SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

MST® CONTINUS® 10 mg prolonged release tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Morphine Sulfate 10 mg.

Excipients with known effect:

Also contains lactose anhydrous 90 mg.

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

Golden brown, film coated, biconvex tablet marked with the NAPP logo on one side and 10 mg on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the prolonged relief of severe and intractable pain.

4 CLINICAL PARTICULARS

4.2 Posology and method of administration

Posology

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.

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

to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4).

Adults:
A patient presenting with severe pain, uncontrolled by weaker opioids (e.g. dihydrocodeine) should normally be started on 30 mg 12 hourly for patients over 70kg, or 20 mg for patients under 70 kg. 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.

Elderly:
A reduction in dosage may be advisable in the elderly

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.

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).

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.

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

MST CONTINUS tablets are contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the constituents listed in section 6.1.
- severe chronic obstructive pulmonary disease
- severe bronchial asthma
- severe respiratory depression with hypoxia and/or hypercapnia
- paralytic ileus
- acute abdomen
- head injury
- delayed gastric emptying
- 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.

Not recommended for pre-operative use or for the first 24 hours post-operatively.

4 CLINICAL PARTICULARS

4.4 Special warnings and precautions for use

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

- impaired respiratory function
- respiratory depression (see below)
- 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)
- Acute alcoholism
- Delirium tremens
- 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
- 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.

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

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 preexisting 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.

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 (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 tablets for 24 hours prior to the intervention. If further treatment with MST CONTINUS tablets is then indicated, the dosage should be adjusted to the new post-operative requirement.

MST CONTINUS tablets should be used with caution following abdominal surgery as morphine impairs intestinal motility and should not be used until the physician is assured of normal bowel function.

Prolonged release opioids should not be used for acute post-operative pain owing to the increased risk of persistent post-operative opioid use (PPOU) and opioid-induced ventilatory impairment (OIVI).

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.

<u>Drug dependence, tolerance and potential for abuse</u>
For all patients, prolonged use of this product may lead to drug 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.

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 (e.g. 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 behaviour (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.

Drug 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.

Drug 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 drug 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.

If women take this drug during pregnancy there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

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.

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.

Biliary tract 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.

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 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, the total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 dosage 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, sedatives and hypnotics (including benzodiazepines), antiepileptics (including gabapentinoids, e.g., pregabalin), general anaesthetics (including barbiturates), antipsychotics (including phenothiazines), other tranquilisers, antidepressants, gabapentin, 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 sulfate should not be co-administered with monoamine oxidase inhibitors or within two weeks of such therapy.

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 sulfate to potentiate anticholinergic adverse events.

Cimetidine inhibits the metabolism of morphine sulfate.

Plasma concentrations of morphine sulfate 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 sulfate, ritonavir induces the hepatic enzymes responsible for the glucuronidation of morphine sulfate, and may possibly decrease plasma concentrations of morphine sulfate.

4.6 Fertility, pregnancy and lactation

Pregnancy
MST CONTINUS tablets are not recommended during pregnancy and labour. Regular use in pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate. If opioid use is required for a prolonged period in pregnant women, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Breast feeding
Administration to nursing women is not recommended as morphine is secreted in breast milk and may cause respiratory depression in the infant.

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.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive.
- Do not drive until you know how the medicine affects you.
- It is an offence to drive while you have this medicine in your body over a specified limit unless you have a defence (called the 'statutory defence').
- This defence applies when:
  - The medicine has been prescribed to treat a medical or dental problem; and
  - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine.
- Please note that it is still an offence to drive if you are unfit because of the medicine (i.e. your ability to drive is being affected)."

Details regarding a new driving offence concerning driving after drugs have been taken in the UK may be found here: https://www.gov.uk/drug-driving-law

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	Drug dependence (see section 4.4)
	Very Common	Common	Uncommon	Not known
			Hallucinations Mood altered	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 impairment	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 Central sleep apnoea syndrome
Gastrointestinal disorders	Constipation Nausea	Abdominal pain Anorexia Dry mouth Vomiting	Dyspepsia Ileus Taste perversion	Pancreatitis
Hepatobiliary disorders			Increased hepatic enzymes	Biliary pain Exacerbation of pancreatitis Sphincter of Oddi dysfunction
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 withdrawal syndrome	Drug tolerance Drug withdrawal (abstinence) syndrome neonatal

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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.

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.

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Toxic leukoencephalopathy has been observed with morphine 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 tablets 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.

5.1 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 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).

Hepatobiliary system

Opioids may induce spasm of the sphincter of Oddi (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 and, in general, peak plasma concentrations are achieved 1-5 hours following administration. The availability is complete when compared to an equivalent dose of immediate release oral solution. Morphine is subject to a significant first-pass effect which results in a lower bioavailability when compared to an equivalent intravenous dose.

The major metabolic transformation of morphine is glucuronidation to morphine 3-glucuronide and morphine-6-glucuronide which then undergo renal excretion. These metabolites are excreted in bile and may be subject to hydrolysis and subsequent re-absorption.

Patients are titrated to appropriate pain control using the wide range of strengths of MST CONTINUS tablets. Consequently, there is a large inter-patient variation in required dosage, the minimum dosage being 5 mg twelve hourly and a dose of 5.6 g 12 hourly has been recorded.

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

Tablet core

Lactose Anhydrous
Hydroxyethylcellulose
Purified Water
Cetostearyl Alcohol
Magnesium Stearate
Purified Talc

Film coat

Polyvinyl alcohol
Macrogol 3350
Talc
Titanium dioxide (E171)
Iron oxides (E172)

6.2. Incompatibilities

None stated.

6.3 Shelf life

Five years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Aluminium foil-backed PVdC/PVC blister packs. Pack size 60 tablets.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Napp Pharmaceuticals Limited
Cambridge Science Park
Milton Road
Cambridge CB4 0GW

8 MARKETING AUTHORISATION NUMBER(S)

PL 16950/0036

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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