PRODUCT INFORMATION

Product Name: SEVREDOL® tablets (10 mg and 20 mg)

NAME OF THE MEDICINE
Morphine sulfate BP.
The structural formula of morphine sulfate is

\[
\begin{align*}
\text{CH}_3 \\
\text{N} \\
\text{H}_2\text{SO}_4\cdot\text{5H}_2\text{O} \\
\text{HO} \\
\text{O} \\
\text{OH}
\end{align*}
\]

CAS Registry Number: 6211 - 15 - 0

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

SEVREDOL® tablets contain the following excipients: tablet core: anhydrous lactose, pregelatinised maize starch, povidone (K25), magnesium stearate and purified talc; film coat: hypromellose, macrogol 400 and Opadry 06B20843 (10 mg tablets) or Opaspray M-1-5503 pink (20 mg tablets).

PHARMACOLOGY

Actions
Morphine is a narcotic analgesic which exerts an agonist effect at specific, saturable opioid receptors in the central nervous system (CNS) and other tissues. In man, morphine produces a variety of effects including analgesia, constipation from decreased gastrointestinal motility, suppression of the cough reflex, respiratory depression from reduced responsiveness of the respiratory centre to carbon dioxide, nausea and vomiting via stimulation of the chemoreceptor trigger zone, changes in mood including euphoria and dysphoria, sedation, mental clouding, and alterations of the endocrine and autonomic nervous systems.

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. In man, the principal pharmacological actions of morphine are in the CNS: analgesia, drowsiness, mood changes, 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.
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 ones.

Pharmacokinetics
Absorption
Morphine is readily absorbed from the gastrointestinal tract, nasal mucosa, lung and after s.c. or i.m. 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 2 to 6 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, metabolism and elimination
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. 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-ethereal sulfate. The mean elimination half-life of morphine is 2 to 3 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 hydrolyzed and reabsorbed from the large bowel.

INDICATIONS
Treatment of chronic severe pain of cancer.

CONTRAINdications
Morphine should not be given to patients with hypersensitivity to opiate narcotics; 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 tumor; paralytic ileus; delayed gastric emptying, suspected surgical and acute abdominal conditions; severe liver disease; severe renal dysfunction, incipient hepatic encephalopathy; concomitant monoamine oxidase (MAO) inhibitors, or within 14 days of such therapy (see Interactions with other medicines). 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.

PRECAUTIONS
Drug dependence
As with other narcotics, tolerance and physical dependence develop upon repeated administration of morphine and there is potential for abuse of the drug and for development of
strong psychological dependence. Morphine sulfate should therefore not be prescribed for patients who have a prior history and 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 narcotic 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 a narcotic 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 by parenteral administration can be expected to result in serious adverse events, which can be fatal.

Morphine should be used only with caution and in reduced dosage during concomitant administration of other narcotic analgesics, general anaesthetics, phenothiazines and other tranquilizers, sedatives/hypnotics, tricyclic antidepressants and other CNS depressants, including alcohol. Respiratory depression, hypotension and profound sedation or coma may result.

General
Severe pain antagonizes 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 interruption of pain transmission pathways 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 new post-operative requirements.

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.

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.

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

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

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 should be used with extreme caution and only if it is judged essential.

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.
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.

Morphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions. 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.

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

Morphine-6-glucuronide may accumulate in patients with renal failure, leading to CNS and respiratory depression.

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.

Driving and operating dangerous machinery
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.

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
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. Long term use in pregnancy may result in a neonatal opioid withdrawal state.

Narcotic 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.

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

Interactions with other medicines
**Acidifying or alkalizing agents**
Generally, the effects of morphine may be antagonized 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.

**Anticholinergics**
Medicinal products that block the action of acetylcholine, for example antihistamines, anti-parkinsonians 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, generalized twitching and periods of apnoea persisted for 80 hours.

**CNS depressants**
The analgesic effect of morphine is potentiated by amphetamines, chlorpromazine and methocarbamol. CNS depressants, such as other opioids, anaesthetics, sedatives, hypnotics, tranquilisers, muscle relaxants, anti hypertensives, barbiturates, phenothiazines, tricyclic antidepressants, chloral hydrate and glutethimide may enhance the depressant effects of morphine. Morphine should be used with caution in patients who are currently taking gabapentin.

**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 the selective MAOIs (e.g. moclobemide and selegiline) and morphine, therefore caution is advised with this drug combination. Pyrazolidone antihistamines, beta-blockers and alcohol may also enhance the depressant effect of morphine. The interactive effects may include respiratory depression, hypotension, profound sedation and coma.
**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**  
Ritonavir may increase the activity of glucuronyl transferases, and co-administration with morphine may result in decreased morphine serum concentrations and possible loss of analgesic effectiveness.

**ADVERSE EFFECTS**  
The major hazards associated with morphine, as with other narcotic 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.

**Most common adverse effects requiring medical attention**  
The most frequently observed side effects of narcotic 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 realized. 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 narcotics or as an early, unwanted effect of regular narcotic 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 20 mg or more of morphine 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 narcotic-induced gastric stasis. In such patients, metoclopramide is often useful.

**Constipation**  
Practically all patients become constipated while taking narcotics on a regular basis. 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 narcotic therapy. Dietary modification, suitable
exercise, softeners, laxatives and other appropriate measures should be used as required.

Other adverse reactions (by body system) include:

**Cardiovascular disorders**
bradycardia, faintness, hypotension, palpitations, postural hypotension, supra-ventricular tachycardia, syncope

**Central nervous system and psychiatric disorders**
asthenia, confusional symptoms, dizziness, dysphoria, euphoria, headache, insomnia, involuntary muscle contractions, thought abnormalities, vertigo, weakness; occasionally, hallucinations; uncommonly, agitation, malaise, mood changes, paraesthesia, seizure, vision abnormalities

**Gastrointestinal disorders**
abdominal pain, anorexia, biliary tract cramps and biliary spasm, constipation, cramps, dry mouth, dyspepsia, gastrointestinal disorders, ileus, taste alterations; uncommonly, elevated hepatic enzymes

**Genitourinary disorders**
amenorrhoea, erectile dysfunction, reduced libido or potency, ureteric spasm, urinary retention or hesitancy

**Endocrine disorders**
uncommonly, pulmonary oedema, peripheral oedema and a syndrome of inappropriate antidiuretic hormone secretion characterized by hyponatremia secondary to decreased free-water excretion may be prominent (monitoring of electrolytes may be necessary)

**Respiratory disorders**
bronchospasm, cough decreased, respiratory depression

**General disorders**
allergic reaction, anaphylactic and anaphylactoid reactions, drug dependence, drug tolerance, facial flushing, hyperhidrosis, hypertonia, miosis, pruritus, urticaria, other skin rashes including contact dermatitis

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

The following withdrawal symptoms may be observed after narcotics 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 narcotics and gradual withdrawal from the drug, these symptoms are usually mild.
DOSAGE AND ADMINISTRATION

Administration and dosing of morphine should be individualized 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 narcotic 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 narcotics 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 drug 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 narcotic, the “oral morphine sulfate 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 dosage that should provide equivalent analgesia.

Table 1. Narcotics: Approximate analgesic equivalences

<table>
<thead>
<tr>
<th>Drug</th>
<th>Equivalent Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>i.m.</td>
</tr>
<tr>
<td>MORPHINE sulfate</td>
<td>10</td>
</tr>
<tr>
<td>OXYCODONE (Percodan, Endone, Proladone)</td>
<td>15</td>
</tr>
<tr>
<td>DEXTROMORAMIDE (Palfium)</td>
<td>15</td>
</tr>
<tr>
<td>PAPAVERETUM (Omnopon)</td>
<td>45</td>
</tr>
</tbody>
</table>


2. Dextromoramide - a single dose is equivalent to morphine 15mg (diamorphine 10mg) in terms of peak effect, but is shorter acting. The overall potency ratio has been adjusted.

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 realized. 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 narcotic dose should be made. Smaller doses or complete discontinuation of the narcotic analgesics may become feasible due to a change in the patient’s condition or improved mental state.

Narcotic agents do not relieve effectively dyesthetic 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 narcotic-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 relief.

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.

**OVERDOSAGE**

**Symptoms**

Serious morphine overdosage is characterized by, respiratory depression (reduced respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), miotic pupils, extreme somnolence progressing to stupor or coma, flaccidity of skeletal muscle, cold or clammy skin, and sometimes hypotension and bradycardia. Severe overdosage may result in apnoea, 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 narcotic 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, (i.v.) adult dose of naloxone is 0.4 mg or higher. 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 narcotics, the administration of the usual dose of narcotic 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 narcotic antagonists in such individuals should be avoided if possible. If a narcotic 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 overdosage but because of the great interindividual variation in sensitivity to opioids it is difficult to determine an exact dose of any opioid that is toxic or lethal.

The pressure of pain or tolerance tends to diminish the toxic effects of morphine. Published data suggest that in a morphine naïve, 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.

STORAGE CONDITIONS
SEVREDOL® tablets have a shelf life of 3 years when stored below 25°C.

PRESENTATION
SEVREDOL® tablets, 10 mg (blue), 20 mg (pink): packs of 20s. All SEVREDOL® tablets are film-coated, biconvex with a scoreline “IR” to the left and “10” or “20” to the right.

MANUFACTURER
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NAME AND ADDRESS OF THE SPONSOR
Mundipharma Pty Limited.
ABN 87 081 322 509
50 Bridge Street
SYDNEY, NSW 2000
TGA APPROVAL DATE
14 December 1993

POISON SCHEDULE OF THE MEDICINE
S8

DATE OF LATEST REVISION
4 February 2003 (Pharmaceutical aspects)
19 February 2003 (Safety change)
23 February 2004 (Safety change)
15 July 2004 (Safety change)
8 April 2005 (Safety change)
11 October 2008 (Safety change)
12 January 2009 (Safety change)
12 March 2010 (Minor editorial change)

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