Public Assessment Report

Decentralised Procedure

MORPHINE SULPHATE 10MG, 15MG, 20MG, AND 30MG/ML SOLUTION FOR INJECTION

UK/H/2512/001-4/DC
UK Licence No: PL 17507/0010-3

AUDEN MCKENZIE LIMITED
LAY SUMMARY

On 17th February 2011, the UK granted Auden McKenzie Limited Marketing Authorisations (licences) for the medicinal products Morphine Sulphate 10mg/ml, 15mg/ml, 20mg/ml and 30mg/ml Solution for Injection.

Morphine Sulphate 10mg/ml, 15mg/ml, 20mg/ml and 30mg/ml Solution for Injection contain morphine sulphate which belongs to a group of medicines called narcotic analgesics.

Morphine Sulphate 10mg/ml, 15mg/ml, 20mg/ml and 30mg/ml Solution for Injection is used:
- for the treatment of severe pain.
- to help with breathing which becomes difficult because fluid has collected in the lungs (pulmonary oedema) due to heart failure.
- prior to having an operation.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Morphine Sulphate 10mg/ml, 15mg/ml, 20mg/ml and 30mg/ml Solution for Injection outweigh the risks; hence these Marketing Authorisations have been granted.
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<td>Not applicable</td>
</tr>
</tbody>
</table>
## Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Morphine Sulphate 10mg/ml, 15mg/ml, 20mg/ml and 30mg/ml Solution for Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>Morphine sulphate</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>10mg/ml, 15mg/ml, 20mg/ml and 30mg/ml Solution for Injection</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Auden McKenzie Limited</td>
</tr>
<tr>
<td><strong>Reference Member State (RMS)</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>Concerned Member States (CMS)</strong></td>
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</tr>
<tr>
<td><strong>Procedure Number</strong></td>
<td>UK/H/2512/001-4/DC</td>
</tr>
<tr>
<td><strong>End of Procedure</strong></td>
<td>Day 210 – 1st February 2011</td>
</tr>
</tbody>
</table>
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Morphine Sulphate 10 mg/ml Solution for Injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml of Morphine Sulphate solution for injection contains 10 mg morphine sulphate.
Also contains 1.1 mg of sodium metabisulphite (E223) in each ml of Morphine Sulphate solution for injection.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Solution for injection.
A clear colourless solution.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Morphine is used for 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
The injection may be given by the intravenous, intramuscular or subcutaneous route.

Adults: The dosage should be based on the severity of the pain and the response and tolerance of the patient. The usual adult subcutaneous or intramuscular dose is 10mg every 4 hours if necessary, but may range from 5mg to 20mg.

The usual adult intravenous dose is 2.5mg to 15mg not more than 4 hourly, where necessary, but dosage and dosing interval must be titrated against the patient's response and adjustments made until analgesia is achieved.

Elderly: Because of the depressant effect on respiration, caution is necessary when giving morphine to the elderly and reduced doses may be required.

Children: Use in children is not recommended.

4.3 Contraindications
Respiratory depression, obstructive airways disease, concurrent treatment with monoamine oxidase inhibitors or within two weeks of their discontinuation of treatment with them.

Known morphine sensitivity, or sensitivity to any of the ingredients. Cerebral oedema, head injuries, coma, convulsive disorders and raised intracranial pressure, biliary colic and acute alcoholism.

Administration of morphine is contra-indicated in patients with phaeochromocytoma, those at risk of paralytic ileus and in patients with acute diarrhoea caused by poisoning or invasive pathogens.

4.4 Special warnings and precautions for use
Morphine is a potent medicine but with considerable potential for harmful effect, including addiction. It should be used only if other drugs with fewer hazards are inadequate, and with the recognition that it may possibly mask significant manifestations of disease which should be identified for proper diagnosis and treatment. It should be used with special caution in patients with a history of drug abuse. Dependence may occur after 1-2 weeks of treatment.

Morphine should be given with caution where there is a reduced respiratory reserve as in emphysema and asthma, chronic cor pulmonale, kyphoscoliosis and excessive obesity. Opiates should also be used cautiously in patients with cardiac arrhythmias, myasthenia gravis or inflammatory or obstructive bowel disorders.

Morphine should be administered with caution or in reduced doses to patients with hypotension, hypothyroidism, adrenocortical insufficiency, impaired kidney or liver function, prostatic hypertrophy,
urethral stricture or shock.

Morphine should be given with great care to infants, especially neonates. Dosage should be reduced in elderly and debilitated patients.

Disappearance of opioid analgesic effects, particularly when associated with an unexplained increase in pain, may indicate the development of tolerance or opioid-induced hyperalgesia. An unexplained increase in abdominal pain associated with disturbed intestinal motility, symptoms of constipation, bloating, abdominal distension and increased gastroesophageal reflux during treatment with morphine sulphate, may indicate the development of opioid-induced bowel dysfunction or narcotic bowel syndrome. In such situations consider the use of alternative analgesics and a morphine detoxification.

Morphine Sulphate Injection contains sodium metabisulphite (E223). This may rarely cause severe hypersensitivity reactions and bronchospasm.

Morphine Sulphate Injection contains 0.24 mg of sodium per ml. This should be taken into consideration for patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction
Concurrent administration of other CNS depressants, including hypnotics and anxiolytics, may potentiate the sedative effects. Morphine should not be administered to patients receiving monoamine oxidase inhibitors (see section 4.3).

Anticholinergic agents such as atropine antagonise morphine-induced respiratory depression and can partially reverse biliary spasm but are additive to the gastro-intestinal and urinary tract effects. Consequently, severe constipation and urinary retention may occur during intensive anticholinergic-analgesic therapy.

Morphine sulphate should not be used for premedication when ciprofloxacin is given for surgical prophylaxis as serum levels of ciprofloxacin are reduced and adequate cover may not be obtained during surgery.

Taking alcohol with morphine sulphate can cause enhanced sedative and hypertensive effects.

4.6 Pregnancy and lactation
Pregnancy: Since morphine rapidly crosses the placental barrier, it is not advised to administer morphine during pregnancy and labour. It may reduce uterine contractions, cause respiratory depression in the foetus and new born infant, and may have significant effects on foetal heart rate.

Lactation: The amount of morphine secreted in breast milk after a single-dose administration seems to be compatible with breast feeding and insufficient to cause major problems or dependence. However long-term treatment with morphine in high doses may cause significant plasma concentration. That is why caution is advised on the use of morphine in breast-feeding patient and the benefit must outweigh the risk to the infant. If breast feeding is continued, the infant should be observed for possible adverse effects.

4.7 Effects on ability to drive and use machines
Morphine may cause drowsiness. If this occurs the patient should not be allowed to drive or operate machinery.

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

Adverse effects can be listed in terms of their frequency of occurrence:
- Very common (≥1/10)
- Common (≥1/100 to <1/10)
- Uncommon (≥1/1,000 to <1/100)
- Not known (cannot be estimated from the available data)

Morphine may cause the following adverse events:
| Nervous system disorders | Very Common: Drowsiness  
Common: Convulsion, headache, increased intracranial pressure, myoclonus, opioid-induced hyperalgesia (or hyperaesthesia), vertigo  
Not Known: Allodynia, coma |
|--------------------------------|--------------------------------------------------|
| Psychiatric disorders | Very Common: Confusional state, hallucinations, physical and psychological dependence  
Common: Decreased libido, mood swings, restlessness |
| Eye disorders | Common: Blurred vision, miosis, nystagmus |
| Respiratory, thoracic and mediastinal disorders | Very Common: Respiratory depression  
Common: Bronchospasm, pulmonary oedema, which can lead to death  
Not Known: Respiratory failure, which also can lead to death |
| Cardiac disorders | Common: Bradycardia, circulatory failure, tachycardia  
Uncommon: Palpitations |
| Vascular disorders | Common: Hypotension, orthostatic hypotension |
| Gastrointestinal disorders | Very Common: Constipation, nausea, vomiting  
Common: Dry mouth, paralytic ileus,  
Not Known: Intestinal functional disorder, narcotic bowel syndrome |
| Hepatobiliary disorders | Common: Biliary spasm  
Uncommon: Hepatic enzyme increase  
Not Known: Spasm of the sphincter of Oddi, |
| Reproductive system and breast disorders | Common: Erectile dysfunction |
| Renal and urinary disorders | Common: Urinary retention  
Uncommon: Urethral spasm  
Not Known: Renal failure |
| Immune system disorders | Uncommon: Anaphylactic reaction, hypersensitivity |
| Musculoskeletal and connective tissue disorders | Not Known: Muscle rigidity, rhabdomyolysis |
| Skin and subcutaneous tissue disorders | Very Common: Pruritus  
Common: Angioedema, contact dermatitis, rash, urticaria |
General disorders and administration site conditions

| Very Common: Drug tolerance, hyperhidrosis |
| Common: Fatigue, facial flushing, hypothermia, injection site pain, injection site irritation, withdrawal syndrome (babies born to opioid-dependent mothers are also at risk to present withdrawal syndrome). |

4.9 Overdose

Symptoms: respiratory depression, pin-point pupils and coma. In addition, shock, reduced body temperature and hypotension may occur. In mild overdose, symptoms include nausea and vomiting, tremor, miosis, dysphoria, hypothermia, hypotension, confusion and sedation. In cases of severe poisoning, hypotension with circulatory failure, rhabdomyolysis progressing to renal failure, respiratory collapse and death may occur.

Treatment: the patient must be given respiratory support and the specific antagonist, naloxone, should be administered at a dose of 0.4-2.0 mg intravenously. This dose should be repeated at 2-3 minute intervals if improvement is not achieved, up to a total of 10 mg. Fluid and electrolyte levels should be maintained.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Natural opium alkaloids ATC Code: N02 AA01

Morphine is a narcotic analgesic obtained from opium, which acts mainly on the central nervous system and smooth muscle.

5.2 Pharmacokinetic properties

Absorption: Variably absorbed after oral administration; rapidly absorbed after subcutaneous or intramuscular administration.

Blood concentration: After an oral dose of 10mg as the sulphate, 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 3 hours; subcutaneous doses give similar concentrations to intramuscular doses at 15 minutes but remain slightly higher during the following 3 hours; serum concentrations measured soon after administration correlate closely with the ages of the subjects studied and are increased in the aged.

Half life: Serum half life in the period 10 minutes to 6 hours following intravenous administration, 2 to 3 hours; serum half life in the period 6 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, with sulphate conjugation. N-demethylation, 0-methylation and N-oxide glucuronide formation occurs in the intestinal mucosa and liver; N-demethylation occurs to a greater extent after oral than parenteral administration; the 0-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 parenteral 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 acid 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
Sodium metabisulphite (E223)
Water for injections
Sodium hydroxide (for pH adjustment)
Sulphuric acid (for pH adjustment)

6.2 Incompatibilities
Morphine salts may be precipitated in alkaline solution.
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life
20 months

6.4 Special precautions for storage
Keep the ampoule in its outer carton to protect from light. Do not refrigerate or freeze.

6.5 Nature and contents of container
Type I Ph Eur clear glass ampoules containing 1 ml.
5 or 10 ampoules per carton.

6.6 Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Auden Mckenzie (Pharma Division) Ltd
McKenzie House
Bury Street
Ruislip
Middlesex
HA4 7TL
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 17507/0010

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
17/02/2011

10 DATE OF REVISION OF THE TEXT
17/02/2011
1 NAME OF THE MEDICINAL PRODUCT
Morphine Sulphate 15 mg/ml Solution for Injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml of Morphine Sulphate solution for injection contains 15 mg morphine sulphate.
Also contains 1.1 mg of sodium metabisulphite (E223) in each ml of Morphine Sulphate solution for injection.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Solution for injection.
A clear colourless solution.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Morphine is used for the symptomatic relief of severe pain; relief of dyspnoea of left ventricular failure and pulmonary oedema; pre-operative use.

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Elderly: Because of the depressant effect on respiration, caution is necessary when giving morphine to the elderly and reduced doses may be required.

Children: Use in children is not recommended.

4.3 Contraindications
Respiratory depression, obstructive airways disease, concurrent treatment with monoamine oxidase inhibitors or within two weeks of their discontinuation of treatment with them.

Known morphine sensitivity, or sensitivity to any of the ingredients. Cerebral oedema, head injuries, coma, convulsive disorders and raised intracranial pressure, biliary colic and acute alcoholism.

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Morphine should be given with caution where there is a reduced respiratory reserve as in emphysema and asthma, chronic cor pulmonale, kyphoscoliosis and excessive obesity. Opiates should also be used cautiously in patients with cardiac arrhythmias, myasthenia gravis or inflammatory or obstructive bowel disorders.

Morphine should be administered with caution or in reduced doses to patients with hypotension, hypothyroidism, adrenocortical insufficiency, impaired kidney or liver function, prostatic hypertrophy, urethral stricture or shock.

Morphine should be given with great care to infants, especially neonates. Dosage should be reduced in elderly and debilitated patients.
Disappearance of opioid analgesic effects, particularly when associated with an unexplained increase in pain, may indicate the development of tolerance or opioid-induced hyperalgesia. An unexplained increase in abdominal pain associated with disturbed intestinal motility, symptoms of constipation, bloating, abdominal distension and increased gastroesophageal reflux during treatment with morphine sulphate, may indicate the development of opioid-induced bowel dysfunction or narcotic bowel syndrome. In such situations consider the use of alternative analgesics and a morphine detoxification.

Morphine Sulphate Injection contains sodium metabisulphite (E223). This may rarely cause severe hypersensitivity reactions and bronchospasm.

Morphine Sulphate Injection contains 0.24 mg of sodium per ml. This should be taken into consideration for patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction
Concurrent administration of other CNS depressants, including hypnotics and anxiolytics, may potentiate the sedative effects.
Morphine should not be administered to patients receiving monoamine oxidase inhibitors (see section 4.3).

Anticholinergic agents such as atropine antagonise morphine-induced respiratory depression and can partially reverse biliary spasm but are additive to the gastro-intestinal and urinary tract effects. Consequently, severe constipation and urinary retention may occur during intensive anticholinergic-analgesic therapy.

Morphine sulphate should not be used for premedication when ciprofloxacin is given for surgical prophylaxis as serum levels of ciprofloxacin are reduced and adequate cover may not be obtained during surgery.

Taking alcohol with morphine sulphate can cause enhanced sedative and hypertensive effects.

4.6 Pregnancy and lactation
Pregnancy: Since morphine rapidly crosses the placental barrier, it is not advised to administer morphine during pregnancy and labour. It may reduce uterine contractions, cause respiratory depression in the foetus and new born infant, and may have significant effects on foetal heart rate.

Lactation: The amount of morphine secreted in breast milk after a single-dose administration seems to be compatible with breast feeding and insufficient to cause major problems or dependence. However long-term treatment with morphine in high doses may cause significant plasma concentration. That is why caution is advised on the use of morphine in breast-feeding patient and the benefit must outweigh the risk to the infant. If breast feeding is continued, the infant should be observed for possible adverse effects.

4.7 Effects on ability to drive and use machines
Morphine may cause drowsiness. If this occurs the patient should not be allowed to drive or operate machinery.

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

Adverse effects can be listed in terms of their frequency of occurrence:
- Very common (≥1/10)
- Common (≥1/100 to <1/10)
- Uncommon (≥1/1,000 to <1/100)
- Not known (cannot be estimated from the available data)

Morphine may cause the following adverse events:
<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th>Very Common: Drowsiness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Common: Convulsion, headache, increased intracranial pressure, myoclonus, opioid-induced hyperalgesia (or hyperaesthesia), vertigo</td>
</tr>
<tr>
<td></td>
<td>Not Known: Allodynia, coma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
<th>Very Common: Confusional state, hallucinations, physical and psychological dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Common: Decreased libido, mood swings, restlessness</td>
</tr>
</tbody>
</table>

| Eye disorders | Common: Blurred vision, miosis, nystagmus |

<table>
<thead>
<tr>
<th>Respiratory, thoracic and mediastinal disorders</th>
<th>Very Common: Respiratory depression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Common: Bronchospasm, pulmonary oedema, which can lead to death</td>
</tr>
<tr>
<td></td>
<td>Not Known: Respiratory failure, which also can lead to death</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiac disorders</th>
<th>Common: Bradycardia, circulatory failure, tachycardia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Uncommon: Palpitations</td>
</tr>
</tbody>
</table>

| Vascular disorders | Common: Hypotension, orthostatic hypotension |

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th>Very Common: Constipation, nausea, vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Common: Dry mouth, paralytic ileus,</td>
</tr>
<tr>
<td></td>
<td>Not Known: Intestinal functional disorder, narcotic bowel syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepatobiliary disorders</th>
<th>Common: Biliary spasm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Uncommon: Hepatic enzyme increase</td>
</tr>
<tr>
<td></td>
<td>Not Known: Spasm of the sphincter of Oddi,</td>
</tr>
</tbody>
</table>

| Reproductive system and breast disorders | Common: Erectile dysfunction |

<table>
<thead>
<tr>
<th>Renal and urinary disorders</th>
<th>Common: Urinary retention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Uncommon: Urethral spasm</td>
</tr>
<tr>
<td></td>
<td>Not Known: Renal failure</td>
</tr>
</tbody>
</table>

| Immune system disorders    | Uncommon: Anaphylactic reaction, hypersensitivity |

| Musculoskeletal and connective tissue disorders | Not Known: Muscle rigidity, rhabdomyolysis |

<table>
<thead>
<tr>
<th>Skin and subcutaneous tissue disorders</th>
<th>Very Common: Pruritis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Common: Angioedema, contact dermatitis, rash, urticaria</td>
</tr>
</tbody>
</table>
4.9 **Overdose**

Symptoms: respiratory depression, pin-point pupils and coma. In addition, shock, reduced body temperature and hypotension may occur. In mild overdose, symptoms include nausea and vomiting, tremor, miosis, dysphoria, hypothermia, hypotension, confusion and sedation. In cases of severe poisoning, hypotension with circulatory failure, rhabdomyolysis progressing to renal failure, respiratory collapse and death may occur.

Treatment: the patient must be given respiratory support and the specific antagonist, naloxone, should be administered at a dose of 0.4-2.0 mg intravenously. This dose should be repeated at 2-3 minute intervals if improvement is not achieved, up to a total of 10 mg. Fluid and electrolyte levels should be maintained.

5 **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

Pharmacotherapeutic Group: Natural opium alkaloids ATC Code: N02 AA01

Morphine is a narcotic analgesic obtained from opium, which acts mainly on the central nervous system and smooth muscle.

5.2 **Pharmacokinetic properties**

Absorption: Variably absorbed after oral administration; rapidly absorbed after subcutaneous or intramuscular administration.

Blood concentration: After an oral dose of 10mg as the sulphate, 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 3 hours; subcutaneous doses give similar concentrations to intramuscular doses at 15 minutes but remain slightly higher during the following 3 hours; serum concentrations measured soon after administration correlate closely with the ages of the subjects studied and are increased in the aged.

Half life: Serum half life in the period 10 minutes to 6 hours following intravenous administration, 2 to 3 hours; serum half life in the period 6 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, with sulphate conjugation. 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 parenteral 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 parenteral 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 acid 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.

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**General disorders and administration site conditions**

| Very Common: Drug tolerance, hyperhidrosis |
| Common: Fatigue, facial flushing, hypothermia, injection site pain, injection site irritation, withdrawal syndrome (babies born to opioid-dependent mothers are also at risk to present withdrawal syndrome). |
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
Sodium metabisulphite (E223)
Water for injections
Sodium hydroxide (for pH adjustment)
Sulphuric acid (for pH adjustment)

6.2 Incompatibilities
Morphine salts may be precipitated in alkaline solution.
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life
20 months

6.4 Special precautions for storage
Keep the ampoule in its outer carton to protect from light. Do not refrigerate or freeze.

6.5 Nature and contents of container
Type I Ph Eur clear glass ampoules containing 1 ml.
5 or 10 ampoules per carton.

6.6 Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Auden Mckenzie (Pharma Division) Ltd
McKenzie House
Bury Street
Ruislip
Middlesex
HA4 7TL
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 17507/0011

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
17/02/2011

10 DATE OF REVISION OF THE TEXT
17/02/2011
1 NAME OF THE MEDICINAL PRODUCT
Morphine Sulphate 20 mg/ml Solution for Injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml of Morphine Sulphate solution for injection contains 20 mg morphine sulphate. Also contains 1.1 mg of sodium metabisulphite (E223) in each ml of Morphine Sulphate solution for injection. For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Solution for injection. A clear colourless solution.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Morphine is used for 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
The injection may be given by the intravenous, intramuscular or subcutaneous route.

Adults: The dosage should be based on the severity of the pain and the response and tolerance of the patient. The usual adult subcutaneous or intramuscular dose is 10mg every 4 hours if necessary, but may range from 5mg to 20mg.

The usual adult intravenous dose is 2.5mg to 15mg not more than 4 hourly, where necessary, but dosage and dosing interval must be titrated against the patient's response and adjustments made until analgesia is achieved.

Elderly: Because of the depressant effect on respiration, caution is necessary when giving morphine to the elderly and reduced doses may be required.

Children: Use in children is not recommended.

4.3 Contraindications
Respiratory depression, obstructive airways disease, concurrent treatment with monoamine oxidase inhibitors or within two weeks of their discontinuation of treatment with them.

Known morphine sensitivity, or sensitivity to any of the ingredients. Cerebral oedema, head injuries, coma, convulsive disorders and raised intracranial pressure, biliary colic and acute alcoholism.

Administration of morphine is contra-indicated in patients with phaeochromocytoma, those at risk of paralytic ileus and in patients with acute diarrhoea caused by poisoning or invasive pathogens.

4.4 Special warnings and precautions for use
Morphine is a potent medicine but with considerable potential for harmful effect, including addiction. It should be used only if other drugs with fewer hazards are inadequate, and with the recognition that it may possibly mask significant manifestations of disease which should be identified for proper diagnosis and treatment. It should be used with special caution in patients with a history of drug abuse. Dependence may occur after 1-2 weeks of treatment.

Morphine should be given with caution where there is a reduced respiratory reserve as in emphysema and asthma, chronic cor pulmonale, kyphoscoliosis and excessive obesity. Opiates should also be used cautiously in patients with cardiac arrhythmias, myasthenia gravis or inflammatory or obstructive bowel disorders.

Morphine should be administered with caution or in reduced doses to patients with hypotension, hypothyroidism, adrenocortical insufficiency, impaired kidney or liver function, prostatic hypertrophy, urethral stricture or shock.

Morphine should be given with great care to infants, especially neonates. Dosage should be reduced in elderly and debilitated patients.
Disappearance of opioid analgesic effects, particularly when associated with an unexplained increase in pain, may indicate the development of tolerance or opioid-induced hyperalgesia. An unexplained increase in abdominal pain associated with disturbed intestinal motility, symptoms of constipation, bloating, abdominal distension and increased gastroesophageal reflux during treatment with morphine sulphate, may indicate the development of opioid-induced bowel dysfunction or narcotic bowel syndrome. In such situations consider the use of alternative analgesics and a morphine detoxification.

Morphine Sulphate Injection contains sodium metabisulphite (E223). This may rarely cause severe hypersensitivity reactions and bronchospasm.

Morphine Sulphate Injection contains 0.24 mg of sodium per ml. This should be taken into consideration for patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction
Concurrent administration of other CNS depressants, including hypnotics and anxiolytics, may potentiate the sedative effects.
Morphine should not be administered to patients receiving monoamine oxidase inhibitors (see section 4.3).

Anticholinergic agents such as atropine antagonise morphine-induced respiratory depression and can partially reverse biliary spasm but are additive to the gastro-intestinal and urinary tract effects. Consequently, severe constipation and urinary retention may occur during intensive anticholinergic-analgesic therapy.

Morphine sulphate should not be used for premedication when ciprofloxacin is given for surgical prophylaxis as serum levels of ciprofloxacin are reduced and adequate cover may not be obtained during surgery.

Taking alcohol with morphine sulphate can cause enhanced sedative and hypertensive effects.

4.6 Pregnancy and lactation
Pregnancy: Since morphine rapidly crosses the placental barrier, it is not advised to administer morphine during pregnancy and labour. It may reduce uterine contractions, cause respiratory depression in the foetus and new born infant, and may have significant effects on foetal heart rate.

Lactation: The amount of morphine secreted in breast milk after a single-dose administration seems to be compatible with breast feeding and insufficient to cause major problems or dependence. However long-term treatment with morphine in high doses may cause significant plasma concentration. That is why caution is advised on the use of morphine in breast-feeding patient and the benefit must outweigh the risk to the infant. If breast feeding is continued, the infant should be observed for possible adverse effects.

4.7 Effects on ability to drive and use machines
Morphine may cause drowsiness. If this occurs the patient should not be allowed to drive or operate machinery.

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

Adverse effects can be listed in terms of their frequency of occurrence:
- Very common (≥1/10)
- Common (≥1/100 to <1/10)
- Uncommon (≥1/1,000 to <1/100)
- Not known (cannot be estimated from the available data)

Morphine may cause the following adverse events:
<table>
<thead>
<tr>
<th>Disorder Type</th>
<th>Very Common:</th>
<th>Common:</th>
<th>Not Known:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>Drowsiness</td>
<td>Convulsion, headache, increased intracranial pressure, myoclonus, opioid-induced hyperalgesia (or hyperaesthesia), vertigo</td>
<td>Allodynia, coma</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Confusional state, hallucinations, physical and psychological dependence</td>
<td>Decreased libido, mood swings, restlessness</td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Blurred vision, miosis, nystagmus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Respiratory depression</td>
<td>Bronchospasm, pulmonary oedema, which can lead to death</td>
<td>Respiratory failure, which also can lead to death</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Bradycardia, circulatory failure, tachycardia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypotension, orthostatic hypotension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Constipation, nausea, vomiting</td>
<td>Dry mouth, paralytic ileus,</td>
<td>Intestinal functional disorder, narcotic bowel syndrome</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Biliary spasm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Erectile dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Urinary retention</td>
<td>Urethral spasm</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Anaphylactic reaction, hypersensitivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Muscle rigidity, rhabdomyolysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Pruritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Angioedema, contact dermatitis, rash, urticaria</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
General disorders and administration site conditions

| Very Common: Drug tolerance, hyperhidrosis |
| Common: Fatigue, facial flushing, hypothermia, injection site pain, injection site irritation, withdrawal syndrome (babies born to opioid-dependent mothers are also at risk to present withdrawal syndrome). |

4.9 Overdose
Symptoms: respiratory depression, pin-point pupils and coma. In addition, shock, reduced body temperature and hypotension may occur. In mild overdose, symptoms include nausea and vomiting, tremor, miosis, dysphoria, hypothermia, hypotension, confusion and sedation. In cases of severe poisoning, hypotension with circulatory failure, rhabdomyolysis progressing to renal failure, respiratory collapse and death may occur.

Treatment: the patient must be given respiratory support and the specific antagonist, naloxone, should be administered at a dose of 0.4-2.0 mg intravenously. This dose should be repeated at 2-3 minute intervals if improvement is not achieved, up to a total of 10 mg. Fluid and electrolyte levels should be maintained.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic Group: Natural opium alkaloids ATC Code: N02 AA01
Morphine is a narcotic analgesic obtained from opium, which acts mainly on the central nervous system and smooth muscle.

5.2 Pharmacokinetic properties
Absorption: Variably absorbed after oral administration; rapidly absorbed after subcutaneous or intramuscular administration.

Blood concentration: After an oral dose of 10mg as the sulphate, 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 3 hours; subcutaneous doses give similar concentrations to intramuscular doses at 15 minutes but remain slightly higher during the following 3 hours; serum concentrations measured soon after administration correlate closely with the ages of the subjects studied and are increased in the aged.

Half life: Serum half life in the period 10 minutes to 6 hours following intravenous administration, 2 to 3 hours; serum half life in the period 6 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, with sulphate conjugation. N-demethylation, 0-methylation and N-oxide glucuronide formation occurs in the intestinal mucosa and liver; N-demethylation occurs to a greater extent after oral than parenteral administration; the 0-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 parenteral 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 acid 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**
Sodium metabisulphite (E223)
Water for injections
Sodium hydroxide (for pH adjustment)
Sulphuric acid (for pH adjustment)

6.2  **Incompatibilities**
Morphine salts may be precipitated in alkaline solution.
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3  **Shelf life**
20 months

6.4  **Special precautions for storage**
Keep the ampoule in its outer carton to protect from light. Do not refrigerate or freeze.

6.5  **Nature and contents of container**
Type I Ph Eur clear glass ampoules containing 1 ml.
5 or 10 ampoules per carton.

6.6  **Special precautions for disposal and other handling**
Any unused product or waste material should be disposed of in accordance with local requirements.

7  **MARKETING AUTHORISATION HOLDER**
Auden Mckenzie (Pharma Division) Ltd
McKenzie House
Bury Street
Ruislip
Middlesex
HA4 7TL
UK

8  **MARKETING AUTHORISATION NUMBER(S)**
PL 17507/0012

9  **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
17/02/2011

10  **DATE OF REVISION OF THE TEXT**
17/02/2011
NAME OF THE MEDICINAL PRODUCT
Morphine Sulphate 30 mg/ml Solution for Injection.

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml of Morphine Sulphate solution for injection contains 30 mg morphine sulphate.
Also contains 1.1 mg of sodium metabisulphite (E223) in each ml of Morphine Sulphate solution for injection.

For a full list of excipients, see section 6.1.

PHARMACEUTICAL FORM
Solution for injection.
A clear colourless solution.

CLINICAL PARTICULARS
4.1 Therapeutic indications
Morphine is used for 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
The injection may be given by the intravenous, intramuscular or subcutaneous route.

Adults: The dosage should be based on the severity of the pain and the response and tolerance of the patient. The usual adult subcutaneous or intramuscular dose is 10mg every 4 hours if necessary, but may range from 5mg to 20mg.

The usual adult intravenous dose is 2.5mg to 15mg not more than 4 hourly, where necessary, but dosage and dosing interval must be titrated against the patient's response and adjustments made until analgesia is achieved.

Elderly: Because of the depressant effect on respiration, caution is necessary when giving morphine to the elderly and reduced doses may be required.

Children: Use in children is not recommended.

4.3 Contraindications
Respiratory depression, obstructive airways disease, concurrent treatment with monoamine oxidase inhibitors or within two weeks of their discontinuation of treatment with them.

Known morphine sensitivity, or sensitivity to any of the ingredients. Cerebral oedema, head injuries, coma, convulsive disorders and raised intracranial pressure, biliary colic and acute alcoholism.

Administration of morphine is contra-indicated in patients with phaeochromocytoma, those at risk of paralytic ileus and in patients with acute diarrhoea caused by poisoning or invasive pathogens.

4.4 Special warnings and precautions for use
Morphine is a potent medicine but with considerable potential for harmful effect, including addiction. It should be used only if other drugs with fewer hazards are inadequate, and with the recognition that it may possibly mask significant manifestations of disease which should be identified for proper diagnosis and treatment. It should be used with special caution in patients with a history of drug abuse. Dependence may occur after 1-2 weeks of treatment.

Morphine should be given with caution where there is a reduced respiratory reserve as in emphysema and asthma, chronic cor pulmonale, kyphoscoliosis and excessive obesity. Opiates should also be used cautiously in patients with cardiac arrhythmias, myasthenia gravis or inflammatory or obstructive bowel disorders.

Morphine should be administered with caution or in reduced doses to patients with hypotension, hypothyroidism, adrenocortical insufficiency, impaired kidney or liver function, prostatic hypertrophy, urethral stricture or shock.

Morphine should be given with great care to infants, especially neonates. Dosage should be reduced in elderly and debilitated patients.
Disappearance of opioid analgesic effects, particularly when associated with an unexplained increase in pain, may indicate the development of tolerance or opioid-induced hyperalgesia. An unexplained increase in abdominal pain associated with disturbed intestinal motility, symptoms of constipation, bloating, abdominal distension and increased gastroesophageal reflux during treatment with morphine sulphate, may indicate the development of opioid-induced bowel dysfunction or narcotic bowel syndrome. In such situations consider the use of alternative analgesics and a morphine detoxification.

Morphine Sulphate Injection contains sodium metabisulphite (E223). This may rarely cause severe hypersensitivity reactions and bronchospasm.

Morphine Sulphate Injection contains 0.24 mg of sodium per ml. This should be taken into consideration for patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction
Concurrent administration of other CNS depressants, including hypnotics and anxiolytics, may potentiate the sedative effects. Morphine should not be administered to patients receiving monoamine oxidase inhibitors (see section 4.3).

Anticholinergic agents such as atropine antagonise morphine-induced respiratory depression and can partially reverse biliary spasm but are additive to the gastro-intestinal and urinary tract effects. Consequently, severe constipation and urinary retention may occur during intensive anticholinergic-analgesic therapy.

Morphine sulphate should not be used for premedication when ciprofloxacin is given for surgical prophylaxis as serum levels of ciprofloxacin are reduced and adequate cover may not be obtained during surgery.

Taking alcohol with morphine sulphate can cause enhanced sedative and hypertensive effects.

4.6 Pregnancy and lactation
Pregnancy: Since morphine rapidly crosses the placental barrier, it is not advised to administer morphine during pregnancy and labour. It may reduce uterine contractions, cause respiratory depression in the foetus and new born infant, and may have significant effects on foetal heart rate.

Lactation: The amount of morphine secreted in breast milk after a single-dose administration seems to be compatible with breast feeding and insufficient to cause major problems or dependence. However long-term treatment with morphine in high doses may cause significant plasma concentration. That is why caution is advised on the use of morphine in breast-feeding patient and the benefit must outweigh the risk to the infant. If breast feeding is continued, the infant should be observed for possible adverse effects.

4.7 Effects on ability to drive and use machines
Morphine may cause drowsiness. If this occurs the patient should not be allowed to drive or operate machinery.

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

Adverse effects can be listed in terms of their frequency of occurrence:
- Very common (≥1/10)
- Common (≥1/100 to <1/10)
- Uncommon (≥1/1,000 to <1/100)
- Not known (cannot be estimated from the available data)

Morphine may cause the following adverse events:
| Nervous system disorders                  | Very Common: Drowsiness                                                                 |
|                                         | Common: Convulsion, headache, increased intracranial pressure, myoclonus, opioid-induced hyperalgesia (or hyperaesthesia), vertigo |
|                                         | Not Known: Allodynia, coma                                                             |
| Psychiatric disorders                   | Very Common: Confusional state, hallucinations, physical and psychological dependence |
|                                         | Common: Decreased libido, mood swings, restlessness                                    |
| Eye disorders                           | Common: Blurred vision, miosis, nystagmus                                               |
| Respiratory, thoracic and mediastinal disorders | Very Common: Respiratory depression                                                  |
|                                         | Common: Bronchospasm, pulmonary oedema, which can lead to death                        |
|                                         | Not Known: Respiratory failure, which also can lead to death                           |
| Cardiac disorders                       | Common: Bradycardia, circulatory failure, tachycardia                                  |
|                                         | Uncommon: Palpitations                                                                |
| Vascular disorders                      | Common: Hypotension, orthostatic hypotension                                            |
| Gastrointestinal disorders              | Very Common: Constipation, nausea, vomiting                                             |
|                                         | Common: Dry mouth, paralytic ileus,                                                   |
|                                         | Not Known: Intestinal functional disorder, narcotic bowel syndrome                     |
| Hepatobiliary disorders                 | Common: Biliary spasm                                                                 |
|                                         | Uncommon: Hepatic enzyme increase                                                     |
|                                         | Not Known: Spasm of the sphincter of Oddi,                                            |
| Reproductive system and breast disorders | Common: Erectile dysfunction                                                          |
| Renal and urinary disorders             | Common: Urinary retention                                                              |
|                                         | Uncommon: Urethral spasm                                                               |
|                                         | Not Known: Renal failure                                                               |
| Immune system disorders                 | Uncommon: Anaphylactic reaction, hypersensitivity                                       |
| Musculoskeletal and connective tissue disorders | Not Known: Muscle rigidity, rhabdomyolysis                                           |
| Skin and subcutaneous tissue disorders  | Very Common: Pruritis                                                                  |
|                                         | Common: Angioedema, contact dermatitis, rash, urticaria                                 |
**General disorders and administration site conditions**

| Very Common: Drug tolerance, hyperhidrosis |
| Common: Fatigue, facial flushing, hypothermia, injection site pain, injection site irritation, withdrawal syndrome (babies born to opioid-dependent mothers are also at risk to present withdrawal syndrome). |

### 4.9 Overdose

Symptoms: respiratory depression, pin-point pupils and coma. In addition, shock, reduced body temperature and hypotension may occur. In mild overdose, symptoms include nausea and vomiting, tremor, miosis, dysphoria, hypothermia, hypotension, confusion and sedation. In cases of severe poisoning, hypotension with circulatory failure, rhabdomyolysis progressing to renal failure, respiratory collapse and death may occur.

Treatment: the patient must be given respiratory support and the specific antagonist, naloxone, should be administered at a dose of 0.4-2.0 mg intravenously. This dose should be repeated at 2-3 minute intervals if improvement is not achieved, up to a total of 10 mg. Fluid and electrolyte levels should be maintained.

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Natural opium alkaloids ATC Code: N02 AA01

Morphine is a narcotic analgesic obtained from opium, which acts mainly on the central nervous system and smooth muscle.

#### 5.2 Pharmacokinetic properties

Absorption: Variably absorbed after oral administration; rapidly absorbed after subcutaneous or intramuscular administration.

Blood concentration: After an oral dose of 10mg as the sulphate, 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 3 hours; subcutaneous doses give similar concentrations to intramuscular doses at 15 minutes but remain slightly higher during the following 3 hours; serum concentrations measured soon after administration correlate closely with the ages of the subjects studied and are increased in the aged.

Half life: Serum half life in the period 10 minutes to 6 hours following intravenous administration, 2 to 3 hours; serum half life in the period 6 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, with sulphate conjugation. N-demethylation, 0-methylation and N-oxide glucuronide formation occurs in the intestinal mucosa and liver; N-demethylation occurs to a greater extent after oral than parenteral administration; the 0-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 parenteral 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 acid 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
Sodium metabisulphite (E223)
Water for injections
Sodium hydroxide (for pH adjustment)
Sulphuric acid (for pH adjustment)

6.2 Incompatibilities
Morphine salts may be precipitated in alkaline solution.
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life
20 months

6.4 Special precautions for storage
Keep the ampoule in its outer carton to protect from light. Do not refrigerate or freeze.

6.5 Nature and contents of container
Type I Ph Eur clear glass ampoules containing 1 ml and 2 ml.
5 or 10 ampoules per carton.

6.6 Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with local requirements.

MARKETING AUTHORISATION HOLDER
Auden Mckenzie (Pharma Division) Ltd
McKenzie House
Bury Street
Ruislip
Middlesex
HA4 7TL
UK

MARKETING AUTHORISATION NUMBER(S)
PL 17507/0013

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
17/02/2011

DATE OF REVISION OF THE TEXT
17/02/2011
Module 3
Product Information Leaflet

MORPHINE SULPHATE 10mg/ml, 15mg/ml, 20mg/ml or 30mg/ml Solution for Injection
(Morphine Sulphate)

Please read all of this leaflet carefully before taking your medicine.

• Keep this leaflet. You may need to read it again.
• If you have any further questions, ask your doctor or pharmacist.
• This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
• If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What is MORPHINE SULPHATE and what is it used for?
2. Before you are given MORPHINE SULPHATE
3. How you will be given MORPHINE SULPHATE
4. Possible side effects
5. Storing MORPHINE SULPHATE
6. Further information

1. What is MORPHINE SULPHATE and what is it used for?

What is MORPHINE SULPHATE?
MORPHINE SULPHATE Injection belongs to a group of medicines called narcotic analgesics which help relieve severe pain.

What is MORPHINE SULPHATE used for?
MORPHINE SULPHATE Injection is for the treatment of severe pain, to help with breathing which becomes difficult because fluid has collected in the lungs (pulmonary oedema) due to heart failure. It can also be given prior to having an operation.

2. Before you are given MORPHINE SULPHATE

Do not use MORPHINE SULPHATE if:
• You are allergic to MORPHINE SULPHATE
• You are allergic to any of the other ingredients of MORPHINE SULPHATE Injection (see section 6)
• You have conditions that make breathing difficult, such as obstructive airways disease or your breathing is weak
• You are taking, or have recently taken (in the past two weeks) any drugs for depression known as Monoamine Oxidase Inhibitors (MAOIs) e.g. phenelzine

Taking other medicines
Always tell your doctor if you are taking any other medicines because taking some medicines together can be harmful. Remember that the doctor at the hospital may not have been informed if you have recently begun a course of treatment for another illness.
• You must not be given MORPHINE SULPHATE Injection if you are taking, or have recently taken (in the past two weeks) any drugs for depression known as Monoamine Oxidase Inhibitors (MAOIs), e.g. phenelzine

Tell your doctor if you are taking any of the following medicines:
• Drugs to help you sleep or reduce your anxiety (hypnotics and anxiolytics) e.g. diazepam
• Anticholinergic drugs to relax smooth muscle and regulate the heart rate e.g. atropine
• An antibiotic called ciprofloxacin
• Any other medicine, including medicines obtained without a prescription.
If any of the above applies to you talk to your doctor or pharmacist.

Pregnancy and breast feeding
If you are pregnant, in labour or breastfeeding, MORPHINE SULPHATE Injection will only be given to you if your doctor considers the benefit of treatment outweighs the risk to the infant foetus or new born baby.
PAR Morphine Sulphate 10mg/ml, 15mg/ml, 20mg/ml and 30mg/ml Solution for Injection

• You have head injuries, headaches or have increased pressure in the skull (raised intracranial pressure)
• You have problems related to fluid on the brain (cerebral oedema)
• You suffer from convulsions (fits)
• You have severe stomach cramps (biliary colic)
• You have been drinking heavily or suffer from alcoholism
• You have a type of adrenal gland tumour called phaeochromocytoma
• You are at risk of having a blocked intestine (paralytic ileus)
• You have a sudden onset of diarrhoea caused by food poisoning or an infection
• You are pregnant or breast feeding
• You are a child.

MORPHINE SULPHATE is never given to patients in a coma.
If any of the above applies to you, do not use this medicine and talk to your doctor or pharmacist.

Special Precautions
Your doctor may take special precautions when giving you MORPHINE SULPHATE if any of the points listed below applies to you:
• You have low blood pressure (hypotension)
• You have a disease that causes difficulty in breathing such as asthma, emphysema, cor pulmonale (high blood pressure causing failure of the right side of the heart), abnormal spinal shape and excessive obesity
• You have an under-active thyroid (hypothyroidism) or adrenal gland (adrenocortical insufficiency)
• You have liver or kidney disease
• You have an inflammatory or obstructive bowel disease such as Crohn’s disease or ulcerative colitis
• You are in circulatory collapse (shock)
• You are male and have an enlarged prostate or have difficulty passing water (prostatic hypertrophy)
• You have muscle weakness (myasthenia gravis)
• You have a tendency to abuse drugs or have ever suffered from drug abuse
• You are on a controlled sodium diet.
• You are elderly.

If any of the above applies to you talk to your doctor or pharmacist.

Morphine may reduce contractions during labour, cause breathing problems to the infant foetus or new born baby and affect the heart rate of the foetus.
If you are breast feeding, your doctor or nurse will observe your baby for any side effects.

Driving and using machines
MORPHINE SULPHATE Injection may cause drowsiness. If this happens to you, do not drive or use machinery.

Taking with food and drink
Taking MORPHINE SULPHATE Injection with alcohol may cause increased sedation.

Warnings about the ingredients:
MORPHINE SULPHATE Injection contains 0.24 mg of sodium per ml and may therefore not be suitable for you if you are on a controlled sodium diet. Tell your doctor or pharmacist before you are given MORPHINE SULPHATE Injection if this applies to you.

MORPHINE SULPHATE Injection contains sodium metabisulphite (E223) which may rarely cause severe allergic reactions and bronchospasm which can lead to difficulty in breathing.

3. How you will be given MORPHINE SULPHATE

Important:
MORPHINE SULPHATE Injection will be given to you by a doctor or nurse in hospital. Your doctor will choose the dose that is right for you.

Adults:
• If this medicine is injected into a muscle or under the skin, the usual dose is 10 mg every 4 hours.
• However, the amount may range from 5 mg to 20 mg depending on how severe your pain is and how you respond to the drug.
• If the drug is injected into a vein, the usual dose for an adult is 2.5 mg to 15 mg with at least 4 hours between doses.
• Your doctor or nurse may adjust the dose of your medicine and the number of injections you are given each day until your pain is relieved.
Elderly:
As this medicine can make breathing difficult, your doctor or nurse may reduce the dose of your medicine.

Children:
MORPHINE SULPHATE Injection is not for use in children.

If you think you have been given more Morphin Sulphate than you should:
As this medicine will be given to you whilst you are in hospital, it is unlikely that you will be given too little or too much, however, tell your doctor or nurse if you have any concerns.

Symptoms of serious overdose include:
breathing difficulties, low blood pressure (hypotension) with your heart finding it difficult to pump blood around your body (circulatory failure), a deepening coma, feeling cold (hypothermia), fits (convulsions) especially in infants and children and rapid break down of muscle tissue (characterised by dark coloured urine and muscle tenderness, stiffness or aching) progressing to kidney failure.

If you have these symptoms, you will be given another medicine called Naloxone to reverse the effects of MORPHINE SULPHATE Injection.

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

4. Possible side effects
Like all medicines MORPHINE SULPHATE Injection can cause side effects, although not everybody gets them.

Seek immediate medical help if you have any of the following symptoms:
- Breathing difficulties (respiratory depression)
- Low blood pressure (hypotension) which may make you feel faint
- Your heart finding it difficult to pump blood around your body (circulatory failure) causing faintness, breathing difficulties, coughing up blood, excessive sweating and/or pale skin
- Allergic reactions causing:
  - Swelling of hands, feet, lips, mouth, tongue or throat
  - Difficulties breathing
  - Itchy skin rash (hives)
- Stomach pains, bloating, vomiting and constipation (obstructive bowel disorder)

The other side effects which have been reported are:
Very Common (more than 1 in 10 patients)
- Seeing or hearing things that are not there (hallucinations)
- Morphine is an addictive substance and its use can result in dependence
- Drowsiness and confusion
- Feeling (nausea) or being sick (vomiting)
- Constipation
- Sweating
- The drug no longer having the same effect as it use to (drug tolerance)

Other possible side effects
- Muscle stiffness with high doses
- Pain, generally on the skin, caused by something that would not normally cause pain such as light touch or pressure
- Coma
- Kidney failure

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. Storing MORPHINE SULPHATE
Keep out of the reach and sight of children.
Do not use MORPHINE SULPHATE Injection after the expiry date on the carton or the ampoule. The expiry date refers to the last day of that month.
Keep the ampoule in the outer carton in order to protect from light. Do not refrigerate or freeze.

Do not use the medicine if the solution is not clear and colourless.

6. Further Information
What MORPHINE SULPHATE contains:
The active substance is MORPHINE SULPHATE 10 mg, 15 mg, 20 mg or 30 mg in each 1ml of solution.
The solution for injection also contains sodium metabisulphite (E223), water for injections, sodium hydroxide and sulphuric acid.

What MORPHINE SULPHATE looks like and contents of the pack:
MORPHINE SULPHATE Injection is a sterile solution for injection in a clear glass container called an ampoule. It is a clear colourless solution.

MORPHINE SULPHATE Injection is supplied in cartons of 5 or 10 ampoules containing either
10 mg/ml, 15 mg/ml, 20 mg/ml, 30 mg/ml and 60 mg/2 ml.

Not all pack sizes may be marketed.

Marketing authorisation holder:
Auden McKenzie (Pharma Division) Ltd.,
Mckenzie House, Bury Street, Ruislip, Middlesex, HA4 7TL, UK

Manufacturer:
SNS Pharmaceuticals Ltd., Mckenzie House,
Bury Street, Ruislip, Middlesex, HA4 7TL, UK

This leaflet was last revised in January 2011.

For information in large print, on tape, on CD or in Braille, phone +44 (0) 1895 627 420.
Common (in less than 1 in 10, but more than 1 in 100 patients)
- Changes in your heart beat, such as slowing (bradycardia) or quickening (tachycardia) of the heart beat
- Low body temperature (hypothermia)
- Raised pressure in the skull (increased intracranial pressure)
- Abdominal pain (biliary spasms)
- Constriction of the pupil (miosis)
- Blurred vision
- Involuntary eye movements (nystagmus)
- A feeling of dizziness or “spinning” (vertigo)
- Dizziness/light headedness on standing (orthostatic hypotension)
- Difficulty passing urine
- Headaches
- Changes of mood
- Decreased libido (interest in sex) or inability to get an erection
- Dry mouth
- Facial flushing (warmth and redness of the skin)
- Restlessness
- Fits (convulsions)
- Increased sensitivity to pain
- Tiredness (fatigue)
- Stopping the drug can lead to withdrawal symptoms such as agitation, anxiety, shaking or sweating. This can also happen to babies born to mothers addicted to morphine.
- Pain and irritation may occur at the site of the injection

Uncommon (in less than 1 in 100, but more than 1 in 1000 patients)
- Being aware that your heart is beating or the rate has changed (palpitations)
- Abdominal pain (urethral spasms)
- An increase in liver enzymes may be noted during blood tests
Information for the Healthcare Professional

(Please detach prior to giving the leaflet to the patient)

MORPHINE SULPHATE 10mg/ml, 15mg/ml, 20mg/ml or 30mg/ml Solution for Injection
(Morphine Sulphate)

1. NAME OF THE MEDICINAL PRODUCT
Morphine Sulphate 10 mg/ml Solution for Injection.
Morphine Sulphate 15 mg/ml Solution for Injection.
Morphine Sulphate 20 mg/ml Solution for Injection.
Morphine Sulphate 30 mg/ml Solution for Injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
10 mg: Each ml of Morphine Sulphate solution for injection contains 10 mg morphine sulphate.
15 mg: Each ml of Morphine Sulphate solution for injection contains 15 mg morphine sulphate.
20 mg: Each ml of Morphine Sulphate solution for injection contains 20 mg morphine sulphate.
30 mg: Each ml of Morphine Sulphate solution for injection contains 30 mg morphine sulphate.

Also contains 1.1 mg of sodium metabisulphite (E223) in each ml of Morphine Sulphate solution for injection.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection.
A clear colourless solution.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Morphine is used for 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
The injection may be given by the intravenous, intramuscular or subcutaneous route.

Adults: The dosage should be based on the severity of the pain and the response and tolerance of the patient. The usual adult subcutaneous or intramuscular dose is 10mg every 4 hours if necessary, but may range from 5mg to 20mg.
The usual adult intravenous dose is 2.5mg to 15mg not more than 4 hourly, where necessary, but dosage and dosing interval must be titrated against the patient’s response and adjustments made until analgesia is achieved.

Elderly: Because of the depressant effect on respiration, caution is necessary when giving morphine to the elderly and reduced doses may be required.

Children: Use in children is not recommended.

Disappearance of opioid analgesic effects, particularly when associated with an unexplained increase in pain, may indicate the development of tolerance or opioid-induced hyperalgesia.
An unexplained increase in abdominal pain associated with disturbed intestinal motility, symptoms of constipation, bloating, abdominal distension and increased gastroesophageal reflux during treatment with morphine sulphate, may indicate the development of opioid-induced bowel dysfunction or narcotic bowel syndrome. In such situations consider the use of alternative analgesics and a morphine detoxification.

Morphine Sulphate Injection contains sodium metabisulphite (E223). This may rarely cause severe hypersensitivity reactions and bronchospasm.

Morphine Sulphate Injection contains 0.24 mg of sodium per ml. This should be taken into consideration for patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction
Concurrent administration of other CNS depressants, including hypnotics and anxiolytics, may potentiate the sedative effects.

Morphine should not be administered to patients receiving monoamine oxidase inhibitors (see section 4.3).

Anticholinergic agents such as atropine antagonise morphine-induced respiratory depression and can partially reverse biliary spasm but are additive to the gastro-intestinal and urinary tract effects. Consequently, severe constipation and urinary retention may occur during intensive anticholinergic-analgesic therapy.

Morphine sulphate should not be used for premedication when ciprofloxacin is given for surgical prophylaxis as serum levels of ciprofloxacin are reduced and adequate cover may not be obtained during surgery.

Taking alcohol with morphine sulphate can cause enhanced sedative and hypertensive effects.

4.6 Pregnancy and lactation
Pregnancy: Since morphine rapidly crosses the placental barrier, it is not advised to administer morphine during pregnancy and labour. It may reduce uterine contractions, cause respiratory depression in the foetus and new born infant, and may have significant effects on foetal heart rate.

Lactation: The amount of morphine secreted in
4.3 Contraindications
Respiratory depression, obstructive airways disease, concurrent treatment with monoamine oxidase inhibitors or within two weeks of their discontinuation of treatment with them.

Known morphine sensitivity, or sensitivity to any of the ingredients. Cerebral oedema, head injuries, coma, convulsive disorders and raised intracranial pressure, biliary colic and acute alcoholism.

Administration of morphine is contra-indicated in patients with phaeochromocytoma, those at risk of paralytic ileus and in patients with acute diarrhoea caused by poisoning or invasive pathogens.

4.4 Special warnings and special precautions for use
Morphine is a potent medicine but with considerable potential for harmful effect, including addiction. It should be used only if other drugs with fewer hazards are inadequate, and with the recognition that it may possibly mask significant manifestations of disease which should be identified for proper diagnosis and treatment. It should be used with special caution in patients with a history of drug abuse. Dependence may occur after 1-2 weeks of treatment.

Morphine should be given with caution where there is a reduced respiratory reserve as in emphysema and asthma, chronic cor pulmonale, kyphoscoliosis and excessive obesity. Opiates should also be used cautiously in patients with cardiac arrhythmias, myasthenia gravis or inflammatory or obstructive bowel disorders.

Morphine should be administered with caution or in reduced doses to patients with hypotension, hypothyroidism, adrenocortical insufficiency, impaired kidney or liver function, prostatic hypertrophy, urethral stricture or shock.

Morphine should be given with great care to infants, especially neonates. Dosage should be reduced in elderly and debilitated patients.

breast milk after a single-dose administration seems to be compatible with breast feeding and insufficient to cause major problems or dependence. However long-term treatment with morphine in high doses may cause significant plasma concentration. That is why caution is advised on the use of morphine in breast-feeding patient and the benefit must outweigh the risk to the infant. If breast feeding is continued, the infant should be observed for possible adverse effects.

4.7 Effects on ability to drive and use machines
Morphine may cause drowsiness. If this occurs the patient should not be allowed to drive or operate machinery.

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

Adverse effects can be listed in terms of their frequency of occurrence:
- Very common (≥1/10)
- Common (≥1/100 to <1/10)
- Uncommon (≥1/1,000 to <1/100)
- Not known (cannot be estimated from the available data)

Morphine may cause the following adverse events:

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th>Very Common: Drowsiness</th>
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<tbody>
<tr>
<td></td>
<td>Common: Convulsion, headache, increased intracranial pressure, myoclonus, opioid-induced hyperalgesia (or hyperaesthesia), vertigo</td>
</tr>
<tr>
<td></td>
<td>Not Known: Allodynia, coma</td>
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</tbody>
</table>

<table>
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<tr>
<th>Psychiatric disorders</th>
<th>Very Common: Confusional state, hallucinations, physical and psychological dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Common: Decreased libido, mood swings, restlessness</td>
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</tbody>
</table>
doses give similar concentrations to intramuscular doses at 15 minutes but remain slightly higher during the following 3 hours; serum concentrations measured soon after administration correlate closely with the ages of the subjects studied and are increased in the aged.

Half life: Serum half life in the period 10 minutes to 6 hours following intravenous administration, 2 to 3 hours; serum half life in the period 6 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, with sulphate conjugation. N-demethylation, 0-methylation and N-oxide glucuronide formation occurs in the intestinal mucosa and liver; N-demethylation occurs to a greater extent after oral than parenteral administration; the 0-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 parenteral 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 acid 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.
### Musculoskeletal and connective tissue disorders
- Not Known: Muscle rigidity, rhabdomyolysis

### Skin and subcutaneous tissue disorders
- Very Common: Pruritis
- Common: Angioedema, contact dermatitis, rash, urticaria

### General disorders and administration site conditions
- Very Common: Drug tolerance, hyperhidrosis
- Common: Fatigue, facial flushing, hyperthermia, injection site pain, injection site irritation, withdrawal syndrome (babies born to opioid-dependent mothers are also at risk to present withdrawal syndrome).

### 6. PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients
- Sodium metabisulphite (E223)
- Water for injections
- Sodium hydroxide (for pH adjustment)
- Sulphuric acid (for pH adjustment)

#### 6.2 Incompatibilities
Morphine salts may be precipitated in alkaline solution. In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

#### 6.3 Shelf life
- 20 months

#### 6.4 Special precautions for storage
- Keep the ampoule in its outer carton to protect from light. Do not refrigerate or freeze.

#### 6.5 Nature and contents of container
- 10/15/20 mg/ml: Type I Ph Eur clear glass ampoules containing 1 ml.
- 30 mg/ml: Type I Ph Eur clear glass ampoules containing 1 ml and 2ml.
- 5 or 10 ampoules per carton.

#### 6.6 Special precautions for disposal and other handling
- Any unused product or waste material should be disposed of in accordance with local requirements.

### 7. MARKETING AUTHORISATION HOLDER
Auden McKenzie (Pharma Division) Ltd., McKenzie House, Bury Street, Ruislip, Middlesex, HA4 7TL, UK

### 8. MARKETING AUTHORISATION NUMBER(S)
- 10 mg/ml: PL 17507/0010
- 15 mg/ml: PL 17507/0011
- 20 mg/ml: PL 17507/0012
- 30 mg/ml: PL 17507/0013

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

### 10. DATE OF REVISION OF THE TEXT

Legal category POM

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Auden McKenzie (Pharma Division) Ltd

P010-11-12-13-09-01/1
Module 4
Labelling
Module 5
Scientific discussion during initial procedure

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, Ireland and the UK considered that the applications for Morphine Sulphate 10mg/ml, 15mg/ml, 20mg/ml and 30mg/ml Solution for Injection could be approved. The products are prescription only medicines (POM) and are indicated for:

- the symptomatic relief of severe pain
- the relief of dyspnoea of left ventricular failure and pulmonary oedema
- pre-operative use.

These applications for Morphine Sulphate 10mg/ml, 15mg/ml, 20mg/ml and 30mg/ml Solution for Injection are submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products of Morphine Sulphate Injection BP 10mg/ml, 15mg/ml and 30mg/ml (PL 00039/5681R-2R and 4R) and Morphine Sulphate Injection BP 20mg in 1 ml (PL 01883/6177R), first authorised in the UK to UCB Pharma Limited and Macarthys Laboratories Limited (respectively) on 17th May 1982 and 19th January 1982, respectively.

No new non-clinical studies were conducted, which is acceptable given that the products contain a widely-used, well-known active substance. No clinical studies have been performed and none are required for these applications as the pharmacology of morphine sulphate is well-established.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Marketing Authorisation Holder has provided adequate justification for not submitting a Risk Management Plan.
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Morphine Sulphate 10mg/ml, 15mg/ml, 20mg/ml and 30mg/ml Solution for Injection |
| Name(s) of the active substance(s) (INN) | Morphine sulphate |
| Pharmacotherapeutic classification (ATC code) | Natural opium alkaloids (N02 AA01) |
| Pharmaceutical form and strength(s) | 10mg/ml, 15mg/ml, 20mg/ml and 30mg/ml Solution for Injection |
| Reference numbers for the Decentralised Procedure | UK/H/2512/001-4/DC |
| Reference Member State (RMS) | United Kingdom |
| Member States concerned (CMS) | Ireland (IE) |
| Marketing Authorisation Number(s) | PL 17507/0010-3 |
| Name and address of the authorisation holder | Auden Mckenzie (Pharma Division) Ltd McKenzie House Bury Street Ruislip Middlesex HA4 7TL UK |
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1  QUALITY ASPECTS

S.  Active substance

Morphine Sulphate
INN/Ph.Eur name:  Morphine sulphate
Chemical name:  Di(7,8-didehydro-4,5α-epoxy-17-methylmorphinan-3,6α-diol) sulphate pentahydrate.

Structural formula:

Molecular formula:  C_{34}H_{40}N_{2}O_{10}S_{5}H_{2}O

Appearance:  White or almost white, crystalline powder.
Solubility:  Soluble in water, very slightly soluble in ethanol (96 percent), and practically insoluble in toluene.
Molecular weight:  759

Morphine sulphate complies with the European Pharmacopoeia monograph.

All aspects of the manufacture of the active substance from its starting materials are controlled by a Certificate of Suitability.

Appropriate proof of structure data has been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance morphine sulphate, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guidelines. Suitable Certificates of Analysis have been provided for all reference standards used. Batch analysis data are provided and comply with the proposed specification.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.

P.  Medicinal Product

Other Ingredients
Other ingredients are pharmaceutical excipients sodium metabisulphite (E223), water for injections, sodium hydroxide (for pH adjustment), sulphuric acid (for pH adjustment).

All excipients comply with their European Pharmacopoeia monographs.
None of the excipients used contain material of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these products.

**Pharmaceutical Development**
The objective of the development programme was to produce medicinal products containing morphine sulphate that could be considered generic medicinal products of Morphine Sulphate Injection BP 10mg/ml, 15mg/ml and 30mg/ml and Morphine Sulphate Injection BP 20mg in 1 ml.

The applicant has provided suitable product development sections. Justifications for the use and amounts of each excipient have been provided and are valid.

**Manufacturing Process**
A satisfactory batch formula has been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on commercial-scale batches for each strength have been provided and are satisfactory.

**Finished Product Specification**
The finished product specifications proposed for the products is acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

**Container-Closure System**
These products are packaged in ampoules composed of clear Type I glass.
The ampoules contain:
- 10mg/ml, 15mg/ml, 20mg/ml: 1ml of Solution for injection
- 30mg/ml: 1ml and 2ml of Solution for Injection

Pack sizes are 5 and 10 ampoules.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the European Pharmacopoeia Type I and relevant regulations regarding use of materials in contact with food.

**Stability of the product**
Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 20 months with storage instructions, ‘Keep the ampoule in its outer carton to protect from light’ and ‘do not refrigerate or freeze’. This is satisfactory.

**Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PIL), Labels**
The SmPCs, PIL and labelling are pharmaceutically acceptable.

User testing results have been submitted for a typical PIL for these products. The results indicate that the PIL is well-structured and organised, easy to understand and written in a
comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**MAA forms**
The MAA forms are pharmaceutically satisfactory.

**Expert report**
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

**Conclusion**
It is recommended that Marketing Authorisations are granted for these applications.
III.2 NON-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of morphine sulphate are well-known. As this is a widely used, well-known active substance, the applicant has not provided any additional studies and none are required.

The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

The licensing of these products is not likely to result in an overall increase in environmental exposure to the active substance; therefore an Environmental Risk Assessment is not required.
III.3 CLINICAL ASPECTS

This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier.

CLINICAL PHARMACOLOGY
No new pharmacokinetic or pharmacodynamic data were submitted with these applications and none were required, as per the Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, as the applicant’s products are similar to the reference products in terms of qualitative and quantitative composition and are expected to perform identically in vivo. A human bioavailability study is not relevant to these applications as the compound is intended for intravenous injection.

EFFICACY
No new efficacy data were submitted with these applications and none were required.

SAFETY
No new safety data were submitted with these applications and none were required.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPCs), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
The SmPCs, PIL and labelling are medically satisfactory and consistent with those for the reference products, where appropriate.

CLINICAL EXPERT REPORT
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

MAA FORM
The MAA Forms are medically satisfactory.

CONCLUSIONS
It is recommended that Marketing Authorisations are granted for these applications.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Morphine Sulphate 10mg/ml, 15mg/ml, 20mg/ml and 30mg/ml Solution for Injection are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
No bioequivalence studies have been performed and none are required for these applications, given the composition of the products and their intended route of administration.

No new or unexpected safety concerns arise from these applications.

The SmPCs, PILs and labelling are satisfactory and consistent with that for the reference products.

RISK-BENEFIT ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with morphine sulphate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
Module 5

**STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY**

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<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
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