PACKAGE LEAFLET: INFORMATION FOR THE USER
Morphine Sulfate 10mg/ml, 15mg/ml and 30mg/ml Solution for Injection

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. WHAT MORPHINE INJECTION IS AND WHAT IT IS USED FOR

Morphine is one of a group of medicines called opioid analgesics, which are used to relieve moderate to severe pain. Morphine is used for the relief of severe pain. It is also used to treat breathlessness caused by fluid in the lungs and as a pre-medication before operations.

2. WHAT YOU NEED TO KNOW BEFORE YOU ARE GIVEN MORPHINE INJECTION

Morphine Injection should not be given if you:
- are allergic to morphine sulfate or any of the other ingredients of this medicine (listed in section 6)
- have been told you have a tumour of the adrenal gland near your kidney called phaeochromocytoma
- have severe problems with breathing
- have increased pressure on the brain, have just had a head injury or if you are unconscious
- are suffering from acute alcoholism
- are at risk from a blocked intestine (paralytic ileus)
- have severe stomach cramps caused by a condition known as biliary colic
- are suffering from severe diarrhoea

Warnings and precautions

Talk to your doctor before Morphine Injection is given to you if you:
- are using drugs or have used drugs in the past
- suffer from asthma (your doctor may decide to administer Morphine Injection if your asthma is controlled. However, you should not be given this medicine if you are having an acute asthma attack)
- suffer from bronchitis (an inflammation of the lining of the tubes in the lungs, resulting in coughing spells accompanied by thick phlegm and breathlessness) or emphysema (a lung condition which leaves you struggling for breath)
- suffer from cor-pulmonale (a type of heart failure)
- are severely obese
- have a severely deformed spine
- are suffering from mental illness brought on by an infection
- have liver problems
- have kidney problems
- have problems with your bile duct
- suffer from an enlarged prostate gland (in men) or have difficulty passing urine
- have an under-active thyroid or adrenal gland
- have low blood pressure
- are in a state of severe shock
- are very run down
- have bowel disease, such as Crohn's disease or ulcerative colitis
- suffer from blockages of the bowel
- suffer from convulsions (fits)
- are elderly
- are feeling weak and feeble

If any of the above applies to you, speak to your doctor or nurse before Morphine Injection is given to you.

Children
This medicine is not recommended for use in children.

Other medicines and Morphine Injection

Tell your doctor if you are taking, have recently taken or might take any other medicines. In particular, tell your doctor if you are taking any of the following:
- monoamine oxidase inhibitors (MAOIs) such as moclobemide or phenelzine used in the treatment of depression.
- tricyclic antidepressants, which are used in the treatment of depression
- tranquillising drugs or sleeping tablets such as diazepam, nitrazepam and temazepam.
- medicines used to treat mental illnesses, including schizophrenia (e.g. chlorpromazine, haloperidol).
- medicines used for diarrhoea (e.g. loperamide, kaolin).
- medicines which are used as premedication before operations and after heart attacks such as atropine.
- medicines used to treat nausea and vomiting, such as metoclopramide or domperidone
- mexiletine, used to control heart rhythm.
- some antihistamines, used to treat allergies, hayfever and asthma.
- certain antibiotics, used to treat infections (e.g. ciprofloxacin and linezolid).
- selegiline, used in the treatment of Parkinson's disease.
- pethidine, used to treat pain.

Morphine Injection with food, drink and alcohol

You should not drink alcohol whilst being given Morphine Injection, as it will increase its effects.

Pregnancy and breast-feeding

You should not be given morphine if you are pregnant or think you might be pregnant unless you have discussed this with your doctor first. If you are given morphine during pregnancy and become dependent on it, there is a risk that the new-born baby may also be dependent and suffer from withdrawal symptoms following delivery. If you are given morphine during labour there is a risk that you could be sick and have breathing difficulties, or the baby could have difficulty starting breathing. If you are breast-feeding, ask your doctor for advice before taking this medicine.

Driving and using machines
If the injection makes you feel drowsy, do not drive or operate machinery.
This medicine can affect your ability to drive.
Do not drive whilst taking this medicine until you know how this medicine affects you.
It may be an offence to drive if your ability to drive safely is affected.
There is further information for patients who are intending to drive in Great Britain - go to http://www.gov.uk/drug-driving-law

Morphine Injection contains sodium metabisulfite
Sodium metabisulfite may rarely cause severe hypersensitivity reactions and wheezing.

3. HOW MORPHINE INJECTION SHOULD BE GIVEN

The usual adult dose for relief of pain by subcutaneous injection (an injection underneath the skin) or intramuscular injection (an injection into a muscle) is 10mg every four hours, if necessary. However, this can vary between 5mg and 20mg depending on your size and response to the drug.

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INFORMATION FOR HEALTHCARE PROFESSIONALS

1 NAME OF THE MEDICINAL PRODUCT

Morphine Sulfate 10mg/ml Solution for Injection
Morphine Sulfate 15mg/ml Solution for Injection
Morphine Sulfate 30mg/ml 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.

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 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. Great caution should be exercised in patients with a known tendency or history of 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.

4.5 Interactions 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.

4.6 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 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.

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.

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') 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). Morphine Injection contains sodium metabisulfite, which may rarely cause severe hypersensitivity reactions and bronchospasm.

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.

For severe pain your doctor may give you a slow intravenous injection (an injection given slowly into a vein). The usual dose is quarter to half of the intramuscular dose.

- If you are elderly, severely run down including feeling weak and feeble, or have liver and kidney problems the dose will be lower. You may also be given a reduced dose if you suffer from any of the conditions listed in section 2 entitled "Talk to your doctor before Morphine Injection is given to you if you:"
- Your doctor will decide the dose that is best for you. If you do not understand what you are being given, or are in any doubt, ask your doctor or nurse.

If you miss a dose of Morphine Injection

If you think that an injection has been missed, speak to your doctor or nurse.

If treatment with Morphine Injection is stopped

You should always check with your doctor before the treatment is stopped. It is possible that you could become dependent on morphine and have withdrawal symptoms if it is stopped suddenly. This is more likely if you have a tendency for drug abuse or if you become dependent on Morphine Injection.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor or nurse immediately if you experience the following serious side effect:

- A severe allergic reaction, such as breathing difficulties, shock or low blood pressure. If you suffer such a reaction, you should not be given any more morphine. Your doctor will decide on the appropriate treatment for allergic reactions.

Difficulty in breathing and physical and psychological dependence are possible serious side effects. It is possible that you could become dependent on morphine.

Side effects that are common include:

- drowsiness
- feeling sick or being sick
- constipation
- dizziness.

Apart from constipation, these side effects tend to disappear with time.

Side effects that are less common include:

- sweating
- feeling faint on standing up
- small pupils (in the eye)
- blurred vision
- double vision or other changes in vision
- mental clouding or confusion
- mood changes, feeling extremely happy for no particular reason, or a feeling of emotional and mental unease (dysphoria)
- imagining things (hallucinations)
- headache
- vertigo
- facial flushing
- dry mouth
- difficulty or pain in passing urine
- passing less urine than usual
- biliary spasm (causing pain in the right side of your abdomen, particularly after eating a meal, which may spread towards your right shoulder)
- palpitations (being aware of your heart beat)
- slower or faster pulse
- skin rash
- wheals (lumpy, red rash) or itching
- red, itchy, scaly skin at the injection site
- pain and irritation at the injection site
- reduced sexual drive or impotence after long term use
- muscle twitching.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE MORPHINE INJECTION

Keep out of the sight and reach of children.

Store below 25°C. Keep the ampoule in its outer carton, in order to protect it from light.

Do not use this medicine if you notice signs of discolouration.

Do not use this medicine after the expiry date, which is stated on the carton. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Morphine Injection contains

The active substance is morphine sulfate. The injection is available in three strengths, 10mg/ml (10mg of active ingredient in 1ml of solution), 15mg/ml (15mg of active ingredient in 1ml of solution) and 30mg/ml (30mg of active ingredient in 1ml of solution).

Other ingredients are water for injections, sodium metabisulfite (E223), hydrochloric acid and sodium hydroxide.

What Morphine Injection looks like and contents of the pack

Morphine Injection is a colourless or almost colourless solution, practically free from particles.

Morphine Sulfate 10mg/ml Solution for Injection is available in cartons containing 5 × 1ml glass ampoules and 10 × 1ml glass ampoules.

Morphine Sulfate 15mg/ml Solution for Injection is available in cartons containing 5 × 1ml glass ampoules and 10 × 1ml glass ampoules.

Morphine Sulfate 30mg/ml Solution for Injection is available in cartons containing 5 × 1ml glass ampoules and 10 × 1ml glass ampoules. It is also available in cartons containing 5 x 2ml ampoules.

Not all strengths and pack sizes may be marketed.

Marketing Authorisation Holder: Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 9UF, UK

Manufacturer: CP Pharmaceuticals Ltd, Ash Road North, Wrexham, LL13 9UF, UK.

Other sources of information:

To listen to or request a copy of this leaflet in Braille, large print or audio please call, free of charge:
0800 198 5000 (UK Only)
Please be ready to give the following information:

Product Name	Reference Number
Morphine Sulfate 10mg/ml Solution for Injection	29831/0146
Morphine Sulfate 15mg/ml Solution for Injection	29831/0145
Morphine Sulfate 30mg/ml Solution for Injection	29831/0147

This is a service provided by the Royal National Institute of Blind People.

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

Gastrointestinal: dry mouth, biliary spasm.

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

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.

The euphoric activity of morphine has led to its abuse and physical and psychological dependence may occur (see also 4.4 Special warnings and precautions for use).

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, 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 PHARMACOLOGICAL PROPERTIES

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

There are no pre-clinical data of relevance to the prescriber, which are additional to those included in other sections.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections
Sodium metabisulfite (E223)
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, furosemide, heparin sodium, pethidine hydrochloride, promethazine hydrochloride and tetracyclines. Specialised references should be consulted for specific compatibility information.

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

10mg

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

15mg

5 × 1ml glass ampoules
10 × 1ml glass ampoules

30mg

5 × 1ml Type I glass ampoules
10 × 1ml Type I glass ampoules
5 × 2ml Type I glass ampoules

6.6 Special precautions for disposal

None

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