1. **NAME OF THE MEDICINAL PRODUCT**

Morphine Sulfate 15mg/ml Solution for Injection

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Morphine Sulfate 15mg/ml

For the full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Solution for Injection

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic Indications**

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**

Morphine Sulfate may be given by the subcutaneous, intramuscular or intravenous route. The subcutaneous route is not suitable for oedematous patients. The dosage should be based on the severity of the pain and the response and tolerance of the individual patient. The epidural or intrathecal routes must not be used as the product contains a preservative.

**Adults:**

**Subcutaneous or intramuscular injection:**

10mg every four hours if necessary (the dose may vary from 5-20mg depending on the individual patient).

**Slow intravenous injection (2mg/minute):**

Quarter to half of corresponding intramuscular dose not more than four hourly.
**Elderly and debilitated patients:** The dose should be reduced because of the depressant effect on respiration. Caution is required.

**Children:** Use in children is not recommended.

**Hepatic impairment:**
A reduction in dosage should be considered in hepatic impairment.

**Renal impairment:**
The dosage should be reduced in moderate to severe renal impairment.

For concomitant illnesses/conditions where dose reduction may be appropriate see 4.4 Special Warnings and Precautions for Use.

**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**
Acute respiratory depression, known morphine sensitivity, biliary colic (see also biliary tract disorders 4.4 Special Warnings and Precautions), acute alcoholism. Conditions in which intracranial pressure is raised, comatose patients, head injuries, as there is an increased risk of respiratory depression that may lead to elevation of CSF pressure. The sedation and pupillary changes produced may interfere with accurate monitoring of the patient. Morphine is also contraindicated where there is a risk of paralytic ileus, or in acute diarrhoeal conditions associated with antibiotic-induced pseudomembranous colitis or diarrhoea caused by poisoning (until the toxic material has been eliminated).
Phaeochromocytoma (due to the risk of pressor response to histamine release).

**4.4 Special warnings and precautions for use**
Morphine should be given in reduced doses or with caution to patients with asthma or decreased respiratory reserve (including cor pulmonale, kyphoscoliosis, emphysema, severe obesity). Avoid use during an acute asthma attack (see 4.3 Contraindications). Opioid analgesics in general should be given with caution or in reduced doses to patients with hypothyroidism, adrenocortical insufficiency, prostatic hypertrophy, urethral stricture, hypotension, shock, inflammatory or obstructive bowel disorders, or convulsive 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.
Caution is advised when giving morphine to patients with impaired liver function due to its hepatic metabolism (see 4.2 Posology).

Severe and prolonged respiratory depression has occurred in patients with renal impairment who have been given morphine (see 4.2 Posology).

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.

Dependence can develop rapidly with regular abuse of opioids but is less of a problem with therapeutic use. 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. 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.

Dosage should be reduced in elderly and debilitated patients (see 4.2 Posology).

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

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.

4.5 Interaction with other medicinal products and other forms of interaction

**Alcohol:** enhanced sedative and hypotensive 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.

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

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 newborn 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.

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.

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 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 of 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’)

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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 also 4.9 Overdose). The commonest side-effects of morphine are nausea, vomiting, constipation, drowsiness and dizziness. Tolerance generally develops with long term use, but not to constipation. Other side effects include the following:

Anaphylaxis: Anaphylactic reactions following intravenous injection have been reported rarely.

Cardiovascular: facial flushing bradycardia, palpitations, tachycardia, orthostatic hypotension.

Central Nervous System: myoclonus, mental clouding, confusion (with large doses), hallucinations, headache, vertigo, mood changes including dysphoria and euphoria.

Unknown: allodynia, hyperalgesia (see section 4.4)

Gastrointestinal: dry mouth, biliary spasm.

Disorders of the eye: blurred or double vision or other changes in vision, miosis.

Immune system disorders:

Unknown: anaphylactoid reactions

Psychiatric disorders

Unknown: dependence

General disorders and administration site conditions

Unknown: drug withdrawal (abstinence syndrome)

Sexual dysfunction: long term use may lead to a reversible decrease in libido or potency.

Skin: pruritus, urticaria, rash, sweating. Contact dermatitis has been reported and pain and irritation may occur on injection.

Urinary: difficulty with micturition, ureteric spasm, urinary retention, antidiuretic effect. Tolerance develops to the effects of opioids on the bladder.

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.

The euphoric activity of morphine has led to its abuse.

**Reporting of suspected adverse reactions**

Reporting of suspected adverse reactions after authorization 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 Cars 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, pneumonia aspiration, confusion, severe dizziness, severe drowsiness, hypotension, bradycardia, circulatory failure pulmonary oedema, severe nervousness or restlessness, hallucinations, convulsions (especially in infants and children). Rhabdomyolysis, progressing to renal failure, has been reported in overdosage.

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.

### 5.1 Pharmacodynamic Properties

Morphine is obtained from opium, which acts mainly on the CNS 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 Particulars

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 dose of 10mg, peak serum concentrations of 70 to 80ng/ml are attained in 10 to 20 minutes.

After an intravenous dose 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 three hours.

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

Half-life Serum half-life in the period ten minutes to six hours following intravenous administration-two to three hours; serum half-life in the period six 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.

Metabolic reactions: Mainly glucuronic acid conjugation to form morphine-3 and 6-glucuronides. N-demethylation, O-methylation and N-oxide glucuronide formation occurs in the intestinal mucosa and liver; N-demethylation occurs to a greater extent after oral than
parental administration; the O-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.

**Excretion:**

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 a parental 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 acidic 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.

6.1 List of Excipients

Water for injections
Sodium metabisulfite
Sodium hydroxide
Hydrochloric acid

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.
Physiochemical 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 25°C. Keep container in the outer carton.

6.5 **Nature and contents of container**

5 × 1ml Type I glass ampoules
10 × 1ml Type I glass ampoules

6.6 **Special precautions for disposal**

None

7. **MARKETING AUTHORISATION HOLDER**

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

8. **MARKETING AUTHORISATION NUMBER**

PL 29831/0145

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

21st April 2007

10 **DATE OF REVISION OF THE TEXT**

14/12/2018