

# **MST CONTINUS**<sup>®</sup>

Morphine sulphate 10mg, 30mg, 60mg, 100mg, 200mg, controlled-release tablets

## **Presentation**

**MST CONTINUS**<sup>®</sup> tablets are circular, biconvex, film-coated tablets with the strength on one side and NAPP on the other. The colour of the tablets are as follows: 10 mg brown, 30 mg purple, 60 mg orange, 100 mg grey, and 200 mg teal green.

## **Uses**

### **Actions**

Morphine is a potent opioid analgesic with no antagonistic properties. 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  $\mu$  ( $\mu$ ) receptors.  $\kappa$  ( $\kappa$ ) 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 vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating and/or orthostatic hypotension.

The onset of action of **MST CONTINUS**<sup>®</sup> tablets is about 30-45 minutes after oral administration and, due to its slow release formulation, the duration of action is 12 hours.

### **Pharmacokinetics**

Morphine is well absorbed from the GI tract following administration of **MST CONTINUS**<sup>®</sup> tablets, however, it is subject to extensive first-pass metabolism in the liver. At steady state, **MST CONTINUS**<sup>®</sup> tablets produce peak morphine levels approximately 4-5 hours post-dose and therapeutic levels are maintained for a 12 hour period. The elimination half-life of morphine is 2-3 hours with great interpatient variability.

The major metabolic transformation of morphine is glucuronidation to morphine-3-glucuronide and morphine-6-glucuronide which then undergo renal excretion. These metabolites are excreted in bile and may be subject to hydrolysis and subsequent reabsorption.

Because of the high inter-patient variation in morphine pharmacokinetics, and in analgesic requirements, the daily dosage in individual patients must be titrated to achieve appropriate pain control. Daily doses of up to 11.2g have been recorded from twelve-hourly **MST CONTINUS**<sup>®</sup> tablets.

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**

**MST CONTINUS**<sup>®</sup> tablets are indicated for the prolonged relief of opioid responsive severe and intractable pain.

### **Dosage And Administration**

**MST CONTINUS**<sup>®</sup> tablets should be used twice daily. 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 a morphine sulphate immediate release dose form such as **SEVREDOL**<sup>®</sup> tablets, 10 mg every 4 hours. This dose should be increased every 4 hours until the patient is free of pain at which point the patient should be transferred onto **MST CONTINUS**<sup>®</sup> tablets.

Transfer onto **MST CONTINUS**<sup>®</sup> tablets is performed as follows:

Add up the total amount of morphine needed to completely relieve pain over a 24 hour period.

1. Divide this total in half, & round the answer up to nearest **MST CONTINUS**<sup>®</sup> tablet strength.
2. Administer the resulting **MST CONTINUS**<sup>®</sup> tablet dose twice daily.

The first dose of **MST CONTINUS**<sup>®</sup> tablet should be given with the last dose of the morphine sulphate immediate release dose form used to initiate treatment. Any recurrence of pain will require an increase in the dose but not the frequency of **MST CONTINUS**<sup>®</sup> tablets. Breakthrough pain should be treated with immediate release morphine sulphate dose forms, not extra **MST CONTINUS**<sup>®</sup> tablets.

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

Patients receiving **MST CONTINUS**<sup>®</sup> 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.

**MST CONTINUS**<sup>®</sup> tablets must be swallowed whole, and not broken, chewed or crushed. The administration of opened, chewed or crushed **MST CONTINUS**<sup>®</sup> tablets leads to a rapid release and absorption of a potentially fatal dose of morphine.

At times, oral dosing may be inappropriate as a result of vomiting, dysphagia, decreased level of consciousness or following an anaesthetic. In patients with good pain control, it is beneficial to continue use of **MST CONTINUS**<sup>®</sup> by the rectal route of administration. This route offers many advantages to subcutaneous or intravenous infusion otherwise given.

When changing from oral to rectal administration, the same dose and dose interval is used initially, with adjustments being made according to clinical response. In this way pain control is maintained and it is practical in the home setting.

### **Children**

**MST CONTINUS**<sup>®</sup> tablets are not recommended for paediatric use.

### **Contraindications**

Morphine is contraindicated in known morphine sensitivity and in acute hepatic disease.

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.

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

**MST CONTINUS**<sup>®</sup> tablets are contraindicated in patients with paralytic ileus, acute abdomen, or delayed gastric emptying.

**MST CONTINUS**<sup>®</sup> tablets are not to be used as a pre-operative medication.

**MST CONTINUS**<sup>®</sup> tablets should not be used in patients with pheochromocytoma, as morphine appears to increase catecholamine levels.

**MST CONTINUS**<sup>®</sup> tablets are contraindicated in infants under 1(one) year of age.

**MST CONTINUS**<sup>®</sup> tablets are contraindicated in patients with chronic pain not due to malignancy who have a prior history of substance abuse.

### **Warnings and Precautions**

**As MST CONTINUS**<sup>®</sup> tablets is a controlled release preparation **MST CONTINUS**<sup>®</sup> must be **swallowed whole and not broken, crushed or chewed**. The administration of opened, chewed or crushed **MST CONTINUS**<sup>®</sup> tablets leads to a rapid release and absorption of a potentially fatal dose of morphine. 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 to morphine may develop upon repeated administration and there is potential for abuse of the drug and for development of strong psychological dependence. However, drug abuse is not a problem in patients with severe pain in which morphine is appropriately indicated. Patients on prolonged morphine therapy for pain relief should be withdrawn gradually from the drug if it is no longer required.

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 **MST CONTINUS**<sup>®</sup> tablets within 24 hours of the procedure. Pain in the immediate pre-operative period, and any symptoms of opioid withdrawal, should be managed with short acting analgesic agents.

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 Non-Malignant Pain**

The use of **MST CONTINUS**<sup>®</sup> tablets for the treatment of pain which is not due to malignancy should be restricted to situations where:

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

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. However, data are not available to establish the true incidence of psychological dependence in chronic pain patients. **MST CONTINUS**<sup>®</sup> tablets should be used with particular care in patients with a history of

alcohol and drug abuse.

Prior to long term prescription, a trial of **MST CONTINUS**<sup>®</sup> tablets or shorter acting opioids should be undertaken (e.g. for a period of four to six weeks). Long term administration of **MST CONTINUS**<sup>®</sup> tablets should only occur if this trial demonstrates that the pain is opioid sensitive. Opioid naive patients who require rapid dose escalation with no concomitant pain relief within the trial period should generally be considered inappropriate for long term therapy.

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

Prescribers should consult appropriate clinical guidelines on the use of opioid analgesics in such patients (e.g. Jones D & Shug S., *Opioids in Chronic Pain of Non-Malignant Origin: An Interim Consensus* NZMJ 108: 492, 24 November 1995).

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

### **Use in Pregnancy and lactation**

**MST CONTINUS**<sup>®</sup> 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

- elevated hepatic enzymes
- 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
- paresthesia
- 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**

Although morphine potentiates the effects of tranquillisers, anaesthetics, hypnotics, and sedatives, **MST CONTINUS**<sup>®</sup> tablets may be used in combination (at reduced dose) with phenothiazines. Interactive effects resulting in respiratory depression hypotension, profound sedation, or coma may result if these medicines are taken in combination with the usual doses of morphine.

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, partial opioid agonists (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 monamine 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 **MST CONTINUS**<sup>®</sup> tablets 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 **MST CONTINUS**<sup>®</sup> tablets taken by mouth, the stomach should be emptied by aspiration and lavage. 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 reestablished. **MST CONTINUS**<sup>®</sup> tablets will continue to release and add to the morphine load for up to 12 hours after administration and the management of morphine overdosage should be modified accordingly.

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.

Since **MST CONTINUS**<sup>®</sup> tablet is a sustained release tablet, tablets remaining in the intestine will continue to release morphine sulphate for a period of hours. Gastroscopy should be performed even if spontaneous vomiting has occurred. This should apply even if 12-24 hours have elapsed since ingestion as the sustained release nature of the preparations means absorption can continue over this time. In large overdoses, aggressive measures are indicated including removal of the contents of the stomach and small intestine under endoscopy, intestinal lavage, use of repeated doses of activated charcoal, cathartics and high enemas.

Crushing and taking the contents of **MST CONTINUS**<sup>®</sup> tablets leads to the release of the morphine in an immediate fashion: this might result in a fatal overdose.

### **Pharmaceutical Precautions**

Store below 30°C. Keep out of reach of children.

### **Medicine Classification**

Controlled Drug B1.

### **Package Quantities**

10 mg, 30 mg, 60 mg, 100 mg and 200 mg Tablets. Packed in cartons of 10 tablets.

**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.

Other ingredients of the tablets are:

**10 mg tablets:**

*Core:* Lactose anhydrous, Hydroxyethylcellulose, Cetostearyl alcohol, Magnesium stearate and Purified talc.

*Coat:* Hypromellose, Opaspray M-1-3705B tan and Macrogol 400.

**30 mg tablets:**

*Core:* Lactose anhydrous, Hydroxyethylcellulose, Cetostearyl alcohol, Magnesium stearate and Purified talc.

*Coat:* Opadry OY-6708 violet.

**60 mg tablets**

*Core:* Lactose anhydrous, Hydroxyethylcellulose, Cetostearyl alcohol, Magnesium stearate and Purified talc.

*Coat:* Opadry OY-3508 orange.

**100 mg tablets:**

*Core:* Hydroxyethylcellulose, Cetostearyl alcohol, Magnesium stearate and Purified talc.

*Coat:* Opadry OY-8215.

**200 mg tablets:**

*Core:* Hydroxyethylcellulose, Cetostearyl alcohol, Magnesium stearate and Purified talc.

*Coat:* Opadry 06B21168, Macrogol 400.

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