Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

MST Continus 200 mg Prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200mg morphine sulphate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated, prolonged-release tablet
Teal green tablet marked with the Napp logo on one side and 200mg on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the prolonged relief of severe and intractable pain and in the short term control of post-operative pain.

4.2 Posology and method of administration

Route of administration: Oral.

MST CONTINUS tablets should be swallowed whole and not broken, chewed or crushed. The administration of broken, chewed or crushed tablets may lead to a rapid release and absorption of a potentially fatal dose of morphine (see section 4.9, Overdose).

MST CONTINUS tablets should be used at 12-hourly intervals. The dosage is dependent upon the severity of the pain, the patient's age and previous history of analgesic requirements.

Adults:
A patient presenting with severe pain, uncontrolled by weaker opioids (e.g.dihydrocodeine) should normally be started on 30 mg 12 hourly. Patients previously on normal release oral morphine should be given the same total daily dose as MST CONTINUS tablets but in divided doses at 12-hourly intervals.

Increasing severity of pain will require an increased dosage of the tablets. Higher doses should be made, where possible in 30-50% increments as required. The correct dosage for any individual patient is that which is sufficient to control pain with no, or tolerable, side effects for a full 12 hours. It is recommended that the 200 mg strength is reserved for patients who have already been titrated to a stable analgesic dose using lower strengths of morphine or other opioid preparations.

Patients receiving MST CONTINUS 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 100%. In such patients individual dose adjustments are required.

Children:
For children with severe cancer pain, a starting dose in the range of 0.2 to 0.8 mg morphine per kg bodyweight 12 hourly is recommended. Doses should then be titrated as for adults.

Post-operative pain

MST CONTINUS tablets are not recommended in the first 24 hours post-operatively or until normal bowel function has returned; thereafter it is suggested that the following dosage schedule be observed at the physician's discretion:

(a) MST CONTINUS tablets 20 mg 12 hourly to patients under 70 kg.
(b) MST CONTINUS tablets 30 mg 12 hourly to patients over 70 kg.
(c) Elderly - a reduction in dosage may be advisable in the elderly.
(d) Children - not recommended.

Supplemental parenteral morphine may be given if required but with careful attention to the total dosages of morphine, and bearing in mind the prolonged effects of morphine in this prolonged release formulation.

4.3 Contraindications

Respiratory depression, head injury, paralytic ileus, 'acute abdomen', delayed gastric emptying, obstructive airways disease, known morphine sensitivity or hypersensitivity to any of the tablet constituents, acute hepatic disease, concurrent administration of monoamine oxidase inhibitors or within two weeks of discontinuation of their use.

Children under one year of age.

Pre-operative administration of MST CONTINUS tablets is not recommended, or for the first 24 hours post-operatively.

4.4 Special warnings and precautions for use

As with all narcotics a reduction in dosage may be advisable in the elderly, in hypothyroidism and in patients with significantly impaired renal , hepatic or respiratory function. Use with caution in opiate dependent patients and in patients with severe bronchial asthma, a history of substance abuse, convulsive disorders, raised intracranial pressure, hypotension with hypovolaemia, severe cor pulmonale, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, prostatic hypertrophy , adrenocortical insufficiency, acute alcoholism and delirium tremens**.**

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

Should paralytic ileus be suspected or occur during use, MST CONTINUS tablets should be discontinued immediately. As with all morphine preparations, patients who are about to undergo additional pain relieving procedures (e.g. surgery, plexus blockade) should not receive MST CONTINUS tablets for 24 hours prior to the intervention. If further treatment with MST CONTINUS tablets is then indicated, then the dosage should be adjusted to the new post-operative requirement.

As with all oral morphine preparations, MST CONTINUS tablets should be used with caution post-operatively, and following abdominal surgery as morphine impairs intestinal motility and should not be used until the physician is assured of normal bowel function.

The major risk of opioid excess is respiratory depression.

The patient may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain control. Prolonged use of this product 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.

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. There is potential for development of psychological dependence (addiction) to opioid analgesics, including morphine. The product should be used with particular care in patients with a history of alcohol and drug abuse. The prolonged release tablets must be swallowed whole, and not broken, chewed, dissolved or crushed. The administration of broken, chewed or crushed tablets may lead to a rapid release and absorption of a potentially fatal dose of morphine (see section 4.9).

It is not possible to ensure bio-equivalence between different brands of prolonged release morphine products. Therefore, it should be emphasised that patients, once titrated to an effective dose, should not be changed from MST CONTINUS preparations to other slow, sustained or prolonged release morphine or other potent narcotic analgesic preparations without retitration and clinical assessment.

4.5 Interaction with other medicinal products and other forms of interaction

Morphine potentiates the effects of tranquillisers, general anaesthetics, phenothiazines, other central nervous system depressants including hypnotics or sedatives, alcohol, muscle relaxants, antihypertensives and gabapentin. Morphine should not be co-administered with monoamine oxidase inhibitors or within two weeks of such therapy. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with the usual doses of morphine

Medicinal products that block the action of acetylcholine, for example antihistamines, anti-parkinsonians and anti-emetics, may interact with morphine to potentiate anticholinergic adverse events.

Cimetidine inhibits the metabolism of morphine.

Plasma concentrations of morphine may be reduced by rifampicin.

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

4.6 Pregnancy and lactation

MST CONTINUS tablets are not recommended during pregnancy and labour due to the risk of neonatal respiratory depression. Administration to nursing mothers is not recommended as morphine is excreted in breast milk. Withdrawal symptoms may be observed in the new born of mothers undergoing chronic treatment.

4.7 Effects on ability to drive and use machines

Morphine 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

In normal doses, the commonest side effects of morphine are nausea, vomiting, constipation and drowsiness. With chronic therapy, nausea and vomiting are unusual with MST CONTINUS tablets but should they occur the tablets can be readily combined with an anti-emetic if required. Constipation may be treated with appropriate laxatives.

Common (incidence of >1%) and Uncommon (incidence of < 1%) adverse drug reactions are listed in the table below:

Undersirable effects	**Common ((≥ 1%)**	**Uncommon (≤ 1%)**
Immune system disorders		Allergic reaction Anaphylactic reaction Anaphylactoid reaction
Psychiatric disorders	Confusion Insomnia Thinking disturbances	Agitation Drug dependence Dysphoria Euphoria

		Hallucinations Mood altered
Nervous system disorders	Dizziness Headache Involuntary muscle contractions Myoclonus Somnolence	Convulsions Hypertonia Paraesthesia Syncope Vertigo
Eye disorders		Miosis Visual disturbance
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 Dyspepsia Nausea Vomitting	Gastrointestinal disorders Ileus Taste perversion
Hepatobiliary disorders	Exacerbation of pancreatitis	Biliary pain Increased hepatic enzymes
Skin and subcutaneous tissue disorders	Hyperhidrosis Rash	Urticaria
Renal and urinary disorders		Ureteric spasm Urinary retention
Reproductive system and breast disorders		Amenorrhea Decreased libido Erectile dysfunction
General disorders and administration site conditions	Astenia Pruritus	Drug tolerance Drug withdrawal syndrome Malaise Peripheral oedema

The effects of morphine have led to its abuse and dependence may develop with regular, inappropriate use. This is not a major concern in the treatment of patients with severe pain**.**

4.9 Overdose

Signs of morphine toxicity and overdosage are pin-point pupils, skeletal muscle flaccidity, bradycardia, respiratory depression and hypotension. Circulatory failure and deepening coma may occur in more severe cases. Overdosage can result in death. Rhabdomyolysis progressing to renal failure has been reported in opioid overdosage.

Crushing and taking the contents of a prolonged release dosage form may lead to the release of morphine in an immediate fashion; this might result in a fatal overdose.

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

The pure opioid antagonists are specific antidotes against the effects of opioid overdose. Other supportive measures should be employed as needed. In the case of massive overdosage**,** administer naloxone 0.8 mg intravenously. Repeat at 2-3 minute intervals as necessary, or by an 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. MST CONTINUS 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.

Gastric contents may need to be emptied as this can be useful in removing unabsorbed drug, particularly when a prolonged release formulation has been taken.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloid
ATC code: NO2A A01

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.

Central Nervous System
The principal actions of therapeutic value of morphine are analgesia and sedation (i.e., sleepiness and anxiolysis). Morphine produces respiratory depression by direct action on brain stem respiratory centres.

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.

Gastrointestinal Tract and Other Smooth Muscle
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 generally increases smooth muscle tone, especially the sphincters of the gastrointestinal and biliary tracts. Morphine may produce spasm of the sphincter of Oddi, thus raising intrabiliary pressure.

Cardiovascular System
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.

Endocrine System
Opioids 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 in association with inappropriately low or normal ACTH, LH or FSH levels. Some premenopausal women may have low oestrogen levels. Clinical symptoms may be manifest from these hormonal changes.

Other Pharmacological Effects
In vitro and animal studies indicate various effects of natural opioids, such as morphine, on components of the immune system; the clinical significance of these findings is unknown.

5.2 Pharmacokinetic properties

Morphine is well absorbed from MST CONTINUS tablets. However first pass metabolism does occur. Apart from the liver, metabolism also occurs in the kidney and intestinal mucosa. The major urinary metabolite is morphine-3-glucuronide but morphine-6-glucuronide is also formed. Morphine-3-glucuronide also appears in the bile and is excreted into the intestine, hydrolysed and absorbed as free morphine. The half life for morphine in plasma is approximately 2.5 - 3.0 hours.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hyetellose
Cetostearyl alcohol
Magnesium stearate
Talc

Film-coat:
Hypromellose (E464)
Macrogol 400
Titanium dioxide (E171)
Brilliant blue (E133)
Quinoline yellow (E104)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package.

6.5 Nature and contents of container

Aluminium foil-backed PVdC/PVC blister pack (60 tablets).
Polypropylene container with polyethylene lid (60 tablets).

Not all pack sizes may be marketed

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 913/5/5

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