

AUSTRALIAN PRODUCT INFORMATION

MS CONTIN® (MORPHINE SULFATE PENTAHYDRATE) TABLETS

MS CONTIN® SUSPENSION (MORPHINE SULFATE PENTAHYDRATE) MODIFIED RELEASE GRANULES

1 NAME OF THE MEDICINE

Morphine sulfate pentahydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

MS CONTIN modified release tablets

MS CONTIN modified release tablets 5 mg contains 5 mg morphine sulfate pentahydrate

MS CONTIN modified release tablets 10 mg contains 10 mg morphine sulfate pentahydrate

MS CONTIN modified release tablets 15 mg contains 15 mg morphine sulfate pentahydrate

MS CONTIN modified release tablets 30 mg contains 30 mg morphine sulfate pentahydrate

MS CONTIN modified release tablets 60 mg contains 60 mg morphine sulfate pentahydrate

MS CONTIN modified release tablets 100 mg contains 100 mg morphine sulfate pentahydrate

MS CONTIN modified release tablets 200 mg contains 200 mg morphine sulfate pentahydrate

Excipients with known effects:

- lactose (except 100 mg and 200 mg)

For the full list of excipients, see Section 6.1 List of excipients.

MS CONTIN suspension (modified release granules)

MS CONTIN suspension 20 mg (modified release) contains 20 mg morphine sulfate pentahydrate

MS CONTIN suspension 30 mg (modified release) contains 30 mg morphine sulfate pentahydrate

MS CONTIN suspension 60 mg (modified release) contains 60 mg morphine sulfate pentahydrate

MS CONTIN suspension 100 mg (modified release) contains 100 mg morphine sulfate pentahydrate

MS CONTIN suspension 200 mg (modified release) contains 200 mg morphine sulfate pentahydrate

Excipients with known effects:

- xylitol

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

MS CONTIN modified release tablets

MS CONTIN modified release tablets are film-coated, biconvex and imprinted with the dosage strength on one side.

MS CONTIN modified release tablets 5 mg (white, marked 5 mg on one side)

MS CONTIN modified release tablets 10 mg (light tan, marked 10 mg on one side)

MS CONTIN modified release tablets 15 mg (light green, marked 15 mg on one side)

MS CONTIN modified release tablets 30 mg (purple, marked 30 mg on one side)

MS CONTIN modified release tablets 60 mg (orange, marked 60 mg on one side)

MS CONTIN modified release tablets 100 mg (grey, marked 100 mg on one side)

MS CONTIN modified release tablets 200 mg (teal green, marked 200 mg on one side)

MS CONTIN SUSPENSION (modified release granules)

MS CONTIN SUSPENSION (modified release) are available in a sealed sachet containing a uniform blend of pink granules with an odour of raspberries.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of opioid-responsive, chronic severe pain.

4.2 DOSE AND METHOD OF ADMINISTRATION

Administration and dosing of morphine should be individualised bearing in mind the properties of the drug. In addition, the nature and severity of the pain or pains experienced, and the total condition of the patient must be taken into account. Of special importance is other medication given previously or concurrently.

As with other strong opioid analgesics, use of morphine for the management of persistent pain should be preceded by a thorough assessment of the patient and diagnosis of the specific pain or pains and their causes. Use of opioids for the relief of chronic pain, including cancer pain, important as it is, should be only one part of a comprehensive approach.

MS CONTIN tablets or suspension should be used for the long-term treatment of chronic severe pain only after the pain has been proven to be alleviated by opioids (with a trial of shorter acting opioids or MS CONTIN tablets or suspension itself).

MS CONTIN tablets (modified release):

Adult

Initial adult dose: Individual dosing requirements vary considerably based on each patient's age, weight, severity of pain, and medical and analgesic history. The most frequent initial dose is 30 mg MS CONTIN tablets every 12 hours. MS CONTIN 200 mg tablets should only be used in opioid-tolerant patients.

Patients over 50 and the elderly

Patients over the age of 50 tend to require much lower doses of morphine than in the younger age group. In elderly and debilitated patients and those with impaired respiratory function or significantly decreased renal function, the initial dose should be one half the usual recommended dose.

Children > 25 kg

Initial paediatric dosage (children > 25 kg): the initial dose will depend upon the degree of morphine tolerance and should be titrated in accordance with the patient's needs. (See Section 4.2 Dose and method of administration; Dose titration).

Children ≤ 25 kg

There are no controlled trials of the use of MS CONTIN tablets in children weighing 25 kg or less, nor in children with chronic, severe, non-malignant pain.

Transferring to MS CONTIN tablets from alternate opioids

Patients currently receiving other oral morphine formulations may be transferred to MS CONTIN tablets at the same total daily morphine dosage, equally divided into two 12-hourly MS CONTIN tablet doses.

For patients who are receiving an alternate opioid, the "oral morphine sulfate pentahydrate equivalent" of the analgesic presently being used should be determined. Having determined the total daily dosage of the present analgesic, the following equivalence table can be used to calculate the approximate daily oral morphine sulfate pentahydrate dosage that should provide equivalent analgesia. The total daily oral morphine dosage should then be equally divided into two 12-hourly MS CONTIN tablet doses.

Table 1 - Opioids: Approximate analgesic equivalences¹

Drug	Equivalent Dose (mg)	
	IM	PO
MORPHINE sulfate pentahydrate	10	30
OXYCODONE (Percodan*, Endone, Proladone)		15
DEXTROMORAMIDE (Palfium*) ²		15
PAPAVERTUM (Omnopon*)		45

1. Twycross, RG (1997). Oral morphine advanced cancer. 3rd edition. Beaconsfield, UK, Beaconsfield Publishers Ltd.
2. Dextromoramide - a single 5mg dose is equivalent to morphine 15mg (diamorphine* 10mg) in terms of peak effect but is shorter acting. The overall potency ratio has been adjusted accordingly.

*Not currently available in Australia.

IM – intramuscular; PO – oral administration

Dose titration

Dose titration is the key to success with morphine therapy. PROPER OPTIMISATION OF DOSES SCALED TO THE RELIEF OF THE INDIVIDUAL'S PAIN SHOULD AIM AT THE REGULAR ADMINISTRATION OF THE LOWEST DOSE OF MORPHINE WHICH WILL CONTROL THE PAIN WITH NO OR TOLERABLE SIDE EFFECTS. Dose adjustments should be based on the patient's clinical response. Higher doses may be justified in some patients to cover periods of physical activity.

Because of the sustained release properties of MS CONTIN tablets, dosage adjustments should generally be separated by 48 hours. If dose increments are required, they should be proportionately greater at the lower dose level (in terms of percentage of previous dose), than when adjusting a higher dose.

The usual recommended dose (12-hourly) increments are 5, 10, 15, 20, 30, 40, 60, 90, 120, 150, 180, 200 mg. Above the 200 mg/dose (400 mg/day), increments should be by 30 to 60 mg morphine.

MS CONTIN tablets are designed to allow 12-hourly dosing. If "breakthrough" pain repeatedly occurs at the end of a dose interval, it is generally an indication for a dosage increase, not more frequent administration. However, where judged necessary for optimisation of drug effects, MS CONTIN tablets may be administered 8-hourly. More frequent (than 8-hourly) administration of MS CONTIN tablets is neither rational nor recommended.

Adjustment or reduction of dosage

During the first two or three days of effective pain relief, the patient may exhibit drowsiness or sleep for prolonged periods. This can be misinterpreted as the effect of excessive analgesic dosing rather than the first sign of relief in a pain-exhausted patient. The dose, therefore, should be maintained for at least three days before reduction, provided the sedation is not excessive or associated with unsteadiness and confusional symptoms, and respiratory activity and other

vital signs are adequate. If excessive sedation persists, the reason(s) for such an effect must be sought (see Section 4.8 Adverse effects (Undesirable effects); Sedation).

Following successful relief of severe pain, periodic attempts to reduce the opioid dose should be made. Smaller doses or complete discontinuation of the opioid analgesic may become feasible due to a change in the patient's condition or improved mental state.

MS CONTIN TABLETS SHOULD BE SWALLOWED WHOLE, NOT CHEWED, CRUSHED OR BROKEN.

MS CONTIN SUSPENSION (modified release granules):

The entire contents of the sachet should be reconstituted in water as follows:

20 mg, 30 mg and 60 mg in 10 mL of water

100 mg in 20 mL of water

200 mg in 30 mL of water

Mix thoroughly and take immediately.

The pink granules with an odour of raspberries produce a uniform red dispersion when reconstituted.

MS CONTIN SUSPENSION should be taken with food where possible.

The modified release granules in suspension should be used at 12-hourly intervals. The dosage is dependent upon the severity of the pain, the patient's age and previous history of analgesic requirements.

Adults

The most frequent initial dose is 30 mg MS CONTIN SUSPENSION every 12 hours.

Increasing severity of pain will require an increased dosage of MS CONTIN modified release granules in suspension. A daily increase of 30-50% may be appropriate. The correct dosage for any individual patient is that which is sufficient to control pain for a full 12 hours.

Because of the sustained release properties of MS CONTIN SUSPENSION, dosage adjustments should generally be separated by 48 hours. If dose increments are required, they should be proportionately greater at the lower dose level (in terms of percentage of previous dose), than when adjusting a higher dose.

Patients receiving the 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 requirements are of the order of 100%. In such patients individual dose adjustments are required.

4.3 CONTRAINDICATIONS

MS CONTIN tablets or suspension should not be given to patients with: hypersensitivity to opioids or to any of the excipients; acute asthma or other obstructive airway disease and acute respiratory depression; *cor pulmonale*; cardiac arrhythmias; acute alcoholism; *delirium tremens*;

severe CNS depression; convulsive disorders; increased cerebrospinal or intracranial pressure; head injury; brain tumour; paralytic ileus, delayed gastric emptying, suspected surgical and acute abdomen; severe liver disease, incipient hepatic encephalopathy; severe renal dysfunction; concomitant monoamine oxidase inhibitors (MAOIs), or within 14 days of such therapy (see Section 4.5 Interactions with other medicines and other forms of interactions); children under one year of age; pregnancy.

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

MS CONTIN tablets or suspension are contraindicated in patients with chronic pain not due to malignancy, who have a prior history of substance and alcohol abuse.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Morphine must be administered with caution in patients taking CNS depressants (see Section 4.5 Interactions with other medicines and other forms of interactions).

Opioids, such as morphine sulfate pentahydrate, may influence the hypothalamic-pituitary-adrenal or gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical symptoms may manifest from these hormonal changes.

Head injury and increased intracranial pressure

The respiratory depressant effects of morphine, and the capacity to elevate cerebrospinal fluid pressure, may be greatly increased in the presence of already elevated intracranial pressure produced by trauma. Also, morphine may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, morphine must be used with extreme caution and only if it is considered essential.

Respiratory depression

The major risk of opioid excess is respiratory depression. Morphine should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia. Such patients are often less sensitive to the stimulatory effects of carbon dioxide on the respiratory centre and the respiratory depressant effects of morphine may reduce respiratory drive to the point of apnoea.

Hypotensive effect

Morphine administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of drugs such as phenothiazines or certain anaesthetics.

Abdominal conditions

Morphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions. Where there is a possibility of paralytic ileus occurring, morphine should not be used. Should paralytic ileus be suspected or occur during use, MS CONTIN tablets and suspension should be discontinued immediately. As with all oral morphine preparations, MS CONTIN tablets and 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.

Decreased gastric emptying associated with morphine may be expected to increase the risks of aspiration either associated with morphine-induced CNS depression/coma, or during or after general anaesthesia.

Cordotomy

Severe pain antagonises the subjective and respiratory depressant actions of morphine. Should pain suddenly subside, these effects may rapidly become manifest. Patients who are scheduled for cordotomy or other pain-relieving surgical procedures should not receive MS CONTIN tablets or suspension within 24 hours of the procedure. Pain in the immediate pre-operative period, and any symptoms of opioid withdrawal, should be managed with short-acting analgesic agents. If further treatment with MS CONTIN tablets or suspension is indicated, the dosage should be adjusted to the new post-operative requirement.

Biliary tract and sphincter of Oddi conditions

Because of the spasmogenic properties of morphine in the biliary tract and sphincter of Oddi, it should be used only when necessary, and with caution in biliary colic, operations on the biliary tract and acute pancreatitis.

Acute ulcerative colitis

Morphine may cause toxic dilation in patients with acute ulcerative colitis.

Hyperalgesia

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

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.

Special risk groups

Morphine should be administered with caution, in reduced dosages, to debilitated patients, and in patients with Addison's disease, hypothyroidism, prostatic hypertrophy or urethral stricture.

Morphine should be used with caution in patients with impaired respiratory function, convulsive disorders, inflammatory bowel disorders, adrenocortical insufficiency, hypotension with hypovolaemia, diseases of the biliary tract, pancreatitis and opioid dependency.

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

Formulation

The modified release tablets must be swallowed whole, and not broken, chewed or crushed. The administration of broken, chewed or crushed modified release morphine tablets leads to a rapid release and absorption of a potentially fatal dose of morphine.

The contents of the sachets for the suspension (modified release granules) must be suspended whole and drunk 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.

It is not possible to ensure bioequivalence between different brands of modified release morphine products. Therefore, caution is needed when changing between different brands of sustained or modified release morphine, or other strong opioid analgesic preparations, and the patient should be re-titrated and clinically re-assessed.

Lactose

MS CONTIN tablets (5 mg, 10 mg, 15 mg, 30 mg and 60 mg tablets only) contain lactose. Patients with rare hereditary problems including galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take these strengths of MS CONTIN tablets.

Use in chronic, non-malignant pain

The use of MS CONTIN tablets or suspension for the treatment of chronic pain which is not due to malignancy should be restricted to situations where:

- all other conservative methods of analgesia have been tried and have failed
- the pain is having a significant impact on the patient's quality of life
- there is no psychological contraindication, drug-seeking behaviour or history of drug misuse.

Prior to long-term prescribing, a trial of MS CONTIN tablets or suspension or shorter acting opioids should be undertaken. Long-term administration of MS CONTIN tablets or suspension should only occur if this trial demonstrates that the pain is opioid sensitive. Opioid-naïve patients who require rapid dose escalation with no concomitant pain relief within the trial period should generally be considered inappropriate for long-term therapy.

A single doctor should be responsible for the prescribing and monitoring of the patient's opioid use.

Prescribers should consult appropriate clinical guidelines on the use of opioid analgesics in such patients (e.g. those published by the Australian Pain Society in the Medical Journal of Australia 1997; 167: 30 - 34).

Drug dependence

As with other opioids, tolerance and physical dependence tend to develop upon repeated administration of morphine and there is potential for abuse of the drug and for development of strong psychological dependence. MS CONTIN tablets or suspension should therefore be prescribed and handled with the high degree of caution appropriate to the use of a drug with strong abuse potential.

In the absence of a clear indication for a strong opioid analgesic, drug-seeking behaviour must be suspected and resisted, particularly in individuals with a history of, or propensity for, drug abuse. Withdrawal symptoms may occur following abrupt discontinuation of morphine therapy or upon administration of an opioid antagonist. Therefore, patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control (see Section 4.8 Adverse effects (Undesirable effects)). Morphine should be used with caution and under close supervision in patients with pain not due to malignancy who have a prior history of substance abuse. However, in such cases, prior psychological assessment is essential and the prescribing doctor should consider whether the benefit of treatment outweighs the risk of abuse.

Abuse of oral dosage forms

The abuse of oral dosage forms by parenteral administration can be expected to result in serious adverse events, which may be fatal.

Use during labour/delivery

Morphine crosses the placental barrier and its administration during labour can produce respiratory depression in the neonate. These products should only be used during labour after weighing the needs of the mother against the risk to the foetus.

Use in hepatic impairment

Morphine should be administered with caution and in reduced dosages to patients with severely reduced hepatic function.

Use in renal impairment

Morphine should be administered with caution and in reduced dosages to patients with severely reduced renal function.

Morphine-6-glucuronide may accumulate in patients with renal failure, leading to CNS and respiratory depression.

Use in the elderly

Morphine should be administered with caution and in reduced dosages in elderly patients.

Paediatric use

There are no controlled trials of the use of MS CONTIN tablets in children weighing 25 kg or less, nor in children with chronic, severe, non-malignant pain.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Acidifying or alkalising agents

Generally, the effects of morphine may be antagonised by acidifying agents and potentiated by alkalising agents. 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.

Amphetamines, chlorpromazine and methocarbamol

The analgesic effect of morphine is potentiated by amphetamines, chlorpromazine and methocarbamol.

Anticholinergics

Medicinal products that block the action of acetylcholine, for example antihistamines, anti-parkinsonian drugs and anti-emetics, may interact with morphine to potentiate anticholinergic adverse events.

Cimetidine

Cimetidine inhibits the metabolism of morphine. A potentially lethal interaction between morphine and cimetidine has been reported. The patient exhibited apnoea, significantly

reduced respiratory rate and suffered a grand mal seizure. Naloxone increased the respiratory rate; however, confusion, disorientation, generalised twitching and periods of apnoea persisted for 80 hours.

CNS depressants

Morphine should be used with caution and in reduced dosage in patients who are concurrently receiving other CNS depressants which include, but are not limited to opioids, anaesthetics, sedatives (including benzodiazepines), anxiolytics, hypnotics, barbiturates, phenothiazines, antidepressants (including tricyclic antidepressants), chloral hydrate, antipsychotics, glutethimide, tranquilisers, muscle relaxants, antihypertensives, gabapentin and alcohol as they may enhance the depressant effects of morphine. Pyrazolidone antihistamines and beta-blockers may also enhance the depressant effect of morphine. Interactive effects resulting in respiratory depression, hypotension, profound sedation, coma or death may result if these drugs are taken in combination with the usual doses of morphine.

Coumarin and other anticoagulants

Morphine may increase the anticoagulant activity of coumarin and other anticoagulants.

Mixed agonist/antagonist opioid analgesics

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.

Monoamine oxidase inhibitors

Non-selective MAOIs (including procarbazine hydrochloride) intensify the effects of morphine and other opioid drugs which can cause anxiety, confusion and significant respiratory depression, sometimes leading to coma. Morphine should not be given to patients taking non-selective MAOIs or within 14 days of stopping such treatment. It is unknown whether there is an interaction between selective MAOIs (e.g. moclobemide and selegiline) and morphine, therefore, caution is advised with this drug combination.

Propranolol

The combination of morphine and propranolol is potentially lethal. Propranolol increases the acute CNS toxicity of morphine.

Rifampicin

Plasma concentrations of morphine may be reduced by rifampicin.

Ritonavir

Available data indicate that ritonavir may increase the activity of glucuronyl transferases. Consequently, co-administration of ritonavir and morphine may result in decreased serum concentrations of morphine with possible loss of analgesic effectiveness.

Zidovudine

Morphine may alter the metabolism of zidovudine by competitively inhibiting glucuronidation or directly inhibiting hepatic microsomal metabolism, therefore this combination should be used with caution.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Prolonged use of opioid drugs may result in impairment of reproductive function, including infertility and sexual dysfunction in both sexes and irregular menses in women.

Animal studies have shown that morphine may reduce fertility. In male rats, reduced fertility and chromosomal damage in gametes have been reported.

Use in pregnancy – Pregnancy Category C

Australian Pregnancy Categorisation C. Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible.

Opioid analgesics may cause respiratory depression in the newborn infant. Morphine has been associated with foetal CNS defects in rodent studies.

In humans it is not known whether morphine can cause foetal harm when administered during pregnancy. Use of MS CONTIN tablets or suspension should be avoided to the extent possible in patients who are pregnant. Long-term use of opioids in pregnancy may result in a neonatal opioid withdrawal state.

Use in lactation

Morphine has been detected in human breastmilk. Caution should be exercised if morphine is administered to a nursing mother and use of MS CONTIN tablets or suspension should be avoided to the extent possible.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Morphine may impair the mental and/or physical abilities needed for certain potentially hazardous activities such as driving a car or operating machinery. Patients should be cautioned accordingly.

Patients should also be cautioned about the combined effects of morphine with other CNS depressants, including other opioids, phenothiazines, sedative/hypnotics and alcohol.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The following frequencies are the basis for assessing adverse effects.

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

The major hazards associated with morphine, as with other opioid analgesics, are respiratory depression and, to a lesser degree, circulatory depression. Respiratory arrest, shock and cardiac arrest have occurred following oral or parenteral use of morphine.

Very common adverse effects requiring medical attention

Frequently observed side effects of opioid analgesics such as morphine are sedation, nausea and vomiting, constipation and sweating.

Sedation

Most patients experience initial drowsiness partly for pharmacokinetic reasons and partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Drowsiness usually clears in three to five days and is usually not a reason for concern providing that it is not excessive, or associated with unsteadiness or confusional symptoms. If excessive sedation persists the reason for it must be sought. Some of these are: concomitant sedative medications, hepatic or renal failure, exacerbated respiratory failure, higher doses than tolerated in an older patient, or the patient is actually more severely ill than realised. If it is necessary to reduce the dose, it can be carefully increased again after three or four days if it is obvious that the pain is not being well controlled. Dizziness and unsteadiness may be caused by postural hypotension particularly in elderly or debilitated patients. It can be alleviated if the patient lies down. Because of the slower clearance in patients over 50 years of age, an appropriate dose in this age group may be as low as half or less the usual dose in the younger age group.

Nausea and Vomiting

Nausea and vomiting occur frequently after single doses of opioids or as an early unwanted effect of regular opioid therapy. When instituting prolonged therapy for chronic pain, the routine prescribing of an anti-emetic should be considered. Patients taking the equivalent of a single dose of 20 mg or more of morphine (60 mg q12h of MS CONTIN tablets or suspension) usually require an anti-emetic during early therapy. Small doses of prochlorperazine or haloperidol are frequently prescribed anti-emetics. Nausea and vomiting tend to lessen in a week or so but may persist due to opioid-induced gastric stasis. In such patients, metoclopramide is often useful.

Constipation

As with all opioid analgesics, constipation is very common. In some instances, particularly the elderly or bedridden, patients may become impacted. It is essential to caution the patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged opioid therapy. Dietary modification, suitable exercise, softeners, laxatives and other appropriate measures should be used as required.

Other adverse effects include:

Cardiac disorders

Not known: bradycardia, palpitations, supra-ventricular tachycardia

Ear and labyrinth disorders

Uncommon: vertigo

Endocrine disorders

Uncommon: a syndrome of inappropriate antidiuretic hormone secretion characterised by hyponatremia secondary to decreased free-water excretion may be prominent (monitoring of electrolytes may be necessary)

Eye disorders

Uncommon: visual disturbance
Not known: miosis

Gastrointestinal disorders

Common: abdominal pain, anorexia, dry mouth
Uncommon: dyspepsia, ileus, taste perversion
Not known: cramps, gastrointestinal disorders

General disorders and administration site conditions

Common: asthenic conditions (fatigue, malaise), pruritus
Uncommon: peripheral oedema
Not known: drug tolerance, oedema, drug withdrawal syndrome, drug withdrawal syndrome neonatal

Hepato-biliary disorders

Uncommon: increased hepatic enzyme
Not known: biliary pain, biliary spasm, biliary tract cramps

Immune system disorders

Uncommon: hypersensitivity
Not known: anaphylactic reaction, anaphylactoid reaction

Nervous system disorders

Common: dizziness, headache, involuntary muscle contractions, somnolence
Uncommon: convulsions, hypertonia, paraesthesia, syncope
Not known: hyperalgesia, weakness

Psychiatric disorders

Common: confusion, insomnia
Uncommon: agitation, euphoria, hallucinations, malaise, mood altered
Not known: drug dependence, dysphoria, thinking disturbances

Renal and urinary disorders

Uncommon: ureteric spasm, urinary retention or hesitance

Reproductive system and breast disorders

Not known: amenorrhoea, erectile dysfunction, reduced libido or potency

Respiratory, thoracic and mediastinal disorders

Uncommon: bronchospasm, pulmonary oedema, respiratory depression
Not known: cough decreased

Skin and subcutaneous tissue disorders

Common: hyperhidrosis, other skin rashes including contact dermatitis

Uncommon: urticaria

Vascular disorders

Uncommon: facial flushing, hypotension

Not known: faintness, postural hypotension

Withdrawal (abstinence) syndrome

Physical dependence with or without psychological dependence tends to occur with chronic administration. An abstinence syndrome may be precipitated when opioid administration is discontinued or opioid antagonists administered. Tolerance to the effects of morphine may develop.

The following withdrawal symptoms may be observed after opioids are discontinued: body aches, diarrhoea, gooseflesh, loss of appetite, nervousness or restlessness, runny nose, sneezing, chills, tremors or shivering, stomach cramps, nausea, trouble with sleeping, unusual increase in sweating and yawning, weakness, tachycardia and unexplained fever. With appropriate medical use of opioids and gradual withdrawal from the drug, these symptoms are usually mild.

Post-marketing

Nervous system disorders

Not known: allodynia

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

Symptoms

Serious morphine overdosage is characterised by respiratory depression (reduced respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, pneumonia aspiration, miotic pupils, rhabdomyolysis progressing to renal failure, flaccidity of skeletal muscle, cold or clammy skin, and sometimes hypotension and bradycardia. Severe overdosage may result in apnoea, pulmonary oedema, circulatory collapse, cardiac arrest and death.

Treatment

Primary attention should be given to the establishment of adequate respiratory exchange through the provision of a patent airway and controlled or assisted ventilation. The opioid antagonist naloxone hydrochloride is a specific antidote against respiratory depression due to overdosage or as a result of unusual sensitivity to morphine. An appropriate dose of the antagonists should therefore be administered, preferably by the intravenous route. The usual initial intravenous (IV) adult dose of naloxone is 0.4 mg or higher (please refer to naloxone Product Information for further information). Concomitant efforts at respiratory resuscitation

should be carried out. Since the duration of action of morphine, particularly sustained release formulations, may exceed that of the antagonist, the patient should be under continued surveillance and doses of the antagonist should be repeated as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated to manage the circulatory shock accompanying an overdose. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation. Artificial ventilation should be applied if necessary and fluid and electrolyte metabolism maintained.

In an individual physically dependent on opioids, the administration of the usual dose of opioid antagonist will precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of antagonist administered. The use of opioid antagonists in such individuals should be avoided if possible. If an opioid antagonist must be used to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care by using dosage titration, commencing with 10 to 20% of the usual recommended initial dose.

Gastric lavage with a wide-bore tube followed by a suspension of activated charcoal will aid the removal of morphine. A saline cathartic or sorbitol added to the first dose of activated charcoal may speed gastrointestinal passage of the product.

Toxicity

Morphine toxicity may result from overdosage but because of the great inter-individual variation in sensitivity to opioids it is difficult to determine an exact dose of any opioid that is toxic or lethal. Chewing or crushing and taking the contents of a modified release dosage form leads to the release of morphine in an immediate fashion; this might result in a fatal overdose.

The presence of pain or tolerance tends to diminish the toxic effects of morphine. Published data suggest that in a morphine-naïve, pain-free individual, the lethal dose would be in excess of 120 mg. Patients on chronic oral morphine therapy have been known to take in excess of 3000 mg/day with no apparent toxicity.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Morphine is a phenanthrene alkaloid obtained from opium. Morphine and related compounds interact with specific receptors primarily found in the brain, spinal cord and the myenteric plexus of the gut wall. Morphine has considerably higher affinity for mu receptors than for other opioid receptors. In man, the principal pharmacological actions of morphine are in the central nervous system (CNS); analgesia, drowsiness, mood changes (including euphoria and dysphoria), mental clouding, respiratory depression, nausea or emesis, miosis and on smooth muscle; increased gastrointestinal tone with a reduction in propulsive motion, increased biliary pressure and increased tone of the ureter and vesical sphincter, and alterations of the endocrine and autonomic nervous system

Morphine-induced analgesia is a result of increases in both the pain threshold and pain tolerance. Morphine alters the affective response to pain in that patients remain aware of its existence but are less distressed. Morphine relieves most types of pain but is more effective against dull, constant pain than sharp, intermittent pain.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Morphine is readily absorbed from the gastrointestinal tract, nasal mucosa, lung and after subcutaneous (SC) or intramuscular (IM) injection. Due to "first-pass" metabolism the effect of an oral dose is less than that of the same dose given parenterally. The parenteral to oral morphine potency ratio has been reported to range from 1:6 to 1:2. In general, the greatest difference between parenteral and oral potency is seen in acute studies. With chronic dosing, oral morphine is about 1/2 to 1/3 as potent as when given by injection.

At steady-state, MS CONTIN tablets produce peak morphine concentrations approximately four to five hours post-dose and therapeutic levels tend to persist for a 12-hour period. Peak morphine concentrations are seen with MS CONTIN 5 mg and 15 mg tablets at approximately 2 hours post-dose.

Distribution

Following absorption, approximately 30 to 35% of morphine is reversibly bound to plasma proteins. Free morphine readily leaves the circulation and is concentrated in the liver, kidney, lung, spleen and, to a lesser extent, skeletal muscle. In adults, only small quantities of morphine pass the blood brain barrier.

Metabolism

Conjugation with glucuronic acid is the major metabolic pathway for morphine. The major metabolite is morphine-3-glucuronide. Other metabolites include normorphine, morphine-6-glucuronide, morphine-3,6-diglucuronide and morphine-3-ethereal sulfate.

Excretion

The mean elimination half-life of morphine is two to three hours with great inter-patient variability. The major route of excretion is via the kidney. About 7 to 10% is excreted in the faeces via the bile. Conjugated morphine excreted in the bile may be hydrolysed and reabsorbed from the large bowel.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No regulatory studies to assess the mutagenic potential of morphine have been conducted.

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The inactive ingredients in MS CONTIN modified release tablets (also referred as MS CONTIN tablets) are:

- lactose (except 100 mg and 200 mg)
- hyetellose
- cetostearyl alcohol
- magnesium stearate; and
- purified talc.

MS CONTIN tablets are coated with:

- hypromellose (except 10 mg)
- macrogol 400 (except 10 mg)
- macrogol 3350 (10 mg only)
- titanium dioxide (E171)
- polyvinyl alcohol (10 mg only); and
- purified talc (10 mg only).

The tablet coatings also contain:

- iron oxide red (E172) 10 mg
- iron oxide black (E172) 10 mg and 100 mg
- iron oxide yellow (E172) 10 mg, 15 mg and 100 mg
- quinoline yellow (E104) 15 mg, 60 mg and 200 mg
- brilliant blue FCF (E133) 15 mg and 200 mg
- indigo carmine (E132) 15 mg, 30 mg and 100 mg
- erythrosine (E127) 30 mg and 60 mg; and
- sunset yellow FCF (E110) 30 mg and 60 mg.

The inactive ingredients in MS CONTIN SUSPENSION (modified release granules) are:

- xanthan gum
- polystyrene sulfonate hydrogen xylitol
- raspberry flavour 52354A
- purified water; and
- brilliant scarlet 4R (E124) as colourant.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of these medicines.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C for both MS CONTIN tablets and MS CONTIN SUSPENSION.

6.5 NATURE AND CONTENTS OF CONTAINER

MS CONTIN tablets

Blister packs (PVC/PVdC/Al) of 20, 28 and 60 modified release tablets.

Not all presentations may be marketed.

MS CONTIN SUSPENSION

Pack size of 20 and 28 sachets (CCK/PE/Al/Surlyn).

Not all presentations may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

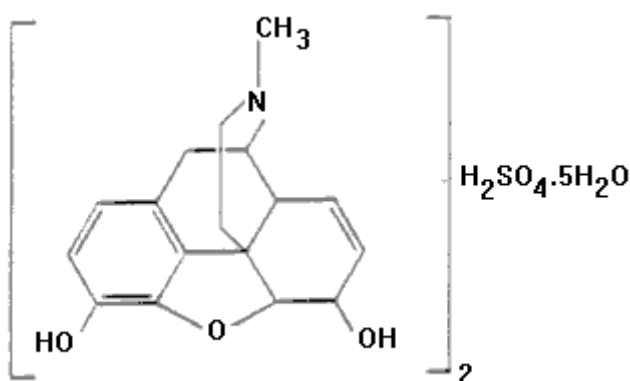
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Morphine sulfate pentahydrate is a white, odourless crystalline powder or needle-like crystals. Morphine sulfate pentahydrate is soluble 1:21 in water and 1:1000 in ethanol. It is practically insoluble in ether or chloroform.

Chemical structure

The structural formula of morphine sulfate pentahydrate is



CAS Number

CAS Registry Number: 6211 - 15 - 0

7 MEDICINE SCHEDULE (POISONS STANDARD)

S8

8 SPONSOR

Mundipharma Pty Limited

ABN 87 081 322 509

88 Phillip Street

SYDNEY NSW 2000

Further information may be obtained from Mundipharma's Medical Information Department
1800 188 009.

9 DATE OF FIRST APPROVAL

MS CONTIN modified release tablets: 5 September 1991

MS CONTIN SUSPENSION (modified release granules): 26 November 1993

10 DATE OF REVISION

25 September 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
2 and 3	Removal of registered trade mark symbol and capitalisation of trade names
4.6	Addition of fertility information in animal studies

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Orbis RA-0280-003

mfpmcon11019 supersedes mfpmcon10719