

# AUSTRALIAN PRODUCT INFORMATION

## MORPHINE MR MYLAN (MORPHINE SULFATE PENTAHYDRATE) MODIFIED RELEASE TABLETS

### 1 NAME OF THE MEDICINE

Morphine sulfate pentahydrate

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified release tablet contains 10 mg, 30 mg, 60 mg or 100 mg of morphine sulfate pentahydrate as the active ingredient.

Morphine sulfate pentahydrate 100 mg corresponds to 75 mg of morphine free base.

List of excipients with known effect: sugars as lactose monohydrate (except for the 100mg strength tablet).

For the full list of excipients, see Section 6.1 List of excipients.

### 3 PHARMACEUTICAL FORM

#### 10 mg Tablet

Buff coloured, biconvex, smooth, round, film coated modified release tablets with 10 on one face

#### 30 mg Tablet

Violet coloured, biconvex, smooth, round, film coated modified release tablets with 30 on one face.

#### 60 mg Tablet

Orange coloured, biconvex, smooth, round, film coated modified release tablets with 60 on one face.

#### 100 mg Tablet

Grey coloured, biconvex, smooth, round, film coated modified release tablets with 100 on one face.

### 4 CLINICAL PARTICULARS

#### 4.1 THERAPEUTIC INDICATIONS

Treatment of opioid responsive, chronic severe pain.

## 4.2 DOSE AND METHOD OF ADMINISTRATION

MORPHINE MR MYLAN modified release tablets are intended for oral administration.

Administration and dosing of morphine should be individualised, bearing in mind the properties of the drug. In addition, the nature and severity of the pain or pains experienced, and the total condition of the patient must be taken into account. Of special importance is other medication given previously or concurrently.

As with other strong opioid analgesics, use of morphine for the management of persistent pain should be preceded by a thorough assessment of the patient and diagnosis of the specific pain or pains and their causes. Use of opioids for the relief of chronic pain, including cancer pain, important as it is, should be only one part of a comprehensive approach.

MORPHINE MR MYLAN should be used for the long-term treatment of chronic severe pain only after the pain has been proven to be alleviated by opioids (with a trial of shorter acting opioids or MORPHINE MR MYLAN itself).

### Initial dose in adults:

Individual dosing requirements vary considerably based on each patient's age, weight, severity of pain, and medical and analgesic history. The most frequent initial dose is 30 mg every 12 hours.

Patients aged over 50 years tend to require much lower doses of morphine than the younger age group. In elderly and debilitated patients and those with impaired respiratory function or significantly decreased renal function, the initial dose should be one-half the usual recommended dose.

### Initial dose in children:

*Over 25 kg.*

The initial dose will depend upon the degree of morphine tolerance and should be titrated in accordance with the patient's needs (see Dose titration).

*25 kg or less.*

There are no controlled trials of the use of morphine sulfate pentahydrate in children weighing 25 kg or less, nor in children with chronic severe non-malignant pain.

Patients currently receiving other oral morphine formulations may be transferred to MORPHINE MR MYLAN at the same total daily morphine dosage, equally divided into two MORPHINE MR MYLAN doses given every 12 hours.

For patients who are receiving an alternate opioid, the oral morphine sulfate pentahydrate equivalent of the analgesic presently being used should be determined. Having determined the total daily dosage of the present analgesic, the following equivalence table can be used

to calculate the approximate daily oral morphine sulfate pentahydrate dosage that should provide equivalent analgesia. The total daily oral morphine dosage should then be equally divided into two MORPHINE MR MYLAN doses given every 12 hours.

**Table 1: Opioids: approximate analgesic equivalence**

Drug	Equivalent dose (mg)	
	Intramuscular	Oral
Morphine sulfate pentahydrate	10	30
Oxycodone	-	15
Dextromoramide	-	15
Papaveretum	-	45

Dose titration:

Dose titration is the key to success with morphine therapy. Proper optimisation of doses scaled to the relief of the individual's pain should aim at the regular administration of the lowest dose of morphine which will maintain the patient free of pain at all times. Dose adjustments should be based on the patient's clinical response. Higher doses may be justified in some patients to cover periods of physical activity.

Because of the sustained release properties of MORPHINE MR MYLAN, dosage adjustments should generally be separated by 48 hours. If dose increments are required, they should be proportionately greater at the lower dose level (in terms of percentage of previous dose), than when adjusting a higher dose.

The usual recommended dose (every 12 hours) increments are 5, 10, 15, 20, 30, 40, 60, 90, 120, 150, 180, 200 mg. Above the 200 mg/dose (400 mg/day) increments should be by 30 to 60 mg.

MORPHINE MR MYLAN tablets are designed to allow dosing every 12 hours. If breakthrough pain repeatedly occurs at the end of a dose interval, it is generally an indication for a dosage increase, not more frequent administration. However, where judged necessary for optimisation of drug effects, MORPHINE MR MYLAN may be administered every eight hours. More frequent (than every eight hours) administration of MORPHINE MR MYLAN is neither rational nor recommended.

Dosage adjustment or reduction:

During the first two or three days of effective pain relief, the patient may exhibit drowsiness or sleep for prolonged periods. This can be misinterpreted as the effect of excessive analgesic dosing rather than the first sign of relief in a pain exhausted patient. The dose, therefore, should be maintained for at least three days before reduction, provided the sedation is not excessive or associated with unsteadiness and confusional symptoms, and respiratory activity and other vital signs are adequate. If excessive sedation persists, the reason(s) for such an effect must be sought (refer section 4.8 Adverse Effects (Undesirable effects) - Sedation).

Following successful relief of severe pain, periodic attempts to reduce the opioid dose should be made. Smaller doses or complete discontinuation of the opioid analgesic may become feasible due to a change in the patient's condition or improved mental state.

Note: MORPHINE MR MYLAN tablets should be swallowed intact, not chewed, crushed or broken.

### **4.3 CONTRAINDICATIONS**

Hypersensitivity to opiate narcotics, or any of the excipients; acute asthma or other obstructive airways disease, acute respiratory depression; *cor pulmonale*; cardiac arrhythmias; acute alcoholism; *delirium tremens*; severe CNS depression; convulsive disorders; increased cerebrospinal or intracranial pressure; head injury; brain tumour; delayed gastric emptying; suspected surgical and acute abdomen; paralytic ileus, severe liver disease, incipient hepatic encephalopathy; severe renal dysfunction; concurrent (or within 14 days of therapy) monoamine oxidase inhibitors (see Section 4.5 Interactions with other medicines and other forms of interactions); children under one year of age; pregnancy. Not recommended for preoperative use or for the first 24 hours postoperatively.

Patients with chronic pain not due to malignancy, who have a prior history of substance and alcohol abuse.

### **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

Morphine must be administered with caution in patients taking CNS depressants (see Section 4.5 Interactions with other medicines and other forms of interactions).

Opioids, such as morphine sulfate pentahydrate, may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical symptoms may manifest from these hormonal changes.

Morphine should be used with caution in patients with impaired respiratory function, convulsive disorders, inflammatory bowel disorders, prostatic hypertrophy, adrenocortical insufficiency, hypotension with hypovolaemia, diseases of the biliary tract, pancreatitis and opioid dependency.

Caution is needed when changing between different presentations of morphine, or other potent opioid analgesic preparations, and the patient should be retitrated and clinically reassessed.

Morphine may lower the seizure threshold in patients with a history of epilepsy.

#### **Head injury and increased intracranial pressure**

The respiratory depressant effects of morphine and the capacity to elevate cerebrospinal fluid pressure, may be greatly increased in the presence of an already elevated intracranial pressure produced by trauma. Also, morphine may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, morphine must be used with extreme caution and only if it is judged essential.

#### **Respiratory depression**

The major risk of opioid excess is respiratory depression. Morphine should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing

respiratory depression, hypoxia or hypercapnia. Such patients are often less sensitive to the stimulatory effects of carbon dioxide on the respiratory centre, and the respiratory depressant effects of morphine may reduce respiratory drive to the point of apnoea.

### **Hypotensive effect**

Morphine administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of such drugs as phenothiazines or certain anaesthetics.

### **Abdominal conditions**

Morphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions. Where there is a possibility of paralytic ileus occurring, morphine should not be used. Should paralytic ileus be suspected or occur during use, morphine should be discontinued immediately. As with all oral morphine preparations, MORPHINE MR MYLAN tablets should be used with caution post-operatively and following abdominal surgery, as morphine impairs intestinal motility and should not be used until the physician is assured of normal bowel function.

Decreased gastric emptying associated with morphine may be expected to increase the risks of aspiration either associated with morphine induced CNS depression/coma, or during or after general anaesthesia.

### **Cordotomy**

Severe pain antagonises the subjective and respiratory depressant actions of morphine. Should pain suddenly subside, these effects may rapidly become manifest. Patients who are scheduled for cordotomy, other interruption of pain transmission pathways or other pain relieving surgical procedures should not receive MORPHINE MR MYLAN tablets within 24 hours of the procedure. Pain in the immediate preoperative period and any symptoms of opioid withdrawal should be managed with short acting analgesic agents. If further treatment with MORPHINE MR MYLAN tablets is indicated, the dosage should be adjusted to the new post-operative requirement.

### **Biliary tract and sphincter of Oddi conditions**

Because of the spasmogenic properties of morphine in the biliary tract and sphincter of Oddi, it should be used only when necessary and with caution in biliary colic, operations on the biliary tract and acute pancreatitis.

### **Acute ulcerative colitis**

Morphine may cause toxic dilatation in patients with acute ulcerative colitis.

### **Hyperalgesia**

Hyperalgesia that will not respond to a further dose increase of morphine sulfate may occur in particular at high doses. A morphine sulfate dose reduction or change in opioid may be required.

### **Acute chest syndrome (ACS) in patients with sickle cell disease (SCD)**

Due to a possible association between ACS and morphine use in SCD patients treated with morphine during a vaso-occlusive crisis, close monitoring for ACS symptoms is warranted.

### **Special Risk Groups**

Morphine should be administered with caution and in reduced dosages to elderly or debilitated patients, to patients with severely reduced hepatic or renal function, and in patients with Addison's disease, hypothyroidism, prostatic hypertrophy or urethral stricture.

Morphine should be used with caution in patients with impaired respiratory function, convulsive disorders, inflammatory bowel disorders, adrenocortical insufficiency, hypotension with hypovolaemia, diseases of the biliary tract, pancreatitis and opioid dependency.

Morphine may lower the seizure threshold in patients with a history of epilepsy.

### **Formulation**

The modified release tablets must be swallowed whole, and not broken, chewed or crushed. The administration of broken, chewed or crushed modified release morphine tablets leads to a rapid release and absorption of a potentially fatal dose of morphine.

It is not possible to ensure bioequivalence between different brands of modified release morphine products. Therefore, caution is needed when changing between different brands of sustained or modified release morphine, or other strong opioid analgesic preparations, and the patient should be re-titrated and clinically re-assessed.

### **Lactose**

MORPHINE MR MYLAN tablets (10 mg, 30 mg and 60 mg tablets only) contain lactose. Patients with rare hereditary problems including galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take these strengths of MORPHINE MR MYLAN tablets.

### **Use in chronic non-malignant pain:**

The use of MORPHINE MR MYLAN for the treatment of chronic pain which is not due to malignancy should be restricted to situations where:

- all other conservative methods of analgesia have been tried and have failed;
- the pain is having a significant impact on the patient's quality of life; and
- there is no psychological contraindication, drug seeking behaviour or history of drug misuse.

Prior to long-term prescription, a trial of MORPHINE MR MYLAN or shorter acting opioids should be undertaken. Long-term administration of MORPHINE MR MYLAN should only occur if this trial demonstrates that the pain is opioid sensitive. Opioid naive patients who require rapid dose escalation with no concomitant pain relief within the trial period should generally be considered inappropriate for long-term therapy.

A single doctor should be responsible for the prescription and monitoring of the patient's opioid use.

Doctors prescribing MORPHINE MR MYLAN should consult appropriate clinical guidelines on the use of opioid analgesics in such patients (e.g. Australian Pain Society publication in *The Medical Journal of Australia* 1997; 167:30-34).

### **Drug Dependence**

As with other opioids, tolerance and physical dependence tend to develop upon repeated administration of morphine, and there is potential for abuse of the drug and for development of strong psychological dependence. MORPHINE MR MYLAN should therefore be prescribed and handled with the high degree of caution appropriate to the use of a drug with strong abuse potential.

Drug abuse is not, however, a problem in patients with severe pain in whom morphine is appropriately indicated. On the other hand, in the absence of a clear indication for a strong opioid analgesic, drug seeking behaviour must be suspected and resisted, particularly in individuals with a history of, or propensity for, drug abuse. Withdrawal symptoms may occur following abrupt discontinuation of morphine therapy or upon administration of an opioid antagonist. Therefore, patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control (see Section 4.8 Adverse effects (Undesirable effects)). Morphine should be used with caution and under close supervision in patients with pain not due to malignancy who have a prior history of substance abuse. However, in such cases, prior psychological assessment is essential and the prescribing doctor should consider whether the benefit of treatment outweighs the risk of abuse.

### **Abuse of oral dosage forms**

Abuse of oral dosage forms by parenteral administration can be expected to result in serious adverse events, which may be fatal.

### **Use during labour/delivery**

Morphine crosses the placental barrier and its administration during labour can produce respiratory depression in the neonate. These products should only be used during labour after weighing the needs of the mother against the risk to the foetus.

### **Use in hepatic impairment**

Morphine should be administered with caution and in reduced dosages to patients with severely reduced hepatic function. See also Special Risk Groups.

### **Use in renal impairment**

Morphine should be administered with caution and in reduced dosages to patients with severely reduced renal function.

Morphine-6-glucuronide may accumulate in patients with renal failure, leading to CNS and respiratory depression. See also Special Risk Groups.

### **Use in the elderly**

Morphine should be administered with caution and in reduced dosages to elderly patients. See also "Special Risk Groups" above, Section 4.2 Dose and method of administration and Section 4.8 Adverse effects (undesirable effects).

### **Paediatric use**

There are no controlled trials of the use of morphine modified release tablets in children weighing 25 kg or less, nor in children with chronic, severe, non-malignant pain.

### **Effects on laboratory tests**

No data available

## **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**

### **Acidifying or alkalisating agents**

Generally, the effects of morphine may be antagonised by acidifying agents and potentiated by alkalinising agents. Concurrent administration of antacids may result in a more rapid release of morphine than otherwise expected; dosing should, therefore, be separated by a minimum of two hours.

### **Amphetamines, chlorpromazine and methocarbamol**

The analgesic effect of morphine is potentiated by amphetamines, chlorpromazine and methocarbamol.

### **Anticholinergics**

Medicinal products that block the action of acetylcholine, for example antihistamines, antiparkinsonians and antiemetics, may interact with morphine to potentiate anticholinergic adverse events.

### **Cimetidine**

Cimetidine inhibits the metabolism of morphine. A potentially lethal interaction between morphine and cimetidine has been reported. The patient exhibited apnoea, a significantly reduced respiratory rate and suffered a grand mal seizure. Naloxone increased respiratory rate, however confusion, disorientation, generalised twitching and periods of apnoea persisted for 80 hours.

### **CNS depressants**

Morphine should be used with caution and in reduced dosage in patients who are concurrently receiving other CNS depressants which include, but are not limited to opioids, anaesthetics, sedatives (including benzodiazepines), anxiolytics, hypnotics, barbiturates, phenothiazines, antidepressants (including tricyclic antidepressants), chloral hydrate, antipsychotics, glutethimide, tranquilisers, muscle relaxants, antihypertensives, gabapentin and alcohol as they may enhance the depressant effects of morphine. Pyrazolidone antihistamines and beta- blockers may also enhance the depressant effect of morphine. Interactive effects resulting in respiratory depression, hypotension, profound sedation, coma or death may result if these drugs are taken in combination with the usual doses of morphine.

### **Coumarin and other anticoagulants**

Morphine may increase the anticoagulant activity of coumarin and other anticoagulants.

### **Mixed agonist/antagonist opioid analgesics**

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

### **Monoamine oxidase inhibitors**

Nonselective MAOIs (including procarbazine hydrochloride) intensify the effects of morphine and other opioid drugs which can cause anxiety, confusion and significant respiratory depression, sometimes leading to coma. Morphine should not be given to patients taking nonselective MAOIs or within 14 days of stopping such treatment. It is unknown whether there is an interaction between the newer selective MAOIs (e.g. moclobemide and selegiline) and morphine, therefore caution is advised with such drug combinations.

### **Propranolol**

The combination of morphine and propranolol is potentially lethal. Propranolol increases the acute CNS toxicity of morphine.

### **Rifampicin**

Plasma concentrations of morphine may be reduced by rifampicin.

### **Ritonavir**

Available data indicate that ritonavir may increase the activity of glucuronyl transferases. Consequently, coadministration of ritonavir and morphine may result in decreased morphine serum concentrations with possible loss of analgesic effectiveness.

### **Zidovudine**

Morphine may alter the metabolism of zidovudine by competitively inhibiting glucuronidation or directly inhibiting hepatic microsomal metabolism, therefore this combination should be used with caution.

## **4.6 FERTILITY, PREGNANCY AND LACTATION**

### **Effects on fertility**

Prolonged use of opioid drugs may result in impairment of reproductive function, including infertility and sexual dysfunction in both sexes and irregular menses in women.

Animal studies have shown that morphine may reduce fertility. In male rats, reduced fertility and chromosomal damage in gametes have been reported.

### **Use in pregnancy - Pregnancy Category C**

Australian Pregnancy Categorisation C. Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible.

Opioid analgesics may cause respiratory depression in the newborn infant. Morphine has been associated with foetal CNS defects in rodent studies.

In humans it is not known whether morphine can cause foetal harm when administered during pregnancy. Use of MORPHINE MR MYLAN tablets should be avoided to the extent possible in patients who are pregnant. Long-term use of opioids in pregnancy may result in a neonatal opioid withdrawal state.

Morphine crosses the placental barrier and its administration during labour can produce respiratory depression in the neonate. These products should only be used during labour after weighing the needs of the mother against the risk to the foetus

#### **Use in lactation.**

Morphine has been detected in human breast milk; caution should be exercised if morphine is administered to a nursing mother and use of morphine sulfate should be avoided to the extent possible

### **4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

Morphine may impair the mental and/or physical abilities needed for certain potentially hazardous activities, such as driving a car or operating machinery. Patients should be cautioned accordingly.

Patients should be cautioned about the combined effects of morphine with other CNS depressants, including other opioids, phenothiazines, sedative/ hypnotics and alcohol.

### **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**

The following frequencies are the basis for assessing adverse effects.

Very common ( $\geq 1/10$ )

Common ( $\geq 1/100$  to  $< 1/10$ )

Uncommon ( $\geq 1/1,000$  to  $< 1/100$ )

Rare ( $\geq 1/10,000$  to  $< 1/1,000$ )

Very rare ( $< 1/10,000$ )

Not known (cannot be estimated from the available data)

The major hazards associated with morphine, as with other opioid analgesics, are respiratory depression and, to a lesser degree, circulatory depression. Respiratory arrest, shock and cardiac arrest have occurred following oral or parenteral use of morphine.

#### **Very common adverse effects requiring medical attention:**

The most frequently observed side effects of opioid analgesics such as morphine are sedation, nausea and vomiting, constipation and sweating.

#### *Sedation*

Most patients experience initial drowsiness, partly for pharmacokinetic reasons and partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Drowsiness usually clears in three to five days and is usually not a reason for concern providing that it is not excessive, or associated with unsteadiness or confusional symptoms. If excessive sedation persists, the reason for it must be sought. Some of these are:

- concomitant sedative medications,
- hepatic or renal failure,
- exacerbated respiratory failure,
- higher doses than tolerated in an older patient, or
- that the patient is actually more severely ill than realised.

If it is necessary to reduce the dose, it can be carefully increased again after three or four days if it is obvious that the pain is not being well controlled. Dizziness and unsteadiness may be caused by postural hypotension, particularly in elderly or debilitated patients. It can be alleviated if the patient lies down. Because of the slower clearance in patients aged over 50 years, an appropriate dose in this age group may be as low as one-half or less the usual dose in the younger age group.

#### *Nausea and vomiting*

Nausea and vomiting occur frequently after single doses of opioids, or as an early unwanted effect of regular opioid therapy. When instituting prolonged therapy for chronic pain, the routine prescription of an antiemetic should be considered. Patients taking the equivalent of a single dose of morphine of 20 mg or more (MORPHINE MR MYLAN 60 mg every 12 hours) usually require an antiemetic during early therapy. Small doses of prochlorperazine or haloperidol are the most frequently prescribed antiemetics. Nausea and vomiting tend to lessen in a week or so, but may persist due to opioid induced gastric stasis. In such patients, metoclopramide is often useful.

#### *Constipation*

As with all opioid analgesics, constipation is very common. In some patients, particularly elderly or bedridden patients, faeces may become impacted. It is essential to caution patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged opioid therapy. Softeners, laxatives and other appropriate measures should be used as required.

#### **Other adverse effects include:**

##### *Cardiac disorders*

*Not known:* bradycardia, palpitations, supra-ventricular tachycardia

##### *Ear and labyrinth disorders*

*Uncommon:* vertigo

##### *Endocrine disorders*

*Uncommon:* a syndrome of inappropriate antidiuretic hormone secretion characterised by hyponatremia secondary to decreased free-water excretion may be prominent (monitoring of electrolytes may be necessary)

##### *Eye disorders*

*Uncommon:* visual disturbance

*Not known:* miosis

##### *Gastrointestinal disorders*

*Common:* abdominal pain, anorexia, dry mouth

*Uncommon:* dyspepsia, ileus, taste perversion

*Not known:* cramps, gastrointestinal disorders

*General disorders and administration site conditions*

*Common:* asthenic conditions (fatigue, malaise), pruritus

*Uncommon:* peripheral oedema

*Not known:* drug tolerance, oedema, drug withdrawal syndrome, drug withdrawal syndrome neonatal

*Hepato-biliary disorders*

*Uncommon:* increased hepatic enzyme

*Not known:* biliary pain, biliary spasm, biliary tract cramps

*Immune system disorders*

*Uncommon:* hypersensitivity

*Not known:* anaphylactic reaction, anaphylactoid reaction

*Nervous system disorders*

*Common:* dizziness, headache, involuntary muscle contractions, somnolence

*Uncommon:* convulsions, hypertonia, paraesthesia, syncope, seizures

*Not known:* hyperalgesia, weakness

*Psychiatric disorders*

*Common:* confusion, insomnia

*Uncommon:* agitation, euphoria, hallucinations, malaise, mood altered

*Not known:* drug dependence, dysphoria, thinking disturbances

*Renal and urinary disorders*

*Uncommon:* ureteric spasm, urinary retention or hesitance

*Reproductive system and breast disorders*

*Not known:* amenorrhoea, erectile dysfunction, reduced libido or potency

*Respiratory, thoracic and mediastinal disorders*

*Uncommon:* bronchospasm, pulmonary oedema, respiratory depression

*Not known:* cough decreased

*Skin and subcutaneous tissue disorders*

*Common:* hyperhidrosis, other skin rashes including contact dermatitis

*Uncommon:* urticaria

*Vascular disorders*

*Uncommon:* facial flushing, hypotension

*Not known:* faintness, postural hypotension

**Withdrawal (abstinence) syndrome**

Physical dependence with or without psychological dependence tends to occur on chronic administration. An abstinence syndrome may be precipitated when opioid administration is discontinued or opioid antagonists administered. Tolerance to the effects of morphine may develop.

The following withdrawal symptoms may be observed after opioids are discontinued: body aches, diarrhoea, gooseflesh, loss of appetite, nervousness or restlessness, runny nose, sneezing, chills, tremors or shivering, stomach cramps, nausea, trouble with sleeping, unusual increase in sweating and yawning, weakness, tachycardia and unexplained fever. With appropriate medical use of opioids and gradual withdrawal from the drug, these symptoms are usually mild

### **Post-marketing**

*Nervous system disorders*

Not known: allodynia

### **Reporting suspected adverse effects**

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at [www.tga.gov.au/reporting-problems](http://www.tga.gov.au/reporting-problems).

## **4.9 OVERDOSE**

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

### **Symptoms**

Serious morphine overdosage is characterised by respiratory depression (reduced respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, pneumonia aspiration, miotic pupils, rhabdomyolysis progressing to renal failure, flaccidity of skeletal muscle; cold or clammy skin, and sometimes hypotension and bradycardia. Severe overdosage may result in apnoea, pulmonary oedema, circulatory collapse, cardiac arrest and death.

### **Treatment**

Primary attention should be given to the establishment of adequate respiratory exchange through the provision of a patent airway and controlled or assisted ventilation. The opioid antagonist naloxone hydrochloride is a specific antidote against respiratory depression due to overdosage or as a result of unusual sensitivity to morphine. An appropriate dose of one of the antagonists should therefore be administered, preferably by the intravenous route. The usual initial intravenous adult dose of naloxone is 0.4 mg or higher (please refer to naloxone Product Information for further information). Concomitant efforts at respiratory resuscitation should be carried out. Since the duration of action of morphine, particularly sustained release formulations, may exceed that of the antagonist, the patient should be under continued surveillance and doses of the antagonist should be repeated as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated.

In an individual physically dependent on opioids, the administration of the usual dose of

opioid antagonist will precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of antagonist administered. The use of opioid antagonists in such individuals should be avoided if possible. If an opioid antagonist must be used to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care by using dosage titration, commencing with 10 to 20% of the usual recommended initial dose.

Gastric lavage with a wide bore tube followed by administration of an activated charcoal suspension will aid the removal of morphine. A saline cathartic or sorbitol added to the first dose of activated charcoal may speed gastrointestinal passage of the product.

### **Toxicity**

Morphine toxicity may result from overdosage, but because of the greater inter-individual variation in sensitivity to opioids, it is difficult to determine an exact dose of any opioid that is toxic or lethal. Chewing or crushing and taking the contents of a modified release dosage form leads to the release of morphine in an immediate fashion; this might result in a fatal overdose.

The presence of pain or tolerance tends to diminish the toxic effects of morphine. Published data suggest that in a morphine naive, pain free individual, the lethal dose would be in excess of 120 mg. Patients on chronic oral morphine therapy have been known to take in excess of 3,000 mg/day with no apparent toxicity.

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 PHARMACODYNAMIC PROPERTIES**

#### **Mechanism of action**

Morphine sulfate pentahydrate is a narcotic analgesic.

Morphine is a phenanthrene alkaloid obtained from opium. Morphine and related compounds interact with specific receptors primarily found in the brain, spinal cord and the myenteric plexus of the gut wall. Morphine has considerably higher affinity for mu receptors than for other opioid receptors. In humans, the principal pharmacological actions of morphine are in the central nervous system (CNS): analgesia, drowsiness, mood changes (including euphoria and dysphoria), mental clouding, respiratory depression, nausea or emesis, miosis and on smooth muscle; (increased gastrointestinal tone with a reduction in propulsive motion, increased biliary pressure and increased tone of the ureter and vesical sphincter, and alterations of the endocrine and autonomic nervous system.

Morphine-induced analgesia is a result of increases in both the pain threshold and pain tolerance. Morphine alters the affective response to pain, in that patients remain aware of its existence but are less distressed. Morphine relieves most types of pain but is more effective against dull constant pain than sharp intermittent pain]

#### **Clinical trials**

No data available.

## 5.2 PHARMACOKINETIC PROPERTIES

### Absorption

Morphine is readily absorbed from the gastrointestinal tract, nasal mucosa and lung, and after subcutaneous or intramuscular injection. Due to first pass metabolism, the effect of an oral dose is less than that of the same dose given parenterally. The parenteral to oral morphine potency ratio has been reported to range from 1:6 to 1:2. In general, the greatest difference between parenteral and oral potency is seen in acute studies. With chronic dosing, oral morphine is about one-half to one-third as potent as when given by injection.

At steady state, morphine sulfate pentahydrate SR tablets produce peak morphine concentrations approximately three to five hours postdose, and therapeutic levels tend to persist for a 12 hour period.

### Distribution

Following absorption, approximately 30 to 35% of morphine is reversibly bound to plasma proteins. Free morphine readily leaves the circulation and is concentrated in the liver, kidney, lung, spleen and, to a lesser extent, skeletal muscle. In adults, only small quantities of morphine pass the blood-brain barrier.

### Metabolism

Conjugation with glucuronic acid is the major metabolic pathway for morphine. The major metabolite is morphine-3-glucuronide. Other metabolites include normorphine, morphine-6-glucuronide, morphine-3,6-diglucuronide and morphine-3-etheral sulfate.

### Excretion

The mean elimination half-life of morphine is two to three hours, with great interpatient variability. The major route of excretion is via the kidney. Approximately 7 to 10% is excreted in the faeces via the bile. Conjugated morphine excreted in the bile may be hydrolysed and reabsorbed from the large bowel.

## 5.3 PRECLINICAL SAFETY DATA

### Genotoxicity

No regulatory studies to assess the mutagenic potential of morphine have been conducted.

### Carcinogenicity

Regulatory studies in animals to evaluate the carcinogenic potential of morphine have not been conducted.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 LIST OF EXCIPIENTS

Excipients contained in each of the four strengths of MORPHINE MR MYLAN tablets are lactose monohydrate (except the 100 mg), hyetellose, hypromellose, povidone, purified talc and magnesium stearate. The tablet coatings contain a different colourant for each strength, as follows:

- 10 mg – Opadry buff OY-3607
- 30 mg – Opadry violet OY-6708
- 60 mg – Opadry orange OY-3533
- 100 mg - Opadry grey OY-8238

## 6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

## 6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

## 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

## 6.5 NATURE AND CONTENTS OF CONTAINER

MORPHINE MR MYLAN modified release (sustained release) tablets come in blisters of PVC/Aluminium in cartons containing 20\*, 28 or 60\* tablets.

\*not currently marketed in Australia

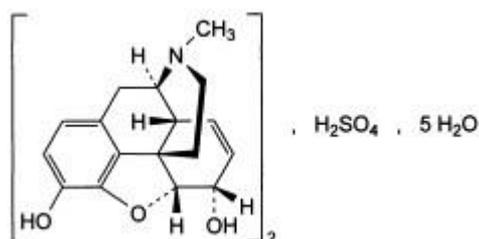
## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

## 6.7 PHYSICOCHEMICAL PROPERTIES

Morphine sulfate pentahydrate is a white, odourless, crystalline powder or needle-like crystals. It is soluble in water and ethanol. It is practically insoluble in ether or chloroform.

### Chemical structure



The chemical name of morphine sulfate pentahydrate is:

Di(7,8-didehydro-4,5 $\alpha$ -epoxy-17-methylmorphinan-3,6 $\alpha$ -diol) sulfate pentahydrate.

Molecular formula: C<sub>34</sub>H<sub>40</sub>N<sub>2</sub>O<sub>10</sub>S.5H<sub>2</sub>O Molecular Weight: 759

**CAS number**

6211-15-0

**7 MEDICINE SCHEDULE (POISONS STANDARD)**

S8 (Controlled Drug)

**8 SPONSOR**

Southern Cross Pharma Pty Ltd

Suite 5/118 Church St

Hawthorn VIC 3122

[info@southernxp.com](mailto:info@southernxp.com)**9 DATE OF FIRST APPROVAL**

22/04/2009

**10 DATE OF REVISION**

24 February 2020

**SUMMARY TABLE OF CHANGES**

Section Changed	Summary of new information
2, 4.2, 4.4, 4.5, 4.6, 4.7, 4.9, 5.1	Minor Editorial Changes
4.3, 4.4, 4.5, 4.6, 4.8, 4.9	Safety Related Changes