

DATA SHEET

SEVREDOL®

Morphine sulphate 10 mg, 20 mg and 50 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, 20 mg pink and 50 mg green.

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 μ (μ) receptors, and the κ (κ) 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.

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 generally contraindicated in respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion. It is also contraindicated in the presence of acute alcoholism, head injuries, and conditions in which intracranial pressure is raised. It should not be given during an attack of bronchial asthma or in heart failure secondary to chronic lung disease. **SEVREDOL** tablets are contraindicated in patients with paralytic ileus and or acute abdomen.

Concurrent administration with monoamine oxidase inhibitors (MAOIs) or within two weeks of discontinuation is contraindicated.

Warnings and Precautions

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.

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.

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.

Use in Pregnancy and lactation: **SEVREDOL** tablets are not recommended for use in pregnancy. Although morphine has been reported to be secreted in breast milk, clinically important concentrations of the drug are probably not present following usual therapeutic doses.

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.

Effects on ability to drive and use machines: Morphine may modify the patient's reactions to a varying extent depending on the dosage and individual susceptibility.

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
vomiting

Uncommon

biliary pain
gastrointestinal disorders
ileus
taste perversion

Central Nervous System

Common

asthenia
confusion
headache
insomnia
involuntary muscle contractions
somnolence
thought abnormalities

Uncommon

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

Genitourinary

Uncommon

amenorrhea
decreased libido
impotence
urinary retention

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

Interactions

SEVREDOL tablets can be readily combined with the phenothiazines but it should be noted that morphine potentiates the effects of tranquillisers, anaesthetics, hypnotics and sedatives.

Pyrazolidene antihistamines, beta-blockers and alcohol may also enhance the depressant effect of morphine. Morphine may increase the anticoagulant activity of coumarin and other anticoagulants.

From a theoretical perspective, agonist/antagonist analgesics (ie. pentazocine, nalbuphine, butorphanol 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 the analgesic effect may be reduced or withdrawal symptoms may be precipitated.

Morphine should not be given to patients receiving monoamine oxidase inhibitors or within fourteen days of their discontinuation.

Morphine may competitively inhibit the hepatic glucuronidation of zidovudine thus reducing its clearance. Concurrent use of **SEVREDOL** and zidovudine should be avoided because the toxicity of either or both medicines may be potentiated.

Cimetidine inhibits the metabolism of morphine.

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.

In acute poisoning by **SEVREDOL** tablets taken by mouth, the stomach should be emptied by aspiration and lavage. A laxative may be given to aid peristalsis.

Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation.

In the case of massive overdosage, administer naloxone 0.8 mg intravenously. Repeat at 2-3 minute intervals as necessary, or by infusion of 2 mg in 500 ml of normal saline or 5% dextrose (0.004 mg/ml).

The infusion should be run at a rate related to the previous bolus doses administered and should be in accordance with the patient's response. However, because the duration of action of naloxone is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established. For less severe overdosage, administer naloxone 0.2 mg intravenously followed by increments of 0.1 mg every 2 minutes if required.

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.

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, 20 mg and 50 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.

50 mg tablet:

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

Coat: Hydroxypropylmethyl cellulose, Polyethylene glycol 400 and Opadry OY-21037.

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