Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

MST CONTINUS suspension 60 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains Morphine equivalent to Morphine Sulfate 60 mg.

Excipients with known effect:
Ponceau 4R (E124)
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release granules for oral suspension
Pink granules.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the prolongedrelief of severe and intractable pain.

4.2 Posology and method of administration

Posology

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.

Paediatric Population:

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.

Method of Administration

The contents of one sachet should be mixed with at least 10 ml water or sprinkled on to soft food, for example yogurt.

The prolonged 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.

Discontinuation of therapy
An abstinence syndrome may be precipitated if opioid administration is suddenly discontinued. Therefore, the dose should be gradually reduced prior to discontinuation.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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, severe bronchial asthma, 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**.**

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

The major risk of opioid excess is respiratory depression.

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

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs
Concomitant use of MST CONTINUS suspension and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible.

If a decision is made to prescribe MST CONTINUS suspension concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).

The patients should be followed 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).

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.

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 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.

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

Dependence and withdrawal (abstinence) syndrome
Morphine has an abuse profile similar to other strong agonist opioids and should be used with particular caution in patients with a history of alcohol and drug abuse. Morphine may be sought and abused by people with latent or manifest addiction disorders. There is potential for development of physical or/and psychological dependence (addiction) or tolerance to opioid analgesics, including morphine. The risk increases with the time the drug is used, and with higher doses. Symptoms can be minimised with adjustments of dose or dosage form, and gradual withdrawal of morphine. For individual symptoms, see section 4.8.

Adrenal insufficiency
Opioid analgesics may cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of adrenal insufficiency may include e.g. nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure.

Decreased sex hormones and increased prolactin
Some changes that can be seen with long-term use of opioid analgesics 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 include decreased libido, impotence or amenorrhea which may be manifested from these hormonal changes.

Plasma concentrations of morphine may be reduced by rifampicin. The analgesic effect of morphine should be monitored and doses of morphine adjusted during and after treatment with rifampicin.

The contents of the prolonged release sachets (granules) must be suspended whole or sprinkled on to soft food and drunk immediately after (see section 4.2), but not be broken, crushed or chewed. 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).

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 interactions

The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited (see section 4.4).

Drugs which depress the CNS include, but are not limited to: other opioids, anxiolytics, hypnotics and sedatives (including benzodiazepines), antipsychotics, antidepressants, general anaesthetics, phenothiazines, muscle relaxants and antihypertensives.

In a study involving healthy volunteers (N = 12), when a 60-mg controlled-release morphine capsule was administered 2 hours prior to a 600-mg gabapentin capsule, mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine. Therefore, patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of gabapentin or morphine should be reduced appropriately.

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 (see section 4.4).

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

Pregnancy
There are no or limited amount of data from the use of morphine in pregnant women.
MST CONTINUS Suspension is not recommended during pregnancy and labour due to the risk of neonatal respiratory depression. Newborns whose mothers received opioid analgesics during pregnancy should be monitored for signs of neonatal withdrawal (abstinence) syndrome. Treatment may include an opioid and supportive care.

Breast-feeding
Administration to nursing mothers is not recommended as morphine is excreted in breast milk.

Fertility
Animal studies have shown that morphine may reduce fertility (see 5.3 Preclinical safety data).

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.

The following frequencies are the basis for assessing undesirable effects:

Very common (≥ 1/10)

Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to <1/100)
Rare (≥ 1/10,000 to < 1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

	Very Common	Common	Uncommon	Not known
Immune system disorders			Hypersensitivity	Anaphylactic reaction Anaphylactoid reaction
Psychiatric disorders		Confusion Insomnia	Agitation Euphoria Hallucinations Mood altered	Drug dependence Dysphoria Thinking disturbances
Nervous system disorders		Dizziness Headache Hyperhidrosis Involuntary muscle contractions Somnolence	Convulsions Hypertonia Myoclonus Paraesthesia Syncope	Allodynia Hyperalgesia (see section 4.4)
Eye disorders			Visual disturbance	Miosis
Ear and labyrinth disorders			Vertigo	
Cardiac disorders			Palpitations	Bradycardia Tachycardia
Vascular disorders			Facial flushing Hypotension	Hypertension
Respiratory thoracic and mediastinal disorders			Bronchospasm Pulmonary oedema Respiratory depression	Cough decreased
Gastrointestinal disorders	Constipation Nausea	Abdominal pain Anorexia Dry mouth Vomiting	Dyspepsia Ileus Taste perversion	
Hepatobiliary disorders			Increased hepatic enzymes	Biliary pain Exacerbation of pancreatitis
Skin and subcutaneous tissue disorders		Rash	Urticaria	
Renal and urinary disorders			Urinary retention	Ureteric spasm
Reproductive system and breast disorders				Amenorrhoea Decreased libido Erectile dysfunction
General disorders and administration site conditions		Asthenia Fatigue Malaise Pruritus	Peripheral oedema	Drug tolerance Drug withdrawal (abstinence) syndrome Drug withdrawal

				(abstinence) syndrome neonatal

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.

Drug dependence and withdrawal (abstinence) syndrome
Use of opioid analgesics may be associated with the development of physical and/or psychological dependence or tolerance. An abstinence syndrome may be precipitated when opioid administration is suddenly discontinued or opioid antagonists administered, or can sometimes be experienced between doses. For management, see section 4.4.

Physiological withdrawal symptoms include: body aches, tremors, restless legs syndrome, diarrhoea, abdominal colic, nausea, flu-like symptoms, tachycardia and mydriasis. Psychological symptoms include dysphoric mood, anxiety and irritability. In drug dependence, "drug craving" is often involved.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Signs of morphine toxicity and overdose are drowsiness, pin-point pupils, skeletal muscle flaccidity, bradycardia, hypotension, pneumonia aspiration, respiratory depression, somnolence and central nervous system depression which can progress to stupor or coma. Death may occur from respiratory failure. Circulatory failure and deepening coma may occur in more severe cases. Overdose can result in death. Rhabdomyolysis progressing to renal failure has been reported in opioid overdose.

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

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

Oral activated charcoal (50g for adults, 1 g/kg for children) may be considered if a substantial amount has been ingested within one hour, provided the airway can be protected.

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 overdose, 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 Suspension will continue to release and add to the morphine load for up to 12 hours after administration and the management of morphine overdose should be modified accordingly.

For less severe overdose, 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 overdose.

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.

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 affect the hypothalamic pituitary adrenal and hypothalamic pituitary gonadal system resulting in adrenal insufficiency or hypogonadism respectively (see section 4.4).

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

In male rats, reduced fertility and chromosomal damage in gametes have been reported. There are no other 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.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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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8 MARKETING AUTHORISATION NUMBER

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