PROFESSIONAL INFORMATION

SCHEDULING STATUS

S6

1 NAME OF THE MEDICINE

MST CONTINUS® 10 mg tablet

MST CONTINUS® 30 mg tablet

MST CONTINUS® 60 mg tablet

MST CONTINUS® 100 mg tablet

Strength

10 mg

30 mg

60 mg

100 mg

Pharmaceutical form

Prolonged release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Qualitative declaration

Morphine sulphate

Quantitative declaration

Each MST CONTINUS® 10 mg tablet contains morphine sulphate 10 mg in a controlled-release matrix. Contains sugar: lactose 90 mg.

Each MST CONTINUS® 30 mg tablet contains morphine sulphate 30 mg in a controlled-release matrix. Contains sugar: lactose 70 mg.

Each MST CONTINUS® 60 mg tablet contains morphine sulphate 60 mg in a controlled-release matrix. Contains sugar: lactose 40 mg.

Each MST CONTINUS® 100 mg tablet contains morphine sulphate 100 mg in a controlled-release matrix. Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-Release Tablets.

MST CONTINUS® 10 mg tablet: Golden brown, film-coated, biconvex tablets marked 10 mg on one side and NAPP on the other.

MST CONTINUS® 30 mg tablet: Purple, film-coated, biconvex tablets marked 30 mg on one side and NAPP on the other.

MST CONTINUS® 60 mg tablet: Orange, film-coated, biconvex tablets marked 60 mg on one side and NAPP on the other.

MST CONTINUS® 100 mg tablet: Grey, film-coated, biconvex tablets marked 100 mg on one side and NAPP on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the relief of severe and intractable pain not controlled with non-narcotic analgesics.

4.2 Posology and method of administration

Posology

MST CONTINUS® tablets should be taken twice daily.

The dosage is dependent upon the severity of pain and the patient's previous history of analgesic therapy.

A patient with intractable pain due to cancer, will normally be started on a dosage of one or two MST CONTINUS® 10 mg tablets twice daily.

Increases in pain or tolerance to the medicine will require increases in dosage using MST CONTINUS® 10 mg, 30 mg, 60 mg and 100 mg tablets alone or in combination.

When substituting MST CONTINUS® tablets for parenteral morphine, patients should be given a sufficiently increased dosage to compensate for the reduction in analgesic effects associated with orally administered morphine.

Method of administration

MST CONTINUS® tablets should be swallowed whole and not chewed.

4.3 Contraindications

- Hypersensitivity to morphine sulphate or any of the excipients (see section 6.1);
- Phaeochromocytoma;
- Respiratory depression, obstructive airways disease;
- Acute alcoholism and consumption of alcoholic beverages while on MST CONTINUS® therapy (see section 4.4);
- Head injuries and conditions in which intracranial pressure is raised;
- After operation of the biliary tract;
- Acute bronchial asthma or heart failure secondary to chronic lung disease;
- Paralytic ileus, delayed gastric emptying;
- Acute hepatic disease;
- Concurrent administration of monoamine oxidase inhibitors (MAO-I) or within two weeks of discontinuation of treatment with them (see section 4.5);
- Comatose patients, pre-operative use, or for the first 24 hours post-operatively;

- Pregnancy and lactation;
- Paediatric use.

4.4 Special warnings and precautions for use

MST CONTINUS® IS A SUSTAINED RELEASE FORMULATION.

THE TABLETS MUST BE SWALLOWED WHOLE AND MUST NOT BE CHEWED, CRUSHED, OR DISSOLVED DUE TO THE RISK OF RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF MORPHINE (see section 4.9).

MST CONTINUS® must be administered with caution in patients with:

- Severely impaired respiratory function
- Respiratory depression (see below)
- Severe cor pulmonale
- Sleep apnoea
- CNS depressants co-administration (see section 4.5)
- Medicine dependence, tolerance and potential for abuse (see below)
- Medicine withdrawal syndrome (see below)
- Hypotension with hypovolemia
- Biliary tract disorder

Asthma and Respiratory depression:

The major risk of opioid excess is respiratory depression.

MST CONTINUS® should be given in reduced doses or with caution to patients with asthma or decreased respiratory reserve (including cor pulmonale, kyphoscoliosis, emphysema, severe obesity). Avoid use during an acute asthma attack (see section 4.3).

Opioids may cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use may increase the risk of CSA in a dose-dependent manner in some patients. Opioids may also cause worsening of pre-existing sleep apnoea (see section 4.8). In patients who present with CSA, consider decreasing the total opioid dosage.

Alcohol:

MST CONTINUS® should be used with particular care in patients with a history of alcohol and drug abuse (see section 4.8 c).

Patients must not consume alcoholic beverages while on MST CONTINUS® therapy. Additionally, patients must not use prescription or non-prescription medications containing alcohol while on MST CONTINUS® therapy (see section 4.3).

CNS depressants co-administration:

Concomitant use of MST CONTINUS® and central nervous system depressants such as benzodiazepines, anaesthetics, hypnotics and phenothiazines may result in sedation, respiratory depression, coma and death. If a decision is made to prescribe Morphine concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible. Patients should be monitored closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

MST CONTINUS® must be given with caution, or in reduced doses, to patients with hypothyroidism, adrenocortical insufficiency, impaired kidney or liver function, prostatic

hypertrophy, myasthenia gravis, hypotension with hypovolaemia, shock, or in patients with inflammatory or obstructive bowel disorders.

The dosage should be reduced in the elderly and debilitated patient.

MST CONTINUS® should also be used with caution in patients with convulsive disorders, opioid dependency and pancreatitis.

Biliary tract disorders:

Morphine can cause an increase in intrabiliary pressure and spasm as a result of its effects on the sphincter of Oddi; therefore, patients with diseases of the biliary tract should be monitored for worsening of symptoms while administering morphine.

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

MST CONTINUS® should be used with caution in patients with constipation.

Opioids, such as MST CONTINUS®, 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.

Acute chest syndrome (ACS) in patients with sickle cell disease (SCD):

Due to a possible association between ACS and morphine use in SCD patients treated with morphine during a vaso-occlusive crisis, close monitoring for ACS symptoms is warranted.

Lactose intolerance:

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption, should not take the 10 mg, 30 mg and 60 mg MST CONTINUS® tablets.

Medicine dependence, tolerance and potential for abuse:

For all patients, prolonged use of this product may lead to medicine dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g. major depression).

Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse or addiction.

The clinical need for analgesic treatment should be reviewed regularly.

Medicine withdrawal syndrome:

Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with morphine.

Medicine withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose

gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

The opioid medicine withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

Neonatal abstinence syndrome:

Infants born to opioid-dependent mothers may suffer withdrawal reactions.

Hyperalgesia:

Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

4.5 Interaction with other medicines and other forms of interaction

Alcohol: See section 4.4.

MAO Inhibitors:

Monoamine oxidase inhibitors (MAOIs) markedly potentiate the action of morphine.

MST CONTINUS® should not be used in patients taking MAOIs or within two weeks of discontinuation of treatment with them (see section 4.3).

Central nervous system (CNS) depressants:

The depressant effects of morphine are enhanced by depressants of the central nervous system such as alcohol, other opioids, anaesthetics, hypnotics and sedatives (including benzodiazepines), tricyclic antidepressants, antipsychotics, gabapentin and phenothiazines. Interactive effects resulting in an increased risk of respiratory depression, hypotension, profound sedation, coma or death may occur if these medicines are taken in combination with the usual doses of MST CONTINUS®. The dose and duration of concomitant use should be limited. (see section 4.4).

Muscle relaxants:

MST CONTINUS® may enhance the degree of respiratory depression induced by neuromuscular blocking agents.

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 such as MST CONTINUS®.

Histamine H^2 receptor antagonists:

Cimetidine inhibits the metabolism of some opioids.
Concomitant administration of morphine and cimetidine has been reported to precipitate apnoea, confusion and muscle twitching in an isolated report.
Patients should be monitored for increased respiratory and CNS depression when receiving cimetidine concomitantly with MST CONTINUS®.

Antibacterial agents:

Rifampicin may reduce the plasma concentration of morphine.

Antiviral agents:

Although there are no pharmacokinetic data available for concomitant use of ritonavir with MST CONTINUS®, ritonavir induces the hepatic enzymes responsible for the glucuronidation of morphine, and may possibly decrease plasma concentrations of morphine.

Metoclopramide:

Metoclopramide may increase the rate of onset and degree of sedation when given concomitantly with delayed-release morphine such as MST CONTINUS®.

4.6 Fertility, pregnancy and lactation

Pregnancy:

MST CONTINUS® tablets are contraindicated during pregnancy and lactation (see section 4.3).

Infants born to mothers taking MST CONTINUS® may suffer withdrawal reactions.

Fertility:

Animal studies have shown that morphine may reduce fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Ambulant patients should be warned against driving or handling dangerous machinery as MST CONTINUS® may modify the patient's reactions to a varying extent depending on the dosage and susceptibility.

If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

a. Summary of safety profile

Frequent side effects are nausea, vomiting, constipation, drowsiness, confusion and headache.

Tolerance to these effects generally develops with long-term use, but not to constipation.

b. Tabulated list of adverse reactions

Undesirable Effects	Common	Uncommon	Unknown
Immune system disorders		Anaphylactic reaction Anaphylactoid reaction Hypersensitivity	
Psychiatric disorders	Confusion Insomnia	Agitation Medicine dependence Dysphoria Euphoria Hallucinations Mood altered Thinking disturbances	
Nervous system disorders	Dizziness Headache Involuntary muscle contractions Somnolence	Convulsions Hyperalgesia Hypertonia Paraesthesia Syncope	Allodynia Sleep apnoea syndrome

Undesirable Effects	Common	Uncommon	Unknown
Eye disorders		Eye pain Miosis Visual disturbance	
Ear and labyrinth disorders		Vertigo	
Cardiac disorders		Bradycardia Palpitations Tachycardia	
Vascular disorders		Facial flushing Hypotension Hypertension	
Respiratory, thoracic and mediastinal disorders		Bronchospasm Cough decreased Pulmonary oedema Respiratory depression	
Gastrointestinal disorders	Abdominal pain Anorexia Constipation Dry mouth Nausea Vomiting	Dyspepsia Gastrointestinal disorders Ileus Taste perversion	

Undesirable Effects	**Common**	**Uncommon**	**Unknown**
Hepatobiliary disorders	Exacerbation of pancreatitis	Biliary pain Increased hepatic enzymes	Sphincter of Oddi dysfunction
Skin and subcutaneous tissue disorders	Hyperhidrosis Rash	Dry skin Pruritus Urticaria	
Renal and urinary disorders		Difficulty in micturition Uretric spasm Urinary retention	
Reproductive system and breast disorders		Abnormal ejaculation Amenorrhoea Decreased libido Erectile dysfunction	
General disorders and administration site conditions	Asthenia Fatigue Malaise Pruritus	Medicine tolerance Medicine withdrawal syndrome Medicine withdrawal syndrome neonatal	

Undesirable Effects	Common	Uncommon	Unknown
		Hypothermia Peripheral oedema	

Adverse events identified through post marketing experience

Adverse Event	Rare
Gastrointestinal disorders	Increased risk of abdominal pain, including pancreatitis has been reported.

c. Tolerance, dependence and withdrawal:

The patient may develop tolerance to morphine with chronic use and require progressively higher doses of MST CONTINUS® to maintain pain control.

Prolonged use of MST CONTINUS® may lead to physical dependence and a withdrawal syndrome may occur upon abrupt cessation of therapy.

When a patient no longer requires therapy with morphine, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

MST CONTINUS® has an abuse profile similar to other strong agonist opioids.

MST CONTINUS® may be sought and abused by people with latent or manifest addiction disorders. There is potential for development of psychological dependence (addiction) to opioid analgesics, including morphine.

MST CONTINUS® should be used with particular care in patients with a history of alcohol and drug abuse.

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

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

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.
Alternatively report to the following e-mail address: ZADrugsafety@mundipharma.co.za

4.9 Overdose

Crushing and taking the contents of MST CONTINUS®, a prolonged-release dosage form, leads to the release of the morphine in an immediate fashion; this might result in a fatal overdose.

Symptoms:

Acute overdosage with MST CONTINUS® is manifested by respiratory depression, somnolence progressing to stupor or coma, pneumonia aspiration, skeletal muscle flaccidity, cold and clammy skin, pin-point pupils, rhabdomyolysis progressing to renal failure and, in some cases, pulmonary oedema, bradycardia, hypotension with circulatory failure, coma and death.

Treatment:

Activated charcoal may be given by mouth in conscious patients if a substantial overdose has been ingested within 1 hour or so; it should be considered in all patients if a substantial amount of a sustained release product has been ingested.

Primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation when an overdose of an extended-release formulation such as MST CONTINUS® has been ingested.

Intensive supportive therapy may be required to correct respiratory failure and shock.

The specific antagonist naloxone is used to counteract, very rapidly, the severe respiratory depression and coma produced by excessive doses of opioid analgesics.

Administer 400 µg naloxone intravenously and repeat at intervals of 2 to 3 minutes if necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Morphine sulphate is an opioid analgesic.

ATC code: N02A A01

A 2.9 Other analgesics

Pharmacotherapeutic group: Natural opium alkaloid. Morphine acts as an agonist at opiate receptors in the CNS, particularly mu and to a lesser extent kappa receptors.

Mu receptors are thought to mediate supraspinal analgesia, respiratory depression and euphoria, and kappa receptors, spinal analgesia, miosis and sedation.

Hepatobiliary system:

Opioids may induce spasm of the sphincter of Oddi.

5.2 Pharmacokinetic properties

Absorption:

Morphine is well absorbed from MST CONTINUS® tablets and, in general, peak plasma concentrations are achieved 1-5 hours following administration.

Distribution and metabolism:

About one third (35 %) of morphine in the plasma is protein-bound after a therapeutic dose.

The major pathway for the metabolism of morphine is conjugation with glucuronic acid.

The two major metabolites formed are morphine-6-glucuronide and morphine-3-glucuronide.

Small amounts of morphine-3; 6-diglucuronide may also be formed.

Although the 3- and 6-glucuronides are quite polar, both still can cross the blood-brain barrier to exert significant clinical effects.

Morphine-6-glucuronide is excreted by the kidney.

In renal failure, the levels of morphine-6-glucuronide can accumulate.

The half-life for morphine in plasma is approximately 2.5 – 3.0 hours.

Excretion:

Morphine is eliminated by glomerular filtration, primarily as morphine-3-glucuronide; 90 % of the total excretion takes place during the first day.

Very little morphine is excreted unchanged.

Enterohepatic circulation of morphine and its glucuronides occurs.

5.3 Preclinical safety data

Genotoxicity

No regulatory studies to assess the mutagenic potential of morphine have been conducted. In the published literature, morphine was found to be mutagenic *in vitro* increasing DNA fragmentation in human T-cells. Morphine was reported to be mutagenic in the *in vivo* mouse micronucleus assay and positive for the induction of chromosomal aberrations in mouse spermatids and murine lymphocytes. Mechanistic studies suggest that the *in vivo* clastogenic effects reported with morphine in mice may be related to increases in glucocorticoid levels produced by morphine in this species. In contrast to the positive findings, *in vitro* studies in the literature have also shown that morphine did not induce

chromosomal aberrations in human leukocytes or translocations or lethal mutations in *Drosophila*.

Carcinogenicity

Regulatory studies in animals to evaluate the carcinogenic potential of morphine have not been conducted.

Reproductive toxicity

Reduced fertility has been shown in male rats administered repeat doses of morphine subcutaneously.

A study reported in the literature in female rats treated i.p. with up to 15 mg/kg/day of morphine before mating, up to 30 mg/kg/day over pregnancy and up to 40 mg/kg/day postpartum showed reduced fertility of the mothers and an increase in stillborns, and in the live offspring reduced growth, morphine withdrawal symptoms, and suppression of sperm production.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

cetostearyl alcohol, hydroxyethyl cellulose, lactose (except 100 mg tablets), magnesium stearate, purified talc, purified water.

Film coat:

MST CONTINUS® 10 mg - Opadry tan and purified water. Opadry tan contains permitted colourants and consists of iron oxide (E172), macrogol, polyvinyl alcohol, purified talc, titanium dioxide (E171).

MST CONTINUS® 30 mg - Opadry violet and purified water. Opadry violet contains permitted colourants and consists of erythrosine (E127), hypromellose, indigo carmine (E132), macrogol, sunset yellow (E110), titanium dioxide (E171).

MST CONTINUS® 60 mg - Opadry orange and purified water. Opadry orange contains permitted colourants and consists of erythrosine (E127), hypromellose, macrogol, quinoline yellow (E104), sunset yellow (E110), titanium dioxide (E171).

MST CONTINUS® 100 mg - Opadry grey and purified water. Opadry contains permitted colourants and consists of hypromellose, indigo carmine (E132), iron oxide (E172), macrogol, titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months

6.4 Special precautions for storage

Store at or below 25 °C. Protect from moisture and light.

6.5 Nature and contents of container

MST CONTINUS® tablets are supplied in clear PVdC coated PVC blister packs with aluminium foil backing packed in boxes containing 60 tablets.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Mundipharma (Pty) Ltd

Block D, Grosvenor Square

Park Lane

Century City

Cape Town

7441

South Africa

info@mundipharma.co.za

8 REGISTRATION NUMBERS

South Africa: S6

MST CONTINUS® 10 mg tablet: R/2.9/294

MST CONTINUS® 30 mg tablet: R/2.9/295

MST CONTINUS® 60 mg tablet: S/2.9/278

MST CONTINUS® 100 mg tablet: S/2.9/279

Namibia: NS4

MST CONTINUS® 10 mg tablet: 90/2.9/00144

MST CONTINUS® 30 mg tablet: 90/2.9/00145

Botswana: S1A

MST CONTINUS® 10 mg tablet: B9300570

MST CONTINUS® 30 mg tablet: B9300575

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

2 July 1984

10 DATE OF REVISION OF THE TEXT

5 September 2025

® = MST CONTINUS is a registered trademark.