MST CONTINUS® TABLETS

NAME OF THE MEDICINAL PRODUCT

MST CONTINUS® 10 mg, 30 mg, 60 mg, 100 mg Prolonged Release Tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablets containing Morphine Sulfate Ph.Eur, 10 mg, 30 mg, 60 mg, 100 mg.

PHARMACEUTICAL FORM

Prolonged release, film-coated, biconvex tablets, plain on one side and the strength of the preparation is marked on the other.

MST CONTINUS® tablets 10 mg are golden brown.
MST CONTINUS® tablets 30 mg are purple.
MST CONTINUS® tablets 60 mg are orange.
MST CONTINUS® tablets 100 mg are grey.

CLINICAL PARTICULARS

Therapeutic indications

Prolonged relief of severe pain

Posology and method of administration

Route of administration: oral

MST CONTINUS® tablets should be swallowed whole and not broken, chewed or crushed. The administration of broken, chewed or crushed tablets may lead to a rapid release and absorption of a potentially fatal dose of morphine (refer to *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.
Drug product is not recommended preoperatively or within the first 24 hours postoperatively.

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 *Warnings and Precautions for use*).

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.

Children:

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

Contraindications

MST CONTINUS® tablets are contraindicated in patients with:

- Known hypersensitivity to morphine or to any of the excipients (listed in section *List of excipients*) .
- severe chronic obstructive pulmonary disease
- severe bronchial asthma
- severe respiratory depression with hypoxia and/orhypercapnia
- 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.

Special warnings and precautions for use

Morphine has to be administered with caution in patients with:

- Impaired respiratory function.
- Respiratory depression.
- Severe cor pulmonale.
- Sleep apnoea.
- CNS depressants co-administration.
- Tolerance, physical dependence and withdrawal.
- Psychological dependence [addiction], abuse profile and history of substance and /or alcohol abuse.
- 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 may 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 manner in some patients. Opioids may also cause worsening of pre-existing sleep apnoea (see *Undesirable effects*). 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.

Risks 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 the decision is made to prescribe ***MST CONTINUS***® tablets concomitantly with sedative medicines, the lowest effective doseshould be used, and the duration of treatment should be as short as possible (See also *Posology and method of administration*).

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 *Interaction with other medicinal products and other forms of interaction)*

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.

Drug dependence, tolerance and potential for abuse
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 *Posology and method of administration*). 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.

Serotonin Svndrome with Concomitant Use of Serotonergic Drugs
Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concurrent use of morphine with serotonergic drugs *(See Interaction with other medicinal products and other forms of interaction).* This may occur within the recommended dosage range.

Serotonin syndrome symptoms may include mental-status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea) and can be fatal *(See Interaction with other medicinal products and other forms of interaction)*. The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that.
Discontinue morphine if serotonin syndrome is suspected.

Adrenal Insufficiency
Opioid analgesics may cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of of adrenal insufficiency may include include e.g. nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, and 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 opioids 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 *Interaction with other medicinal products and other forms of interation*)

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 *Overdose*).

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.

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 *Special warnings and precautions for use*).

Drugs which depress the CNS 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), antidepressants, muscle relaxants, antihypertensives, centrally acting anti-emetics and alcohol.

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 *Special warnings and precautions for use*).

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 *Special warnings and precautions for use*). 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.

Benzodiazepines
Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death.

The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at μ-receptors, and benzodiazepines interact at GABAA sites. When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate *(see Special warnings and precautions for use)*

Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

Serotonergic Drugs
The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue morphine if serotonin syndrome is suspected.

Examples of serotonergic drugs are selective serotonin reuptake inhibitors (SSRls), serotonin and norepinephrine reuptake inhibitors (SNRls), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g. mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) *(see Special warnings and precautions for use)*

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 Preclinical safety data).

Effects on Ability to Drive and Use Machines

Morphine may impair the ability to drive and use machines.

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)

The undesirable effects listed below are classified by body system according to their incidence (common or uncommon). Common adverse drug experiences have an incidence of > 1% and uncommon undesirable effects have an incidence of < 1%.

Undesirable Effects	**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 Involuntary muscle contractions Somnolence	Convulsions Hypertonia Myoclonus Paraesthesia Syncope	Hyperalgesia Allodynia Sleep apnoea syndrome

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			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
Hepato-biliary disorders			Increased hepatic enzymes	Biliary pain Exacerbation of pancreatitis Sphincter of Oddi dysfunction
Skin and subcutaneous tissue disorders		Hyperhidrosis Rash	Urticaria	Acute generalised exanthematous pustulosis (AGEP)
Renal and urinary disorders			Urinary retention	Ureteric spasm
Reproductive system andbreast disorders				Amenorrhea 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

Parenteral epidural or intrathecal use only: Very rarely, serious neurologic symptoms like paresis may be caused by catheter tip granuloma.

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 *Special warnings and precautions for use*).

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 *Special warnings and precautions for use*.

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.

Postmarketing Experience:

Serotonin syndrome *(see Special warnings and precautions for use)*
Adrenal insufficiency *(see Special warnings and precautions for use)*

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids. Chronic use of opioids may influence the hypotha/amic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

Infertility: Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

Overdose

Acute overdosage with morphine can be manifested by respiratory depression, somnolence progressing to stupor or coma, Pneumonia aspiration, miotic pupils, rhabdomyolysis progressing to renal failure, skeletal muscle flaccidity, bradycardia, hypotension and death.

Toxic leukoencephalopathy has been observed with morphine overdose.

A patent airway must be maintained. The pure opioid antagonists are specific antidotes against the effects of opioid overdose. Other supportive measures should be employed as needed.

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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: natural opium alkaloid

ATC code: N02A A01

Morphine is an opioid agonist with no antagonistic action.

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 supraspinalanalgesia, 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.

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 (see Special warnings and precautions for use*)*

Hepatobiliary system
Opioids may induce spasm of the sphincter of Oddi (see *Special warnings and precautions for use*).

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.

Pharmacokinetic Properties

Morphine is well absorbed from ***MST CONTINUS***® tablets and, in general, peak plasma concentrations are achieved 1-6 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 or intramuscular dose. Morphine is also metabolised by the kidneys and the intestinal mucosa. The major metabolic transformation is glucuronidation to morphine-3- glucuronide and to a lesser extent to morphine-6-glucuronide. Both metabolites undergo renal excretion.

Preclinical safety data

Genotoxicity
No regulatory studies to assess the mutagenic potential of morphine have been conducted. In the published literature, morphine was found to be mutagenic *in vitro* increasing DNA fragmentation in human T-cells. Morphine was reported to be mutagenic in the *in vivo* mouse micronucleus assay and positive for the induction of chromosomal aberrations in mouse spermatids and murine lymphocytes. Mechanistic studies suggest that the *in vivo* clastogenic effects reported with morphine in mice may be related to increases in glucocorticoid levels produced by morphine in this species. In contrast to the positive findings, *in vitro* studies in the literature have also shown that morphine did not induce chromosomal aberrations in human leukocytes or translocations or lethal mutations in *Drosophila*.

Carcinogenicity
Regulatory studies in animals to evaluate the carcinogenic potential of morphine have not been conducted.

Reproductive toxicity
In male rats, reduced fertility and chromosomal damage in gametes have been reported.

A study reported in the literature in female rats treated i.p. with up to 15 mg/kg/day of morphine before mating, up to 30 mg/kg/day over pregnancy and up to 40 mg/kg/day postpartum showed reduced fertility of the mothers and an increase in stillborns, and in the live offspring reduced growth, morphine withdrawal symptoms, and suppression of sperm production.

PHARMACEUTICAL PARTICULARS

List of excipients
Lactose Anhydrous NF (except for 100mg)
HydroxyethylcellulosePhEur
Purified Water PhEur
Cetostearyl Alcohol PhEur
Magnesium Stearate PhEur
Purified Talc PhEur

The list of colourants are as follows:
10mg -Opadry 85F270017
30mg - Opadry OY -6708 violet
60mg - Opadry OY –3508 orange
100mg - Opadry OY – 8215 grey

Shelf life
3 years

Special Precautions for storage
Do not store above 30ºC.

Keep out of reach of children.

Nature and contents of container

Aluminium foil-backed PVdC/PVC blister packs. Pack size 30 & 60 tablets. Not all strengths and pack sizes may be marketed locally.

MANUFACTURER

Bard Pharmaceuticals Limited
Cambridge Science Park
Milton Road
Cambridge CB4 0GW
United Kingdom

PRODUCT REGISTRATION HOLDER

DKSH MALAYSIA SDN BHD
B-11-01, The Ascent, Paradigm,
No. 1, Jalan SS7/26A, Kelana Jaya,
47301 Petaling Jaya,
Selangor, Malaysia.

DATE OF REVISION OF THE TEXT

May 2025 (UK SPC 4 Mar 2025, based on CCDSv20)

®: MST CONTINUS is a Registered Trademark.