

# DATA SHEET

## **SEVREDOL<sup>®</sup>**

### **Morphine sulphate 10 mg and 20 mg tablets**

#### **Presentation**

**SEVREDOL** tablets are capsule shaped, biconvex, scored, film-coated tablets approximately 12 mm in length with the strength on one side and "IR" on the other side of the score line. The colours of the tablets are as follows: 10 mg blue and 20 mg pink.

#### **Uses**

##### ***Actions***

Morphine is a potent opioid analgesic. It is about 8 times more potent than pethidine and 10 times more potent than codeine. Morphine combines selectively at opioid binding sites found in the CNS and smooth muscle to produce its pharmacologic effects. These are due to morphine mimicking the action of endogenous endorphins, which are released in response to pain and other stimuli. Morphine relieves most types of pain but is more effective against dull, constant pain than sharp, intermittent pain. Analgesia at the supraspinal level results principally from combination with ( $\mu$ ) receptors, and the ( $\kappa$ ) receptors are responsible primarily for expression of analgesia at the spinal level. In addition to relieving severe constant pain, morphine also alleviates the associated anxiety.

Pharmacological effects include analgesia, drowsiness, mental clouding and mood alteration (euphoria or dysphoria). Such effects may be common at first but tolerance develops on prolonged administration. Other centrally mediated effects include respiratory depression, nausea and vomiting, to which a high degree of tolerance also develops over time.

Morphine depresses the cough reflex by direct effect on the cough centre in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia. Morphine causes miosis, even in total darkness. Pinpoint pupils are a sign of narcotic overdose but are not pathognomonic (e.g., pontine lesions of haemorrhagic or ischaemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of morphine overdose.

Morphine causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm resulting in constipation.

Morphine may produce release of histamine with or without associated peripheral vasodilatation. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, flushing, red eyes, sweating and/or orthostatic hypotension.

The onset of action of **SEVREDOL** tablets is about 15-30 minutes after oral administration. The duration of action is 3-4 hours.

### ***Pharmacokinetics***

Morphine is well absorbed from the GI tract following administration of **SEVREDOL** tablets, however, it is subject to extensive first-pass metabolism in the liver. **SEVREDOL** tablets produce peak morphine levels approximately one hour post-dose. The elimination half-life of morphine is 2-3 hours with great interpatient variability.

Like other phenanthrene derivatives, morphine is mainly metabolised by glucuronide conjugation in the liver. The resultant metabolites are excreted primarily in the urine. The principal metabolites are active, although the relative contributions of these, and parent morphine, to the overall analgesic effect is unclear. The 6-glucuronide metabolite has been shown to be 10 times more potent than parent morphine, however, the 3-glucuronide metabolite may antagonise this effect.

Morphine is widely distributed through the body and diffuses across the placenta. Reduced dosing is necessary in patients with renal or hepatic dysfunction, and also in the elderly due to increased sensitivity to its effect.

### ***Indications***

**SEVREDOL** tablets are indicated for the relief of both acute and chronic severe pain in adults and children aged three years and above.

### **Dosage and Administration**

**SEVREDOL** tablets should be given every four hours. The dosage is dependent upon the nature and severity of the pain, the patient's condition and their previous history of analgesic therapy. A patient initially presenting with severe and intractable pain will normally be started on **SEVREDOL** 10 mg every 4 hours. This dose should be increased every 4 hours until the patient is free of pain. At that stage the patient should be transferred onto a long acting morphine preparation such as **MST CONTINUS** tablets.

To do this, add the amount of morphine needed to completely relieve pain over a 24-hour period. Divide this total in half, rounding up to nearest tablet strength and administer the long acting morphine preparation as a twice daily dose. The first dose of the long acting morphine preparation should be given with the last dose of **SEVREDOL** tablets. Any recurrence of pain will require an increase in the dose but not the frequency of the long acting morphine preparation. Breakthrough pain should be treated with **SEVREDOL** tablets, not extra long acting morphine.

There is no upper dose limit for morphine sulphate tablets. Patients on chronic oral morphine therapy have been known to take in excess of 3000 mg/day with no apparent toxicity or addiction. The dose of morphine used for individual patients must be that dose which completely eliminates their pain irrespective of how large it is.

Patients receiving morphine sulphate tablets in place of parenteral morphine should be given a sufficiently increased dosage to compensate for the reduction in analgesic effects associated with orally administered analgesics.

**SEVREDOL** tablets should be swallowed whole and not chewed unless half tablets are being used. The tablets are film coated to mask the bitter taste of morphine and this masking effect is lost if the tablets are broken.

**Children:** 3-5 years 5 mg 4 hourly. 6-12 years 5-10 mg 4 hourly.

**Elderly:** 5 mg 4 hourly increasing as necessary to completely relieve the pain.

## Contraindications

Morphine is contraindicated in patients

- with known morphine sensitivity
- with acute hepatic disease.
- with respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion.
- with acute alcoholism,
- With head injuries,
- in which intracranial pressure is raised.
- during an attack of bronchial asthma
- with heart failure secondary to chronic lung disease.
- who are taking or have taken monoamine oxidase inhibitors (MAOIs) within the previous two weeks
- with paralytic ileus, acute abdomen, or delayed gastric emptying
- for use as a pre-operative medication.
- with pheochromocytoma, as morphine appears to increase catecholamine levels.
- with chronic pain not due to malignancy who have a prior history of substance abuse.

## Warnings and Precautions

### Special risk patients

Morphine should be given with caution or in reduced doses in patients with impaired kidney or liver function, biliary tract disorders, the elderly, and in patients with Addison's disease, hypothyroidism, prostatic hypertrophy, raised intracranial pressure, hypotension with hypovolemia, pancreatitis, severe chronic obstructive lung disease, severe cor pulmonale, severe bronchial asthma or respiratory depression or urethral stricture.

Opioid analgesics such as morphine sulphate should be used with caution in patients with myasthenia gravis.

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

### Drug dependence and tolerance

Narcotic analgesics may cause respiratory depression and dependence in the newborn infant. Use in pregnancy and breast-feeding is therefore not recommended.

Morphine may impair the mental and/or physical abilities needed for driving a car or operating machinery. Patients should be cautioned accordingly.

As with other narcotics, 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. Drug abuse is not however, a problem in patients with severe pain in which morphine is appropriately indicated. Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control.

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 interruption of pain transmission pathways should not receive morphine sulphate tablets within 24 hours of the procedure.

Morphine has an abuse profile similar to other strong agonist opioids. Morphine may be sought and abused by people with latent or manifest addiction disorders. The development of psychological dependence to opioid analgesics in properly managed patients with pain has been reported to be rare.

### **Use With Other CNS Depressants**

Morphine should be used with caution and in reduced dosage in patients who are concurrently receiving other opioid analgesics, general anaesthetics, phenothiazines, other tranquillisers, sedative hypnotics, tricyclic antidepressants, and other CNS depressants (including alcohol). Respiratory depression, hypotension and profound sedation or coma may result.

### **Impaired Respiration**

The respiratory depressant effects of morphine and its capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. Furthermore, opioids produce adverse reactions, including confusion, miosis and vomiting, which may obscure the clinical course of patients with head injuries.

### **Hypotensive Effect**

The administration of morphine may result in severe hypotension in the post-operative patient or any individual whose ability to maintain blood pressure has been compromised by a depleted blood volume, shock, or the administration of such drugs as the phenothiazines or certain anaesthetics. Morphine may produce orthostatic hypotension in ambulatory patients.

### **Supraventricular Tachycardias**

Because of possible vagolytic action that may produce a significant increase in the ventricular response rate, morphine should be used with caution in patients with atrial flutter and other supraventricular tachycardias.

### **Acute Abdominal Condition**

The administration of morphine or other opioids may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Morphine should be used with caution in patients with inflammatory or obstructive bowel disorders, or with ulcerative colitis, and should only be used when necessary in patients with acute pancreatitis.

### **Renal or Hepatic Disease**

Morphine may have a prolonged duration and cumulative effect in patients with kidney or liver dysfunction. In these patients, analgesia may be prolonged.

Caution should be observed when morphine is administered to patients with impaired renal function, as the pharmacologically active metabolite, morphine-6-glucuronide, may accumulate in these patients. This may lead to CNS and respiratory depression.

### **Impairment of 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 and lactation:**

#### **Category C**

Morphine has been associated with foetal CNS defects in rodent studies. It is not known whether morphine can cause foetal harm in humans when administered during pregnancy. Pregnant patients should only be given morphine when the benefits clearly outweigh potential risks to the foetus.

Long term use of morphine during pregnancy may result in a neonatal opioid withdrawal state. Babies born to mothers who are physically dependent on morphine may also be physically dependent on the drug.

Morphine is excreted in human milk and breast-feeding is not recommended while a patient is receiving morphine. Withdrawal symptoms have been observed in breast-fed infants when maternal administration of morphine is stopped.

### **Effects on ability to drive and use machines:**

Morphine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. Morphine in combination with other opioid analgesics, phenothiazines, sedative-hypnotics and alcohol has additive depressant effects. Patients should be cautioned accordingly.

## Adverse Effects

The adverse effects listed below are classified by body system according to their incidence (common [ $\geq 1\%$ ] or uncommon [ $< 1\%$ ]).

### Gastrointestinal

*Common*

abdominal pain  
anorexia  
constipation  
dry mouth  
dyspepsia  
nausea

*Uncommon*

vomiting  
biliary pain  
gastrointestinal disorders  
ileus  
taste perversion

### Central Nervous System

*Common*

asthenia  
confusion  
headache  
insomnia  
involuntary muscle contractions  
somnolence

*Uncommon*

thought abnormalities  
agitation  
dysphoria  
euphoria  
hallucinations  
malaise  
mood changes  
respiratory depression  
seizure  
vertigo  
vision abnormalities  
withdrawal syndrome

### Genitourinary

*Uncommon*

amenorrhea  
decreased libido  
impotence  
urinary retention  
hypogonadism

### Cardiovascular

*Uncommon*

hypotension  
syncope

### Metabolic and Nutritional

*Uncommon*

peripheral edema  
pulmonary edema

## Respiratory

*Common*

bronchospasm  
cough decreased  
respiratory depression

## Dermatological

*Common*

rash

*Uncommon*

urticaria

## General

*Common*

chills

pruritus

sweating

*Uncommon*

allergic reaction

anaphylactic/anaphylactoid reactions

drug dependence

facial flushing

hypertonia

miosis

tolerance

### **Withdrawal (Abstinence) Syndrome:**

Chronic use of opioid analgesics may be associated with the development of physical dependence, with or without psychological dependence. An abstinence syndrome may be precipitated when opioid administration is suddenly discontinued or opioid antagonists administered.

Withdrawal symptoms that may be observed after discontinuation of opioid use include; body aches, diarrhoea, piloerection, anorexia, nervousness or restlessness, rhinorrhoea, sneezing, tremors or shivering, abdominal colic, nausea, sleep disturbance, unusual increase in sweating and yawning, weakness, tachycardia and unexplained fever. With appropriate dose adjustments and gradual withdrawal these symptoms are usually mild.

## Interactions

Acidifying agents generally increase the clearance of morphine, thus antagonising its effects, while alkalisating agents decrease clearance and so potentiate the effects of morphine.

**CNS Depressants:** Morphine should be used with great caution and in reduced dosage in patients concurrently receiving other central nervous system depressants including other opioids, sedatives, hypnotics, general anaesthetics, phenothiazines, other tranquillisers and alcohol because of the risk of respiratory depression, hypotension and profound sedation or coma. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Significant impairment of motor function has also been noted following concomitant morphine administration and alcohol ingestion.

Concurrent administration with tricyclic antidepressants or beta-blockers may enhance the CNS depressant effects of morphine.

Diazepam, when used following high doses of morphine, exacerbates the hypotensive effects produced by morphine, and is associated with reduced plasma catecholamine levels.

**Antihypertensive Agents:** Concurrent administration of morphine may increase the hypotensive effects of antihypertensive agents or other drugs with hypotensive effects.

**Muscle Relaxants:** Morphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

**Mixed Agonist/Antagonist Opioid Analgesics:**

From a theoretical perspective, mixed agonist/antagonist opioid analgesics (e.g. pentazocine and buprenorphine) should **NOT** be administered to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic. In these patients, mixed agonist/antagonist analgesics may reduce the analgesic effect or may precipitate withdrawal symptoms.

**Monoamine Oxidase Inhibitors (MAOIs):**

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

**Cimetidine and Other H<sub>2</sub> Receptor Antagonists:**

There is a report of confusion and severe respiratory depression when a haemodialysis patient was administered morphine and cimetidine. A potentially lethal interaction between cimetidine and morphine, in which the patient exhibited apnoea, a significantly reduced respiratory rate and suffered a grand mal seizure, has been reported. Administration of naloxone increased the respiratory rate; however, confusion, disorientation, generalised twitching and periods of apnoea persisted for 80 hours. Confusion has also been associated with concomitant use of ranitidine and morphine.

**Diuretics:**

Morphine reduces the efficacy of diuretics by inducing the release of antidiuretic hormone. Morphine may also lead to acute retention of urine by causing spasm of the sphincter of the bladder, particularly in men with prostatism.

**Phenothiazines:**

The analgesic effect of morphine is potentiated by chlorpromazine.

**Amphetamines:**

Dexamphetamine and other amphetamines may enhance the analgesic effects, and decrease the sedation and lack of alertness caused by morphine.

**Anticoagulants:**

Morphine may potentiate the anticoagulant activity of coumarin anticoagulant agents.

**Metoclopramide:**

Morphine may antagonise the effects of metoclopramide on gastrointestinal motility. Intravenous metoclopramide antagonises the effects of morphine on gastric emptying.

**Zidovudine:**

Morphine may alter the metabolism of zidovudine, by competitively inhibiting glucuronidation or directly inhibiting hepatic microsomal metabolism. Zidovudine and morphine should therefore not be administered concurrently, because the toxicity of either or both of these drugs may be increased.

**Ritonavir:**

Ritonavir may increase the activity of glucuronyl transferases and co-administration with morphine may result in decreased morphine serum levels and possible loss of analgesic activity.

**Oral Drugs:**

Morphine delays gastric emptying, so may affect the absorption of orally administered drugs. For example, morphine delays the absorption of paracetamol and mexiletine.

**Anticholinergic Agents:**

Concurrent administration of morphine and anticholinergic agents or other drugs with anticholinergic activity may increase the risk of severe constipation; this may lead to paralytic ileus and/or urinary retention.

**Antidiarrhoeal Agents:**

Concurrent administration of morphine and antidiarrhoeal agents with antiperistaltic actions may increase the risk of severe constipation and CNS depression.

**Opioid Antagonists:**

Naloxone antagonises the analgesic, CNS and respiratory depressive effects of morphine, and may precipitate withdrawal in patients who are physically dependent on opioids. Naltrexone blocks the therapeutic effects of opioids, so should be discontinued several days prior to elective surgery if administration prior to, during, or following surgery is unavoidable. Administration of naltrexone to a patient who is physically dependent on morphine will precipitate withdrawal symptoms.

**Effect on Laboratory Tests:**

Morphine delays gastric emptying, thereby invalidating test results in gastric emptying studies. Morphine may interfere with hepatobiliary imaging using technetium  $T_{C99m}$  diosfenin. Morphine may constrict the sphincter of Oddi and increase biliary tract pressure, preventing delivery of  $T_{C99m}$  diosfenin to the small bowel. These actions result in delayed visualisation, and thus resemble obstruction of the common bile duct.

## Overdosage

Symptoms: serious morphine overdosage is characterised by respiratory depression, 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.

The triad of coma, pinpoint pupils, & respiratory depression is considered indicative of overdosage; dilatation of the pupils occurs as hypoxia develops.

**Treatment**

Immediate attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. In patients physically dependent on opioids, respiratory support is the first line of treatment. In these patients, the use of naloxone is potentially dangerous. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated.

The opioid antagonist, naloxone, is a specific antidote against respiratory depression which may result from overdosage or unusual sensitivity to opioids. The recommended adult dose of naloxone for the treatment of severe opiate induced respiratory depression is 0.4 to 2 mg intravenously every 2 to 3 minutes as necessary, simultaneously with assisted respiration.

For children, the initial dose recommended is 0.01 mg/kg naloxone. A response should be seen after 2 to 3 doses. Note the duration of action of naloxone is usually shorter than that of morphine and thus the patient should be carefully observed for signs of CNS depression returning.

If the response to naloxone is suboptimal or not sustained, additional naloxone may be administered as needed, or given by continuous intravenous infusion to maintain alertness and respiratory function. There is no information available about the cumulative dose of naloxone that may be safely administered.

Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdosage.

Naloxone should be administered cautiously to persons who are known or suspected to be physically dependent on morphine. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. If it is necessary to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care and by titration with smaller than usual doses of the antagonist.



Morphine toxicity may be a result of overdosage but because of the large inter-individual variation in sensitivity to opioids, it is difficult to assess the exact dose of any opioid that is toxic or lethal. The toxic effects of morphine tend to be overshadowed by the presence of pain or tolerance. Patients having chronic morphine therapy have been known to take in excess of 3,000 mg/day with no apparent toxic effects being present.

## Pharmaceutical Precautions

Store below 30 °C. Protect from light and moisture. Keep out of reach of children.

## Medicine Classification

Controlled Drug B1.

## Package Quantities

10 mg and 20 mg tablets, packed in 10's

## Further Information

Morphine sulphate is the pentahydrate of the sulphate of 7,8-didehydro-4,5-epoxy-17-methyl morphinan-3,6-diol. It has a molecular formula and weight of  $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$  and 758.8 respectively.

**SEVREDOL** tablets are substitutable with oral morphine solution when titrating for pain relief or treating break through pain.

Other ingredients of the tablets are:

### **10 mg tablet:**

*Core:* Lactose anhydrous, Pregelatinised maize starch, Povidone K25, Magnesium stearate and Purified talc.

*Coat:* Hydroxypropylmethyl cellulose, Polyethylene glycol 400 and Opadry 06B20843.

### **20 mg tablet:**

*Core:* Lactose anhydrous, Pregelatinised maize starch, Povidone K25, Magnesium stearate and Purified talc.

*Coat:* Hydroxypropylmethyl cellulose, Polyethylene glycol 400 and Opaspray M-1-5503.

## Name and Address

Douglas Pharmaceuticals Ltd  
PO Box 45-027, Auckland 0651  
New Zealand  
Ph: (09) 835-0660. Fax: (09) 835-0665

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