PRODUCT INFORMATION

MS CONTIN® controlled release tablets
(5 mg, 10 mg, 15 mg, 30 mg, 60 mg, 100 mg and 200 mg)
MS CONTIN® controlled release suspension
(20 mg, 30 mg, 60 mg, 100 mg and 200 mg)

NAME OF THE MEDICINE  Morphine sulfate B.P.

The structural formula of morphine sulfate is

\[
\begin{align*}
\text{CH}_3 \\
\text{N} \\
\text{H}_2\text{SO}_4\cdot\text{5H}_2\text{O} \\
\text{HO} \\
\text{O} \\
\text{OH}
\end{align*}
\]

CAS Registry Number: 6211 - 15 - 0

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

The inactive ingredients in MS CONTIN® tablets are: lactose (5 mg, 10 mg, 15 mg, 30 mg and 60 mg tablets only), hydroxyethyl cellulose, cetostearyl alcohol, magnesium stearate and talc. All MS CONTIN® tablets are coated with hypromellose, macrogol 400 and titanium dioxide (E171). 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; sunset yellow FCF (E110) 30 mg and 60 mg.

The inactive ingredients in MS CONTIN® suspension are: xanthan gum, polystyrene sulfonate - hydrogen, xylitol, raspberry flavour 52354T, purified water and brilliant Scarlet 4R (E127) as colourant.

PHARMACOLOGY

Actions
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. In man, the principal pharmacological actions of morphine are in the 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.

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.

Pharmacokinetics

Absorption
Morphine is readily absorbed from the gastrointestinal tract, nasal mucosa, lung, and after s.c. or i.m. 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.

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 and elimination
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. The mean elimination half-life of morphine is 2 to 3 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.

At steady-state, MS CONTIN® tablets produce peak morphine concentrations approximately 4 to 5 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.

INDICATIONS
Treatment of opioid responsive, chronic severe pain.

CONTRAINDICATIONS
MS CONTIN® tablets or suspension should not be given to patients with: hypersensitivity to opiate narcotics 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; suspected surgical and acute abdomen; paralytic ileus, delayed gastric emptying, severe liver disease, incipient hepatic encephalopathy; severe renal dysfunction; concurrent MAO inhibitors (or within 14 days of such therapy) (see Interactions with other medicines), 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.

PRECAUTIONS

The respiratory depressant effects of morphine, and the capacity to elevate cerebrospinal fluid pressure, may be greatly increased in the presence of an 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 judged essential.

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.

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 such drugs as phenothiazines or certain anaesthetics.

Morphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions. 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.

Severe pain antagonizes 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 interruption of pain transmission pathways 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.

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.

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

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

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

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

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

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

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 prescription, 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 naive 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 prescription 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 ADVERSE EFFECTS – Withdrawal (abstinence) syndrome). 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. The abuse of oral dosage forms by parenteral administration can be expected to result in serious adverse events, which may be fatal.

Special risk groups
Morphine should be administered with caution, in reduced dosages, to elderly or debilitated patients, to patients with severely reduced hepatic or renal function, and in patients with Addison's disease, hypothyroidism, prostatic hypertrophy or urethral stricture.

Driving and operating dangerous machinery
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.

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.

Use in pregnancy
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. Long term use in pregnancy may result in a neonatal opioid withdrawal state.

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.

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 lactation
Morphine has been detected in human breast milk, 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.

Interactions with other medicines

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

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

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 respiratory rate, however, confusion, disorientation, generalised twitching and periods of apnoea persisted for 80 hours.

CNS depressants
The analgesic effect of morphine is potentiated by amphetamines, chlorpromazine and methocarbamol. CNS depressants, such as other opioids, anaesthetics, sedatives, hypnotics, barbiturates, phenothiazines, tranquilisers, muscle relaxants, antihypertensives, tricyclic antidepressants, chloral hydrate and glutethimide may enhance the depressant effects of morphine. Pyrazolidone antihistamines, beta-blockers and alcohol may also enhance the depressant effect of morphine. The interactive effects may include respiratory depression, hypotension, profound sedation and coma. Morphine should be used with caution in patients who are currently taking gabapentin.

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

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 the new selective MAOIs (e.g. moclobemide and selegiline) and morphine therefore, caution is advised with this drug combination.

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.
**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 morphine serum concentrations 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.

**ADVERSE EFFECTS**
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.

**Most common adverse effects requiring medical attention**
The most 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 prescription of antiemetic 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 antiemetic during early therapy. Small doses of prochlorperazine or haloperidol are the most frequently prescribed antiemetics. Nausea and
vomiting tend to lessen in a week or so but may persist due to narcotic-induced gastric stasis. In such patients, metoclopramide is often useful.

**Constipation**
As with all opioid analgesics, constipation is a common occurrence. 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. Softeners, laxatives and other appropriate measures should be used as required.

**Other adverse reactions include:**

**Cardiovascular disorders**
bradycardia, faintness, hypotension, palpitations, postural hypotension, supra-ventricular tachycardia, syncope

**Central nervous system and psychiatric disorders**
asthenia, confusional symptoms, dizziness, dysphoria, euphoria, headache, insomnia, involuntary muscle contractions, thought abnormalities, vertigo, weakness; occasionally, hallucinations; uncommonly, agitation, malaise, mood changes, paraesthesia, seizure, vision abnormalities

**Gastrointestinal disorders**
abdominal pain, anorexia, biliary spasm, biliary tract cramps, constipation, cramps, dry mouth, dyspepsia, gastrointestinal disorders, ileus, taste alterations; uncommonly, elevated hepatic enzymes

**Genitourinary disorders**
amenorrhoea, erectile dysfunction, reduced libido or potency, ureteric spasm, urinary retention or hesitance

**Respiratory disorders**
bronchospasm, cough decreased, respiratory depression

**Endocrine disorders**
Uncommonly, pulmonary oedema, peripheral oedema and 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)

**General disorders**
allergic reaction, anaphylactic and anaphylactoid reaction, drug dependence, drug tolerance, facial flushing, hyperhidrosis, hypertonia, miosis, oedema, pruritus, urticaria, other skin rashes including contact dermatitis

**Withdrawal (abstinence) syndrome**
Physical dependence with or without psychological dependence tends to occur on 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.

**DOSAGE AND 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® controlled release tablets**

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 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.

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 patients needs. (See Dose Titration).

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.

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 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 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 equivalences

<table>
<thead>
<tr>
<th>Drug</th>
<th>Equivalent dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MORPHINE sulfate</td>
<td>10</td>
</tr>
<tr>
<td>OXYCODONE (Percodan, Endone, Proladone)</td>
<td>15</td>
</tr>
<tr>
<td>DEXTROMORAMIDE (Palfium)</td>
<td>15</td>
</tr>
<tr>
<td>PAPAVERETUM (Omnopon)</td>
<td>45</td>
</tr>
</tbody>
</table>


2 Dextromoramide - a single dose is equivalent to morphine 15 mg (diamorphine 10 mg) in terms of peak effect but is shorter acting. The overall potency ratio has been adjusted accordingly.

Dose titration
Dose titration is the key to success with morphine therapy. PROPER OPTIMIZATION 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 MAINTAIN THE PATIENT FREE OF PAIN AT ALL TIMES. 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 (q12h) 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 q8h. More frequent (than q8h) 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 ADVERSE 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 INTACT, NOT CHEWED, CRUSHED OR BROKEN.

MS CONTIN® controlled release suspension
The contents of sachets 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
Mixed thoroughly and taken immediately.

MS CONTIN® suspension should be taken with food where possible.

The controlled 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® controlled 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 turn out to be 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.

OVERDOSAGE
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, flaccidity of skeletal muscle, miotic pupils, 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 one of the antagonists should therefore be administered, preferably by the intravenous route. The usual initial intravenous (i.v.) adult dose of naloxone is 0.4 mg or higher. 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.

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. 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 naive, 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.

**STORAGE CONDITIONS**

Store below 25ºC.
PRESENTATION

MS CONTIN® controlled release tablets, 5 mg (white), 10 mg (light tan), 15 mg (light green), 30 mg (purple), 60 mg (orange), 100 mg (grey), 200 mg (teal green): blister packs of 20's, 28’s and 60's.

All controlled release tablets are film-coated, biconvex and imprinted with the dosage on one side. The 15 mg tablets also carry the Napp logo.

MS CONTIN® controlled release suspension, 20 mg, 30 mg, 60 mg, 100 mg & 200 mg: supplied in packs of sachets of 20's and 28’s.

MANUFACTURER
Bard Pharmaceuticals Ltd
(A member of the NAPP Pharmaceutical Group)

NAME AND ADDRESS OF THE SPONSOR
Mundipharma Pty Limited
ABN 87 081 322 509
50 Bridge Street
SYDNEY NSW 2000

POISON SCHEDULE OF THE MEDICINE  S8

DATE OF TGA APPROVAL  14 July 1998

DATE OF MOST RECENT AMENDMENT
12 March 2002
20 February 2004 (Safety related changes)
15 July 2004 (Safety related changes)
6 April 2005 (Safety-related changes)
11 October 2008 (Safety-related changes)
12 March 2010 (Minor editorial changes)
25 November 2010 (Minor editorial changes)

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