PRODUCT INFORMATION

MS MONO® controlled release capsules (30 mg, 60 mg, 90 mg and 120 mg)

NAME OF THE MEDICINE          Morphine sulfate BP
The structural formula of morphine sulfate is

![Structural formula of morphine sulfate](image)

CAS Registry Number: 6211 - 15 - 0

DESCRIPTION
Morphine sulfate is a white, odourless crystalline powder or needle like crystals. Morphine sulfate has solubility of 1:21 in water and 1:1000 in ethanol. The chemical name is 7,8-didehydro-4,5α-epoxy-17-methylmorphinan-3,6α-diol sulfate salt (2:1) pentahydrate. It is practically insoluble in ether or chloroform.

MS MONO® capsules are a range of modified release capsules containing a multi-particulate formulation of morphine sulfate, intended for once-daily oral administration. The inactive ingredients in MS MONO® capsules are hydrogenated vegetable oil, macrogol 6000, magnesium stearate and purified talc. The capsule shells contain gelatin and sodium lauryl sulphate. They also contain the following colouring materials:

<table>
<thead>
<tr>
<th>Strength</th>
<th>30 mg</th>
<th>60 mg</th>
<th>90 mg</th>
<th>120 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrosine (E127)</td>
<td></td>
<td></td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Indigo carmine (E132)</td>
<td>●</td>
<td>●</td>
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<td>●</td>
</tr>
<tr>
<td>Iron oxide black (E172)</td>
<td>●</td>
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<td>●</td>
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<tr>
<td>Iron oxide red (E172)</td>
<td></td>
<td></td>
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<tr>
<td>Iron oxide yellow (E172)</td>
<td></td>
<td>●</td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Titanium dioxide (E171)</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
</tbody>
</table>

The capsules are all printed in black ink which contains shellac, iron oxide black (E172) and propylene glycol.
PHARMACOLOGY

Pharmacodynamics
Morphine and related compounds interact with specific receptors primarily found in the brain, spinal cord and the myenteric plexus of the gut wall. In humans, 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
Conjugation with glucuronic acid is the major metabolic pathway for morphine. The two major metabolites are morphine-3-glucuronide (50%) and morphine-6-glucuronide (5 –15%). Other metabolites include normorphine, morphine-3,6-diglucuronide and morphine-3-ethereal sulfate. Morphine-6-glucuronide binds to opioid receptors and has been shown to be pharmacologically active. Morphine-3-glucuronide has negligible affinity for opioid receptors and is considered to have no analgesic activity.

At steady state the glucuronide-to-plasma ratios are about 30:1 for morphine-3-glucuronide and 5:1 for morphine-6-glucuronide. The oral administration of morphine results in 2-3 fold higher levels of glucuronide metabolites than parenteral administration.

Elimination
The mean elimination half-life of morphine is 2 to 3 hours with great inter-patient variability. The major route of elimination is via the kidney. About 7 to 10% is excreted in the faeces via the bile. Conjugated morphine excreted in the bile may be hydrolised and reabsorbed from the large bowel.
Clinical Studies
After a single oral dose of MS MONO® capsules, peak morphine concentrations are seen approximately 4 hours post dose. MS MONO® capsules provide an equivalent bioavailability of morphine, with a reduced maximum plasma concentration, when compared with immediate release oral solution or MS CONTIN® tablets. The pharmacokinetics of morphine are linear across a very wide dose range. Clinical studies have shown that therapeutic levels persist for 24 hours.

Because of the high inter-patient variation of morphine pharmacokinetics, and of analgesic requirements, the daily dosage in individual patients must be titrated to achieve appropriate pain control. For this reason, the capsules have been formulated in strengths of 30 mg, 60 mg, 90 mg and 120 mg.

INDICATIONS
Treatment of opioid responsive, chronic severe pain.

CONTRAINDICATIONS
MS MONO® capsules 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 arrhythmia; 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 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 MONO® capsules are contraindicated in patients with chronic pain not due to malignancy, who have a prior history of substance and alcohol abuse.

PRECAUTIONS
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 an already elevated intracranial pressure produced by trauma. Also, morphine may produce confusion, miosis, and 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.

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 such drugs as phenothiazines or certain anaesthetics.

Abdominal conditions
Morphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions. As with all oral morphine preparations, MS MONO® capsules 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.

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 interruption of pain transmission pathways should not receive MS MONO® capsules 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 MONO® capsules is indicated, the dosage should be adjusted to the new post-operative requirement.

Biliary tract & 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.

Gastrointestinal motility
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.

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

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.

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

MS MONO® capsules should be used with caution in patients with 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, MS MONO® capsules should not be used. Should paralytic ileus be suspected or occur during use, MS MONO® capsules should be discontinued immediately.
It is not possible to ensure bioequivalence between different brands of controlled release morphine products. Therefore, it should be emphasised that patients, once titrated to an effective dose should not be changed from MS MONO® capsules to other slow, sustained or controlled release morphine or other potent opioid analgesic preparations without re-titration and clinical assessment.

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

The controlled release capsules or their contents must be swallowed whole, and not broken, chewed, dissolved 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.

**Use in chronic, non-malignant pain**

The use of MS MONO® capsules 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.

Prior to long term prescription, a trial of MS MONO® capsules or shorter acting opioids should be undertaken. Long term administration of MS MONO® capsules 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 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 MONO® capsules 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.

**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 of opioids 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 MONO® capsules 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 MONO® capsules should be avoided to the extent possible.

**Interactions with other medicines**

*Acidifying and 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-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
CNS depressants, such as other opioids, anaesthetics, sedatives, hypnotics, barbiturates, phenothiazines, tricyclic antidepressants, chloral hydrate, glutethimide, tranquilisers, muscle relaxants, antihypertensives and alcohol 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
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 that 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.

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.

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 an antiemetic should be considered. Patients taking the equivalent of a single dose of 20 mg or more of morphine (120 mg q24h of MS MONO® capsules) 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. Dietary modification, suitable exercise, 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; and 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**
- amenorrhea, erectile dysfunction, reduced libido or potency, urinary retention or hesitance, ureteric spasm

**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)

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

**General disorders**
- allergic reaction, anaphylactic and anaphylactoid reactions, 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
MS MONO® capsules should be swallowed whole. However, if the patient has difficulty swallowing the capsules whole, the capsule contents may be administered in one of the following ways:

The capsule contents (pellets) may be sprinkled onto a small amount of soft food (yoghurt, custard, apple puree or ice cream). Following sprinkling of the pellets, the soft food should be consumed within 60 minutes. The pellets must not be chewed or crushed and the mouth should be rinsed to ensure that all pellets have been swallowed.

The pellets may be sprinkled into a glass of liquid (milk, orange juice or water). Following sprinkling of the pellets, the liquid should be consumed within 60 minutes. The pellets must not be chewed or crushed. Some of the pellets may stick to the side of the glass, therefore a further small amount of liquid may be added, the glass should be swirled so that all remaining pellets are taken with the liquid.

The pellets may be administered through a 16 or 20 French gastrostomy tube as follows: flush the gastrostomy tube with liquid feed to ensure it is wet. Sprinkle the pellets into 20 mL of liquid feed and disperse using a swirling motion. Draw the liquid into a 50 mL irrigation tip syringe and administer through the Y port connector attached to the gastrostomy tube. Rinse the beaker with a further 10 mL of feed and administer as above. Repeat rinsing until no further pellets remain in the beaker.

The capsules should be used at 24 hourly intervals.

The capsule and contents should not be crushed or chewed.

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, all important as it may be, should be only one part of a comprehensive approach.

MS MONO® capsules 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 MONO® capsules themselves).

Adults
A patient presenting with severe pain, uncontrolled by weaker opioids should normally be started on 60 mg daily.

Patients previously on normal release oral morphine, MS CONTIN® tablets or MS CONTIN® suspension should be given the same daily dose as MS MONO® capsules. Patients previously on other controlled release morphine preparations should not be transferred to MS MONO® capsules without re-titration and clinical assessment.
Increasing severity of pain will require an increased dosage of MS MONO® capsules using 30 mg, 60 mg, 90 mg or 120 mg alone or in combination to achieve pain relief. Higher doses should be given, where appropriate in 30% - 50% increments as required.

THE CORRECT DOSAGE FOR ANY INDIVIDUAL PATIENT IS THAT WHICH CONTROLS THE PAIN WITH NO OR TOLERABLE SIDE EFFECTS FOR A FULL 24 HOURS.

Patients receiving MS MONO® capsules 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 50% to 100%. In such patients individual dose adjustments are required.

Children > 25 kg
An initial dose for chronic severe pain in cancer in the range of 0.4 to 1.6 mg/kg daily is recommended, but will depend upon the degree of morphine tolerance and should be titrated in accordance with the patients needs in the normal way as for adults.

There are no controlled trials of the use of MS MONO® capsules in children weighing 25 kg or less, or in children with chronic severe non-cancer associated pain.

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

Transferring to MS MONO® capsules from alternate opioids
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. This dose should be given as MS MONO® capsules in a single dose.

Table 1. Opioids: approximate analgesic equivalences

<table>
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<tr>
<th>Drug</th>
<th>Equivalent dose (mg)</th>
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<tr>
<td>MORPHINE sulfate</td>
<td>10</td>
</tr>
<tr>
<td>OXYCODONE</td>
<td>15</td>
</tr>
<tr>
<td>DEXTROMORAMIDE</td>
<td>15</td>
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</table>

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

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.

OVERDOSSAGE

Symptoms

Serious morphine overdose is characterised by respiratory depression (reduced respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, pin-point pupils, 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 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.

Consideration should be made to whole bowel irrigation.

Prolonged periods of observation (days) may be required for patients who have overdosed with long acting morphine preparations.

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 controlled release dosage
form leads to the release of the 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.

**STORAGE CONDITIONS**
Store capsules below 25°C.

**PRESENTATION**
MS MONO® controlled release capsules 30 mg - size 4, light blue capsules marked MS OD 30
MS MONO® controlled release capsules 60 mg - size 3, brown capsules marked MS OD 60
MS MONO® controlled release capsules 90 mg - size 2, pink capsules marked MS OD 90
MS MONO® controlled release capsules 120 mg - size 1, olive capsules marked MS OD 120
MS MONO® controlled release capsules are available in packs of 10 and 14 capsules.

**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

**TGA APPROVAL DATE**
7 August 2000

**DATE OF THIS AMENDMENT**
19 January 2004
24 February 2004 (Safety related)
15 July 2004 (Safety related)
8 April 2005 (Safety related)
11 October 2008 (Safety-related)
12 March 2010 (Minor editorial changes)
16 July 2010 (Minor editorial change)
25 November 2010 (Minor editorial changes)

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