Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

MST Continus 30 mg Prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains morphine equivalent to morphine sulfate 30 mg.

Excipients with known effect:
Lactose anhydrous 70 mg
Sunset Yellow (E110)

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated, prolonged-release tablet
Purple tablet marked with the Napp Logo on one side and 30mg 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

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 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.

Paediatric population

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.

Method 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.

Treatment goals and discontinuation
Before initiating treatment with MST CONTINUS tablets, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with MST CONTINUS tablets, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

Duration of treatment
MST CONTINUS tablets should not be used longer than necessary.

4.3 Contraindications

Morphine products are contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Severe chronic obstructive pulmonary disease
- Severe bronchial asthma
- Severe respiratory depression with hypoxia and/or hypercapnia
- Paralytic ileus
- Head injury
- Acute abdomen
- Delayed gastric emptying
- Acute hepatic disease

- Concurrent administration of monoamine oxidase inhibitors or within two weeks of discontinuation

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

MST CONTINUS tablets should be administered with caution in patients with:

- Severely impaired respiratory function
- Respiratory depression
- Severe cor pulmonale
- Sleep apnoea
- CNS depressants co-administration (see below and section 4.5)
- Tolerance, physical dependence and withdrawal (see below)
- Opioid Use Disorder
- Psychological dependence[addiction], abuse profile and history of substance and/or alcohol abuse (see below)
- Head injury, intracranial lesions or increased intracranial pressure, reduced level of consciousness of uncertain origin.
- hypotension with hypovolaemia
- hypothyroidism
- adrenocortical insufficiency
- convulsive disorders
- biliary tract disorders
- pancreatitis
- prostatic hypertrophy
- inflammatory bowel disorders
- severely impaired renal function
- severely impaired hepatic function
- severe bronchial asthma
- delirium tremens
- constipation

As with all narcotics a reduction in dosage may be advisable in the elderly. ,

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

Respiratory Depression

The major risk of opioid excess is respiratory depression.

Sleep-related breathing disorders

Opioids can 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 fashion. 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.

Severe cutaneous adverse reactions (SCARs)

Acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, has been reported in association with morphine treatment. Most of these reactions occurred within the first 10 days of treatment. Patients should be informed about the signs and symptoms of AGEP and advised to seek medical care if they experience such symptoms.

If signs and symptoms suggestive of these skin reactions appear, morphine should be withdrawn and an alternative treatment considered.

Hepatobiliary disorders

Morphine may cause dysfunction and spasm of the sphincter of Oddi, thus raising intrabiliary pressure and increasing the risk of biliary tract symptoms and pancreatitis.

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 tablets 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 tablets concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

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.

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 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. MST CONTINUS tablets are not recommended preoperatively or within the first 24 hours postoperatively.

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

Opioid Use Disorder (abuse and dependence)
Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as MST CONTINUS tablets.

Repeated use of MST CONTINUS tablets can lead to Opioid Use Disorder (OUD). A higher dose and longer duration of opioid treatment, can increase the risk of developing OUD. Abuse or intentional misuse of MST CONTINUS tablets may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (eg. major depression, anxiety and personality disorders).

Before initiating treatment with MST CONTINUS tablets and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician.

Patients will require monitoring for signs of drug-seeking behavior (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

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 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 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.

Oral P2Y12 inhibitor antiplatelet therapy
Within the first day of concomitant P2Y12 inhibitor and morphine treatment, reduced efficacy of P2Y12 inhibitor treatment has been observed (see section 4.5)

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).

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 tablets may increase the undesirable effects of MST CONTINUS tablets; concomitant use should be avoided.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine

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

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 dose and duration of concomitant use should be limited (see section 4.4).

Morphine should be used with caution in patients who are concurrently receiving other central nervous system depressants, which include, but are not limited to: other opioids, anxiolytics, tranquillisers, sedatives and hypnotics (including benzodiazepines), antiepileptics (including gabapentinoids e.g. pregabalin or gabapentin), general anaesthetics (including barbiturates), antipsychotics (including phenothiazines), other tranquilisers, antidepressants, muscle relaxants, antihypertensives, centrally acting anti-emetics and alcohol. 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.

Morphine should not be co-administered with monoamine oxidase inhibitors or within two weeks of such therapy (see section 4.3).

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

Medicinal products that block the action of acetylcholine, for example antihistamines, anti-parkinsons 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 (see section 4.4).

A delayed and decreased exposure to oral P2Y12 inhibitor antiplatelet therapy has been observed in patients with acute coronary syndrome treated with morphine. This interaction may be related to reduced gastrointestinal motility and apply to other opioids. The clinical relevance is unknown, but data indicate the potential for reduced P2Y12 inhibitor efficacy in patients co-administered morphine and a P2Y12 inhibitor (see section 4.4). In patients with acute coronary syndrome, in whom morphine cannot be withheld and fast P2Y12 inhibition is deemed crucial, the use of a parenteral P2Y12 inhibitor may be considered.

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 Fertility, pregnancy and lactation

Pregnancy
MST CONTINUS tablets are 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 tablets but should they occur the tablets can 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	Thinking disturbances Drug dependence Dysphoria
Nervous system disorders		Dizziness Headache Hyperhidrosis Involuntary muscle contractions Somnolence	Convulsions Hypertonia Paraesthesia Syncope Myoclonus	Allodynia Hyperalgesia (see section 4.4)
Eye disorders			Visual impairment	Miosis
Ear and labyrinth disorders			Vertigo	
Cardiac disorders			Palpitations	Bradycardia Tachycardia
Vascular disorders			Facial flushing Hypotension	Hypertension
Respiratory, thoracic and mediastinal disorders			Pulmonary oedema Respiratory depression Bronchospasm	Cough decreased Central sleep apnoea syndrome
Gastrointestinal disorders	Nausea Constipation	Abdominal pain Anorexia Dry mouth Vomiting	Ileus Taste perversion Dyspepsia	Pancreatitis
Hepatobiliary disorders			Increased hepatic enzymes	Biliary pain Exacerbation of pancreatitis Spasm of sphincter of Oddi
Skin and subcutaneous tissue disorders		Rash	Urticaria	Acute generalised exanthematous pustulosis (AGEP)
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

Repeated use of MST CONTINUS tablets can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

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. Website: www.hpra.ie

4.9 Overdose

Signs of morphine toxicity and overdose are pin-point pupils, skeletal muscle flaccidity, bradycardia, hypotension, respiratory depression, pneumonia aspiration, 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.

Toxic leukoencephalopathy has been observed with morphine overdose.

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

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

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

Lactose anhydrous
Hyetellose
Cetostearyl alcohol
Magnesium stearate
Talc

Film-coat:
Hypromellose (E464)
Macrogol 400
Titanium dioxide (E171)
Erythrosine (E127)
Indigo carmine (E132)
Sunset yellow (E110)

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 and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Mundipharma Pharmaceuticals Limited
United Drug House
Magna Drive Magna Business Park
Citywest Road
Dublin 24
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8 MARKETING AUTHORISATION NUMBER

PA1688/004/004

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