

AUSTRALIAN PRODUCT INFORMATION – SEVREDOL® (MORPHINE SULFATE PENTAHYDRATE) TABLETS

1 NAME OF THE MEDICINE

Morphine sulfate pentahydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SEVREDOL 10 mg tablets contain 10 mg morphine sulfate pentahydrate.

SEVREDOL 20 mg tablets contain 20 mg morphine sulfate pentahydrate.

SEVREDOL tablets contain the following excipients: tablet core: lactose, pregelatinised maize starch, povidone, magnesium stearate and purified talc; film coat: OPADRY complete film coating system 06B20843 Blue (10 mg) or OPADRY II complete film coating system 85F240092 PINK (20 mg).

Excipients with known effect: lactose

3 PHARMACEUTICAL FORM

SEVREDOL 10 mg: blue film-coated, biconvex capsule shaped tablets with a scoreline and “IR” to the left and “10” to the right.

SEVREDOL 20 mg: pink film-coated, biconvex capsule shaped tablets with a scoreline and “IR” to the left and “20” to the right.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of chronic severe pain of cancer.

4.2 DOSE AND METHOD OF 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, all important as it may be, should be only one part of a comprehensive approach to pain control including other treatment modalities or drug therapy, non-pharmacological measures and psychosocial support.

Individual dosing requirements vary considerably based on each patient’s age, weight, severity of pain, and medical and analgesic history.

Patients over the age of 50 tend to require much lower doses of morphine than in 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.

For patients who are receiving an alternative 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.

Table 1 - Opioids: Approximate analgesic equivalences¹

Drug	Equivalent Dose (mg)	
	IM	PO
MORPHINE sulfate pentahydrate	10	30
OXYCODONE (Percodan*, Endone, Proladone)		15
DEXTROMORAMIDE (Palfium*) ²		15
PAPAVRETUM (Omnopon*)		45

1. Twycross, RG (1997). Oral morphine advanced cancer. 3rd edition. Beaconsfield, UK, Beaconsfield Publishers Ltd.
2. Dextromoramide - a single 5mg dose is equivalent to morphine 15mg (diamorphine* 10mg) in terms of peak effect but is shorter acting. The overall potency ratio has been adjusted.

*Not currently available in Australia.

IM – intramuscular; PO – oral administration

Adjustment or reduction of dosage

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. Some of these are: concomitant sedative medications, hepatic or renal failure, exacerbated respiratory failure, higher doses than tolerated by an older patient, or 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.

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.

Opioid agents do not effectively relieve dysesthetic pain, post-herpetic neuralgia, stabbing pains, activity-related pain, and some forms of headache. This is not to say that patients with advanced cancer suffering from some of these forms of pain should not be given an adequate trial of opiate analgesics, but it may be necessary to refer such patients at an early time for other forms of pain therapy. Pain without nociception is usually not opioid responsive.

Adults and children over 12 years of age

SEVREDOL tablets should be used at four-hourly intervals. A patient presenting with severe pain should normally be started on a dosage of one tablet 10 mg four-hourly. Increasing severity of pain or tolerance to morphine will require increases in the dosage of SEVREDOL tablets, using 10 mg and 20 mg alone or in combination to achieve the desired reduction in levels of pain.

Patients receiving SEVREDOL tablets in place of parenteral morphine should be given a sufficiently increased dosage to compensate for any reduction in analgesic effects associated with oral administration. Usually such increased requirement is of the order of 50% to 100%. In such patients, individual dose adjustments are required.

Elderly

A reduction in adult dosage may be advisable.

4.3 CONTRAINDICATIONS

Morphine should not be given to patients with hypersensitivity to opioids; known hypersensitivity to any of the excipients; acute asthma; other obstructive airway 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; paralytic ileus; delayed gastric emptying, suspected surgical and acute abdominal conditions; severe liver disease; severe renal dysfunction, incipient hepatic encephalopathy; concomitant monoamine oxidase inhibitors (MAOIs), or within 14 days of such therapy (see Section 4.5 – Interactions with other medicines and other forms of interactions). Not recommended in pregnancy or for children below three years of age.

SEVREDOL tablets should be used with caution pre-operatively and within the first 24 hours post-operatively.

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. Also see Section 4.8 – Adverse effects (undesirable effects), Endocrine disorders.

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 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 should 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 drugs such 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, SEVREDOL tablets should be discontinued immediately. As with all oral morphine preparations, SEVREDOL tablets should be used with caution post-operatively including, but not limited to, 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 or other pain-relieving surgical procedures should not receive SEVREDOL tablets within 24 hours of the procedure. If further treatment with SEVREDOL tablets is indicated then the dosage should be adjusted to the new post-operative requirements.

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 dilation in patients with acute ulcerative colitis.

Hyperalgesia

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

Special risk groups

Morphine should be administered with caution, and in reduced dosages, to debilitated patients 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.

Lactose

SEVREDOL tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 sulfate pentahydrate should therefore not be prescribed for patients who have a prior history of substance and alcohol use, and should be handled with the high degree of caution appropriate to the use of a drug with strong abuse potential.

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.

Abuse of oral dosage forms

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

Use during labour /delivery

Not indicated. Morphine crosses the placental barrier and its administration during labour can produce respiratory depression in the neonate. SEVREDOL tablets 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.

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.

Use in the elderly

Morphine should be administered with caution, and in reduced dosages to elderly patients.

Paediatric use

Not recommended for children below three years of age.

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, anti-parkinsonian drugs and anti-emetics, may interact with morphine to potentiate anti-cholinergic adverse events.

Cimetidine

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

CNS depressants

Morphine should be used only 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

Non-selective MAO inhibitors (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 non-selective MAOIs or within 14 days of stopping such treatment. It is unknown whether there is an interaction between selective MAOIs (e.g. moclobemide and selegiline) and morphine, therefore caution is advised with this drug combination.

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, co-administration of ritonavir and morphine may result in decreased serum concentrations of morphine 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.

Use in pregnancy – Pregnancy Category C

Category 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 effects in rodent studies.

In humans it is not known whether morphine can cause foetal harm when administered during pregnancy or can affect reproductive capacity. Use of SEVREDOL 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.

Use in lactation.

Morphine has been detected in human breastmilk. Caution should be exercised if morphine is administered to a nursing mother and use of SEVREDOL tablets 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 also 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 and parenteral use of morphine.

Very common adverse effects requiring medical attention

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 from 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 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 over 50 years of age, an appropriate dose in this age group may be as low as 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 prescribing of an anti-emetic should be considered. Patients taking the equivalent of a single dose of 20 mg or more of morphine usually require an anti-emetic during early therapy. Small doses of prochlorperazine or haloperidol are frequently prescribed anti-emetics. 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 instances, particularly the elderly or bedridden, patients may become impacted. It is essential to caution the patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged opioid therapy. Dietary modification, suitable exercise, 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

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

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 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 with 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.

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.

4.9 OVERDOSE

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

Symptoms

Serious morphine overdose 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 overdose 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 overdose 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 (IV) 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 to manage the circulatory shock accompanying an overdose. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation. Artificial ventilation should be applied if necessary and fluid and electrolyte metabolism maintained.

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.

Evacuation of gastric contents may be useful in removing unabsorbed drug, particularly when a sustained release formulation has been taken.

Toxicity

Morphine toxicity may result from overdose but because of the great inter-individual variation in sensitivity to opioids it is difficult to determine an exact dose of any opioid that is toxic or lethal.

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 3000 mg/day with no apparent toxicity.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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 man, 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, 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 pains than sharp, intermittent pain.

Clinical trials

No data included.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Morphine is readily absorbed from the gastrointestinal tract, nasal mucosa, lung and after subcutaneous (SC) or intramuscular (IM) injection. Due to first pass metabolism, the effect of an oral dose is less than that of the same dose given parenterally. Morphine given parenterally has been reported to be from two to six times more potent than oral administration. In general, the greatest difference between parenteral and oral potency is seen in acute studies. With chronic dosing, oral morphine is about 1/2 to 1/3 as potent as when given by injection.

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. Minor 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 inter-patient variability. The major route of elimination is via the kidney. About 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

Refer to Section 2 – Qualitative and quantitative composition.

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 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Blister packs (PVC/PVdC/Al) of 20 tablets.

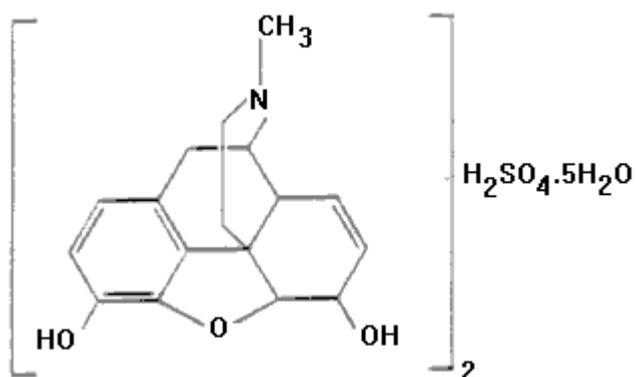
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Morphine sulfate pentahydrate is a white, odourless crystalline powder or needle-like crystals. Morphine sulfate pentahydrate is soluble 1:21 in water and 1:1000 in ethanol. It is practically insoluble in ether or chloroform.

Chemical structure



CAS number

6211 - 15 - 0

7 MEDICINE SCHEDULE (POISONS STANDARD)

S8

8 SPONSOR

Mundipharma Pty Limited

ABN 87 081 322 509

88 Phillip Street

SYDNEY NSW 2000

Further information may be obtained from Mundipharma's Medical Information Department
1800 188 009.

9 DATE OF FIRST APPROVAL

12 April 1994

10 DATE OF REVISION

24 December 2018

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.2	Correction to Table 1: figures for OXYCODONE and PAPAVERETUM were moved back under the "PO" column,

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Orbis RA-0253

mfpsevre11218 supersedes mfpsevre10918