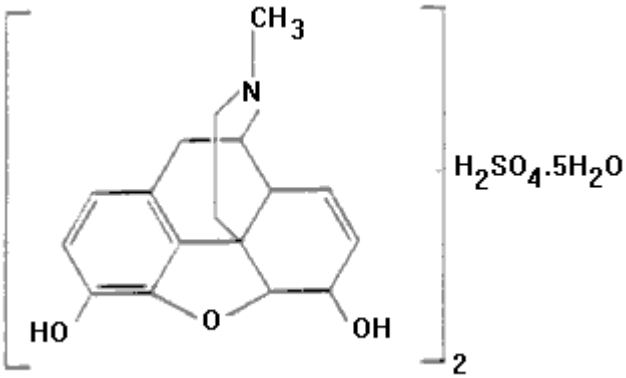
PRODUCT INFORMATION

MS Mono® modified release capsules
30 mg, 60 mg, 90 mg and 120 mg

NAME OF THE MEDICINE

Morphine sulfate
The structural formula of morphine sulfate is:



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 sulfate. They also contain the following colouring materials:

	Strength			
Colouring Material	**30 mg**	**60 mg**	**90 mg**	**120 mg**
Erythrosine (E127)			●	
Indigo carmine (E132)	●	●		●
Iron oxide black (E172)			●	●
Iron oxide red (E172)		●	●	
Iron oxide yellow (E172)		●		●
Titanium dioxide (E171)	●	●	●	●

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

PHARMACOLOGY

Pharmacodynamics

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 humans, 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.

Pharmacokinetics

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.

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-morphine 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.

Excretion

The mean elimination half-life of morphine is two to three 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 hydrolysed and reabsorbed from the large bowel.

CLINICAL TRIALS

After a single oral dose of MS Mono capsules, peak morphine concentrations are seen approximately four 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 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 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

Morphine must be administered with caution in patients taking CNS depressants (see INTERACTIONS WITH OTHER MEDICINES).

Opioids, such as morphine sulfate, 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 judged 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, MS Mono capsules should not be used. Should paralytic ileus be suspected or occur during use, MS Mono capsules should be discontinued immediately. 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.

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 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 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 sulfate may occur in particular at high doses. A morphine sulfate dose reduction or change in opioid may be required.

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 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 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.

It is not possible to ensure bioequivalence between different brands of modified 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 modified release morphine or other potent opioid analgesic preparations without re-titration and clinical assessment.

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, drug-seeking behavior or history of drug misuse.

Prior to long-term prescribing, 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-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 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 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.

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.

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.

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 Mono capsules 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 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 breastmilk. 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.

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.

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-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.

ADVERSE 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 (120 mg q24h of MS Mono capsules) 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.

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 total daily dose of morphine as MS Mono capsules. Patients previously on other modified 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 patient's needs in the normal way as for adults.

Children ≤ 25 kg

There are no controlled trials of the use of MS Mono capsules in children weighing 25 kg or less, nor in children with chronic severe non-cancer associated pain.

The elderly

As with all opioids, 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

Drug	Equivalent dose (mg)	
	IM	PO
MORPHINE sulfate	10	30
OXYCODONE		15
DEXTROMORAMIDE [1]		15

[1] Dextromoramide - a single 5 mg dose is equivalent to morphine 15 mg in terms of peak effect but is shorter acting. The overall potency ratio has been adjusted accordingly.
IM – intramuscular; PO – oral administration

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.

OVERDOSAGE

For information on the management of overdose, contact the Poisons Information Centre on 131126 (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 one 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.

Whole bowel irrigation (e.g. one or two litres of polyethylene glycol solution orally per hour until rectal effluent is clear) may be useful for gut decontamination.

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 modified 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-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.

PRESENTATION AND STORAGE CONDITIONS

MS Mono® modified release capsules 30 mg - size 4, light blue capsules marked MS OD 30
MS Mono® modified release capsules 60 mg - size 3, brown capsules marked MS OD 60
MS Mono® modified release capsules 90 mg - size 2, pink capsules marked MS OD 90
MS Mono® modified release capsules 120 mg - size 1, olive capsules marked MS OD 120

MS Mono® modified release capsules are available in packs of 10 and 14 capsules in blister packs or bottles.

Not all presentations may be marketed.

Store below 25ºC.

NAME AND ADDRESS OF THE 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.

POISON SCHEDULE OF THE MEDICINE

S8

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

26 September 2000

DATE OF MOST RECENT AMENDMENT

26 June 2017

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Orbis RA-0124