# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

MST CONTINUS suspension 100 mg.

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Morphine equivalent to Morphine Sulphate 100 mg
For excipients see 6.1

## 3 PHARMACEUTICAL FORM

Pink granules
Prolonged release granules for oral suspension

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

For the prolonged relief of severe and intractable pain.

### 4.2 Posology and method of administration

Route of administration: oral

The contents of one sachet should be mixed with at least 20 ml water or sprinkled on to soft food, for example yogurt.

The controlled release granules must be suspended whole and ingested immediately, but not be broken, chewed or crushed. The administration of broken, chewed or crushed morphine granules leads to a rapid release and absorption of a potentially fatal dose of morphine *(see section 4.9, Overdose).*

MST CONTINUS suspension 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 suspension but in divided doses at 12-hourly intervals.

Increasing severity of pain will require an increased dosage of the suspension. 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 suspension 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:

The use of MST CONTINUS suspension in children has not been extensively evaluated. 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 suspension is 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 suspension 20 mg 12 hourly to patients under 70 kg
(b) MST CONTINUS suspension 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 controlled release formulation.

## 4.3 Contraindications

Hypersensitivity to any of the constituents.
Respiratory depression, head injury, paralytic ileus, 'acute abdomen', delayed gastric emptying, obstructive airways disease, known morphine sensitivity, 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 suspension is not recommended.

## 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 or hepatic function. Use with caution in patients with impaired respiratory function, convulsion disorders, acute alcoholism, delirium tremens, and in patients with raised intracranial pressure, hypotension with hypovolaemia, severe cor pulmonale, patients with a history of substance abuse, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, prostatic hypertrophy, adrenocortical insufficiency and opiate dependent patients**.**

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

Should paralytic ileus be suspected or occur during use, MST CONTINUS suspension should be discontinued immediately.

Patients about to undergo additional pain relieving procedures (e.g. surgery, plexus blockade) should not receive MST CONTINUS suspension for 24 hours prior to the intervention. If further treatment with MST CONTINUS suspension is indicated, then the dosage should be adjusted to the new post-operative requirement.

MST CONTINUS suspension 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. MST CONTINUS suspension is not recommended preoperatively or within the first 24 hours postoperatively.

It is not possible to ensure bio-equivalence between different brands of controlled 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 controlled release morphine or other potent narcotic analgesic preparations without retitration and clinical assessment.

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. The product 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.

Concomitant use of alcohol and MST CONTINUS suspension may increase the undesirable effects of MST CONTINUS suspension; concomitant use should be avoided.

The excipient Ponceau 4R may cause allergic reactions.

## 4.5 Interaction with other medicinal products and other forms of interaction

Morphine potentiates the effects of tranquillisers, anaesthetics, phenothiazines, hypnotics, sedatives, muscle relaxants and antihypertensives. . 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.

Alcohol may enhance the pharmacodynamic effects of MST CONTINUS suspension; concomitant use should be avoided.

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.

Concurrent administration of antacids may result in a more rapid release of morphine than otherwise expected; dosing should therefore be separated by a minimum of two hours. Cimetidine inhibits the metabolism of morphine.

Monoamine oxidase inhibitors are known to interact with narcotic analgesics producing CNS excitation or depression with hyper- or hypotensive crisis. Morphine should not be co-administered with monoamine oxidase inhibitors or within two weeks of such therapy.

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.

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.

## 4.6 Fertility, pregnancy and lactation

MST CONTINUS Suspension is 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 suspension but should they occur the suspension could 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:

| **Undesirable Effects** | **Common (≥ 1%)** | **Uncommon (≤ 1%)** |
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| Immune system disorders | | Allergic reaction<br>Anaphylactic reaction<br>Anaphylactoid reaction |
| Psychiatric disorders | Confusion<br>Insomnia<br>Thinking disturbances | Agitation<br>Drug dependence<br>Dysphoria<br>Euphoria<br>Hallucinations<br>Mood altered |
| Nervous system disorders | Headache<br>Involuntary muscle contractions<br>Myoclonus<br>Somnolence | Convulsions<br>Hypertonia<br>Paraesthesia<br>Syncope<br>Vertigo |
| Eye disorders | | Miosis<br>Visual disturbance |
| Cardiac disorders | | Bradycardia<br>Palpitations<br>Tachycardia |
| Vascular disorders | | Facial flushing<br>Hypotension Hypertension |
| Respiratory, thoracic and mediastinal disorders | Bronchospasm<br>Cough decreased | Pulmonary oedema<br>Respiratory depression |
| Gastrointestinal disorders | Abdominal pain<br>Anorexia<br>Constipation<br>Dry mouth<br>Dyspepsia<br>Exacerbation of pancreatitis<br>Nausea<br>Vomiting | Gastrointestinal disorders<br>Ileus<br>Colic<br>Taste perversion |
| Hepatobiliary disorders | | Biliary pain<br>Increased hepatic enzymes |
| Skin and subcutaneous tissue disorders | Hyperhidrosis<br>Rash | Urticaria |
| Renal and urinary disorders | | Ureteric spasm<br>Urinary retention |
| Reproductive system and breast disorders | | Amenorrhea<br>Decreased libido<br>Erectile dysfunction |
| General disorders and administration site conditions | Asthenia<br>Pruritus | Drug tolerance<br>Drug withdrawal syndrome<br>Malaise<br>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 drowsiness, 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 controlled release dosage form leads to the release of the 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 Suspension 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 modified release formulation has been taken.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: natural opium alkaloid
ATC code: N02A 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 centers.

Morphine depresses the cough reflex by direct effect on the cough center 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 hemorrhagic or ischemic 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, oestrogen and testosterone in association with inappropriately low or normal ACTH, LH or FSH levels. Clinical symptoms may be manifest from these hormonal changes.

*Other Pharmacologic 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 bound to a cationic exchange resin and drug release is effected when morphine is displaced by ions in the gastrointestinal tract**.** Morphine is well absorbed and adequate plasma morphine levels are achieved following the recommended dosage regimen. However, first pass metabolism occurs in the liver.
In a single dose study in healthy volunteers, the systemic availability of morphine from MST CONTINUS suspension 30 mg was equivalent to that from an immediate release solution 30 mg (mean 91%, 95% CI 81-102%) and from MST CONTINUS tablet 30 mg (mean 101%, 95% CI 93-109%). The suspension provided a retarded plasma profile which was comparable to that of the MST CONTINUS tablet.

## 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

Dowex 50WX8 100-200 mesh cationic exchange resin
Xylitol
Xanthan gum
Raspberry flavour
Ponceau 4R (E 124)

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

2 years.

## 6.4 Special precautions for storage

Do not store above 25°C.

## 6.5 Nature and contents of container

Pack type: Surlyn lined, laminated aluminium foil sachets coated with polyethylene and clay coated Kraft paper.

Pack size: Boxboard cartons of 10, 20, 30, 60 sachets or medical sample packs of up to 14 sachets.

## 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

The contents of the sachet should be added to water or sprinkled onto soft food, e.g. yoghurt *(see 4.2 posology and method of administration).*

## 7 MARKETING AUTHORISATION HOLDER

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CB4 0GW
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## 8 MARKETING AUTHORISATION NUMBER

PA 0913/005/011

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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## 10 DATE OF REVISION OF THE TEXT

**July 2011**