Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Morphine Sulfate 30mg/ml, Solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml of solution for injection contains 30mg Morphine Sulfate.
metabisulfite

Excipients with known effect:
Total sodium content is 2.23 mg per ml, including 1.1mg of sodium metabisulfite (E223).

For a 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 Sulfate injection is indicated in adults & children for the management of moderate to severe pain

4.2 Posology and method of administration

Posology

Adults
The usual dose by subcutaneous or intramuscular injection is 10 to 15mg repeated every four hours if required.

The dosage should be adjusted according to the severity of the pain and the response of the patient. In cases of terminal pain, higher doses may be required.

Slow intravenous injection:
For intravenous use, 4 to 10mg, diluted in 4 to 5ml of Water for Injections should be administered slowly over four to five minutes

The Elderly and debilitated patients:
Caution is advised. A reduction in dose is advisable because of the depressant effect on respiration.

Paediatric population:
Children from age one year: 0.1 to 0.2 mg/kg body weight by subcutaneous or intramuscular injection every four hours as required, not to exceed 15mg per dose.

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 Section 4.4

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
Morphine Sulfate Injection is for subcutaneous, intramuscular or intravenous administration.

Treatment goals and discontinuation

Before initiating treatment with <Invented name>, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with <Invented name>, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

Duration of treatment
Morphine Sulfate Injection should not be used longer than necessary.

4.3 Contraindications

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

- Use in patients with ulcerative colitis because of the risk of toxic megacolon.

- Use in patients with respiratory depression, cyanosis, excessive bronchial exudation, bronchoconstriction (reversible or irreversible), or chronic pulmonary disease.

- Use in patients immediately after operative interventions in the biliary tract biliary colic, head injury, paralytic ileus, acute abdomen of unknown origin, delayed gastric emptying and phaeochromocytoma.

- Severe and prolonged respiratory depression may occur in patients with renal impairment given morphine; this is attributed to the accumulation of the active metabolite morphine-6-glucuronide. Therefore, Morphine Injection should not be administered to patients with moderate or severe renal impairment (glomerular filtration rate <20 ml/min).

- As with other opioid analgesic containing preparations Morphine Injection should not be administered to patients with severe hepatic impairment as it may precipitate coma.

- Use in patients with acute alcoholism, increased intracranial pressure, or in coma, or with convulsive disorders.

- Use in patients who are receiving, or have within two weeks received, monoamine oxidase inhibitors.

4.4 Special warnings and precautions for use

Repeated use can cause tolerance and dependence requiring an increase in dosage to achieve the required effect.

Use with caution in patients with impaired respiratory function, severe bronchial asthma, convulsive disorders, acute alcoholism, delirium tremens, hypotension with hypovolemia, severe cor pulmonale, opioid dependent patients, patients with a history of substance abuse, inflammatory bowel disorders.

Morphine should not be used where there is a possibility of paralytic ileus occurring.
Should paralytic ileus be suspected or occur during use, Morphine sulfate should be discontinued immediately.

Extreme caution in use should be exercised and a reduction in dose may be advisable in the elderly, neonates, premature infants, the debilitated, or in patients with hypothyroidism, adrenocortical insufficiency, shock, liver dysfunction, prostatic hypertrophy, hepatic or renal insufficiency.

Patients about to undergo additional pain-relieving procedures (e.g. Surgery, plexus blockade) should not receive Morphine for 4 hours prior to the intervention. If further treatment with Morphine is indicated, then the dosage should be adjusted to the new post-operative requirement. Morphine should be used with caution pre-operatively and within the first 24 hours post-operatively. Morphine should also be used with caution following abdominal surgery.

Psychological and physical dependence may result from repeated administration of morphine and may occur after treatment for one or two weeks with therapeutic doses. The product should be used with particular care in patients with a history of alcohol and drug abuse.
Morphine can induce severe respiratory depression, particularly in neonates, for which reason it should not be used in obstetric delivery (see section 4.6).

Patient may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain control. Prolonged use of this product may lead to physical dependence and a withdrawal syndrome may occur upon abrupt cessation of therapy. When a patient no longer requires therapy with morphine, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

Morphine has an abuse profile similar to other strong agonist opioids. Morphine may be sought and abused by people with latent or manifest addiction disorders. There is potential for development of psychological dependence (addiction) to opioid analgesics, including morphine. The product should be used with particular care in patients with a history of alcohol and drug abuse.

Morphine may lower the seizure threshold in patients with a history of epilepsy.
Sodium Metabisulfite may rarely cause severe hypersensitivity reactions and bronchospasm. Hepatobiliary disorders
Morphine may cause dysfunction and spasm of the sphincter of Oddi, thus raising intrabiliary pressure and increasing the risk of biliary tract symptoms and pancreatitis.

<u>Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:</u>
Concomitant use of Morphine Sulfate 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 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).

<u>Acute chest syndrome (ACS) inpatients with sicklecell disease (SCD)</u>

ACS symptoms is warranted. 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.

4.5 Interaction with other medicinal products and other forms of interaction

Morphine should be used with caution in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anaesthetics, phenothiazines, other tranquilisers, muscle relaxants, antihypertensives, gabapentin or pregabalin and alcohol. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with the usual doses of morphine.

It is recommended that opiate premedicants, (e.g. morphine) are not used concomitantly with ciprofloxacin, as the serum levels of ciprofloxacin are reduced.

Mixed agonist/antagonist opioid analgesics (e.g. buprenorphine, nalbuphine, pentazocine) should not be administered to a patient who has received a course of therapy with a pure opioid agonist analgesic.

Cimetidine inhibits the metabolism of morphine.

Monoamine oxidase inhibitors are known to interact with narcotic analgesics producing CNS excitation or depression with hyper- or hypotensive crisis.

Morphine should not be co-administered with monoamine oxidase inhibitors or within two weeks of such therapy.

Plasma concentrations of morphine may be reduced by rifampicin. Although there are no pharmacokinetic data available for concomitant use of ritonavir with morphine, ritonavir induces the hepatic enzymes responsible for the glucuronidation of morphine and may possibly decrease plasma concentrations of morphine.

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

There is inadequate evidence of safety in human pregnancy and administration of morphine during pregnancy should only be considered if the expected benefit to the mother clearly outweighs any possible risk to the foetus. Withdrawal symptoms may be observed in the newborn of mothers undergoing chronic treatment.

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

All the narcotic analgesics are able to traverse the placenta and are excreted in the milk. This should be borne in mind. when considering their use in patients during pregnancy and lactation. Morphine may cause respiratory depression in neonates particularly if premature.
Morphine is not recommended for use during lactation in nursing mothers.

Fertility

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

4.7 Effects on ability to drive and use machines

May cause drowsiness, and patients receiving it should not drive or operate machinery unless its effects on physical and mental activity have gone.

4.8 Undesirable effects

Like all medicines, morphine can cause side effects, although not everybody gets them.
Side effects grouped by frequency of occurrence
Common (incidence of _1/100 to <1/10) Uncommon (incidence of _1/1000 to <1/100) and Not known: frequency cannot be estimated from the available data adverse drug reactions are listed in the table below:

Body System	Common	Uncommon	Not Known
Immune system disorders		Allergic reaction Anaphylactic reaction Anaphylactoid reaction	
Psychiatric disorders	Confusion Insomnia Thinking disturbances	Agitation Drug dependence Dysphoria Euphoria Hallucinations Mood altered	
Nervous system disorders	Dizziness Headache Involuntary muscle contractions Myoclonus Somnolence	Convulsions Hypertonia Paraesthesia Syncope Vertigo	Allodynia** Hyperaesthesia*** Hyperalgesia (see section 4.4) Hyperhidrosis
Eye disorders		Miosis Visual disturbance	
Cardiac disorders		Bradycardia Palpitations Tachycardia	
Vascular disorders		Facial flushing Hypertension Hypotension	
Respiratory, thoracic and mediastinal disorders	Bronchospasm Cough decreased	Pulmonary oedema Respiratory depression	
Gastrointestinal disorders	Abdominal pain Anorexia Constipation	Ileus Toxic megacolon Taste perversion	Narcotic bowel syndrome*

	Dry mouth Dyspepsia Nausea Vomiting		
Hepatobiliary disorders	Exacerbation of pancreatitis	Biliary pain Increased hepatic enzymes	
Skin and subcutaneous tissue disorders	Hyperhidrosis Rash	Urticaria	
Renal and urinary disorders		Ureteric spasm Urinary retention	
Reproductive system and breast disorders		Amenorrhoea Decreased libido Erectile dysfunction	
General disorders and administration site conditions	Asthenia Pruritus	Drug tolerance Drug withdrawal syndrome Malaise Peripheral oedema	Hypothermia

*Long term narcotics use may cause Narcotic bowel Syndrome (NBS). By the time, narcotics can slow the bowel and lead to symptoms of constipation, bloating, or nausea, and abdominal distension
**Allodynia (Pain due to stimulus which does not normally provoke pain)
***Hyperaesthesia (is a condition that involves an abnormal increase in sensitivity to stimuli of the sense i.e increased response to a painful stimulus)
The most serious side effect of morphine is respiratory depression. Maximal respiratory depression occurs within 5 to 10 minutes after intravenous administration of morphine, within 30 minutes following intramuscular injection, and within 90 minutes after subcutaneous administration.

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.

Symptoms of drug withdrawal symptoms are dysphoric mood, anxiety

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: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms:

Signs of morphine toxicity and overdosage arepin point pupils, skeletal muscle flaccidity, bradycardia, respiratory depression and hypotension. Aspiration pneumonia may also occur. Overdosage can result in death. Rhabdomyolysis progressing to renal failure has been reported in opioid overdosage. Circulatory failure and coma may occur in severe cases. Death may occur from respiratory failure.

Treatment:

Adequate respiratory exchange should be established through provision of a patent airway and institution of assisted or controlled ventilation if required.

The pure opioid antagonists are specific antidotes against the effects of opioid overdose. Other supportive measures should be employed as needed.
In the case of massive overdosage, administer naloxone 0.8 mg intravenously. Repeat at 2-3-minute intervals as necessary, or by an infusion of 2 mg in 500 ml of normal saline or 5% dextrose (0.004 mg/ml).

The infusion should be run at a rate related to the previous bolus doses administered and should be in accordance with the patient's response. However, because the duration of action of naloxone is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established.

For less severe over dosage, administer naloxone 0.2 mg intravenously followed by increments of 0.1 mg every 2 minutes if required.

Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine over dosage. Naloxone should be administered cautiously to persons who are known, or suspected, to be physically dependent on morphine. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids,
ATC Code: N02AA01

Morphine is a narcotic analgesic. The drug exerts its major effects on the central nervous system and organs containing smooth muscle, apparently by acting as an agonist on opioid receptors. Pharmacologic effects include analgesia, drowsiness and dose-related respiratory depression.

5.2 Pharmacokinetic properties

Absorption
Following subcutaneous or intramuscular injection, morphine is readily absorbed into the blood. About one-third of the drug is protein bound.

Distribution
Morphine is distributed throughout the body but mainly in the kidneys, liver, lungs and spleen. Although the CNS is the primary site of action of morphine, only small quantities cross the blood-brain barrier in adults. Morphine diffuses across the placenta and traces also appear in milk and sweat.

Biotransformation
In the liver, morphine is conjugated with glucuronic acid to form both active and inactive metabolites. In normal healthy adults, the half-life of morphine is about two hours. Little morphine is excreted unchanged. About 90% of total morphine is excreted in 24 hours, mainly by glomerular filtration and the remainder via bile into faeces.

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
Water for Injection
Sodium Hydroxide (for pH adjustment)
Sulphuric Acid (for pH adjustment)

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.

Physicochemical incompatibility (formation of precipitates) has been demonstrated between solutions of morphine sulfate and 5- fluorouracil.

6.3 Shelf life

3 years.

The product should be used immediately after opening.

6.4 Special precautions for storage

Do not store above 25°C. Keep ampoules in the original package in order to protect from light.

6.5 Nature and contents of container

Clear, colourless type I Ph. Eur. 1ml 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

For single use only. Discard any unused contents.

7 MARKETING AUTHORISATION HOLDER

Ethypharm
194 Bureaux de la Colline - Bâtiment D
92213 Saint-Cloud Cedex
France

8 MARKETING AUTHORISATION NUMBER

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