.

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

PA1339/051/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

June 2020