

1. PRODUCT NAME

m-Eslon SR, morphine sulphate, modified release capsule, 10 mg, 30 mg, 60 mg, 100 mg and 200 mg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

m-Eslon SR 10 mg: each capsule contains microgranules providing 10 mg of morphine sulphate.

m-Eslon SR 30 mg: each capsule contains microgranules providing 30 mg of morphine sulphate.

m-Eslon SR 60 mg: each capsule contains microgranules providing 60 mg of morphine sulphate.

m-Eslon SR 100 mg: each capsule contains microgranules providing 100 mg of morphine sulphate.

m-Eslon SR 200 mg: each capsule contains microgranules providing 200 mg of morphine sulphate.

For the full list of excipients see 6.1.

3. PHARMACEUTICAL FORM

Modified release capsules filled with off-white spherical microgranules.

m-Eslon SR 10 mg: size 4 capsules with natural transparent body and yellow cap, printed 10 mg in black ink.

m-Eslon SR 30 mg: size 4 capsules with natural transparent body and pink cap, printed 30 mg in black ink.

m-Eslon SR 60 mg: size 3 capsules with natural transparent body and orange cap, printed 60 mg in black ink.

m-Eslon SR 100 mg: size 2 capsules with natural transparent body and white cap, printed 100 mg in black ink.

m-Eslon SR 200 mg: size 0 capsules with natural transparent body and cap, printed 200 mg in black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the prolonged relief of chronic, moderate to severe pain in adults.

Use in Non-Malignant Pain

The use of m-Eslon SR for the treatment of 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.

4.2 Dose and method of administration

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

As with other strong opioid analgesics, use of morphine for the management of persistent pain should be preceded by a thorough assessment of the patient and diagnosis of the specific pain or pains and their causes. Use of opioids for the relief of chronic pain, including cancer pain, all important as it may be, should be only one part of a comprehensive approach to pain control including other treatment modalities or drug therapy, non-drug measures and psychosocial support.

Prior to long term prescription, a trial of m-Eslon SR capsules or shorter acting opioid analgesics should be undertaken (e.g. for a period of four to six weeks). Long term administration of m-Eslon SR 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 prescription and monitoring of the patient's opioid use.

The use of morphine for managing chronic pain of non-malignant origin should be restricted to cases where: all other conservative methods of analgesia have been tried and 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. Therapy should only be initiated by a specialist with experience in chronic pain management and in accordance with guidelines approved by the New Zealand Medical Association.

When the cause of pain is treated simultaneously e.g. post-operative pain, the doses of morphine should be adjusted according to the results of the treatment administered.

Children

m-Eslon SR capsules are not recommended for pediatric use.

Adults

Initial dosing

All strengths: One capsule every 12 hours or as prescribed by a physician.

The dosage is dependent upon the severity of the pain and the patient's previous history of analgesic requirements. The capsules should normally be administered twice daily at 12 hourly intervals. One or two 10 mg capsules twice daily is the recommended starting dosage for a patient presenting with severe pain. With increasing severity of pain it is recommended that

the dosage of morphine be increased to achieve the desired relief. The dosage may be varied by choosing combinations of available strengths (10 mg, 30 mg, 60 mg, 100 mg and 200 mg) or by using higher strength capsules alone.

When m-Eslon SR capsules are to be given for the relief of post-operative pain, it is not advisable to administer it during the first 24 hours. Following this initial period, the dosage should be at the physician's discretion.

Some patients may require supplemental parenteral morphine which is perfectly acceptable. Careful attention should be paid to the total morphine dosage however, and the prolonged effects of morphine in the m-Eslon SR capsules should also be borne in mind.

m-Eslon SR capsules should be used with caution post operatively (as with all morphine preparations) but especially in cases of 'acute abdomen' and following abdominal surgery. Gastric motility should have returned and be maintained before treatment with m-Eslon SR is initiated.

Because of the high inter-patient variation in morphine pharmacokinetics, and in analgesic requirements, the daily dosage in individual patients must be titrated to achieve appropriate pain control. Reduced dosing is necessary in patients with renal or hepatic dysfunction, and also in the elderly due to increased sensitivity to its effect.

Converting from immediate release morphine

It is recommended that a patient transferred from another oral morphine preparation, having a similar bioavailability to immediate release morphine tablets, should receive the same total morphine dose in one 24 hour period. This total dose should be divided between the morning and evening administration. Dosage titration and clinical assessment may be appropriate.

Where a patient has previously received parenteral morphine prior to being transferred to m-Eslon SR capsules, a higher total dosage of morphine may be required. Individual dosage adjustment will be necessary to compensate for any reduction in analgesic effect associated with oral administration.

Administration

m-Eslon SR is intended for oral administration only.

The microgranules should not be chewed or crushed because of the risk of rapid release of morphine leading to toxic concentrations.

The capsules may be opened, and the microgranules given mixed with soft food or liquids. Alternatively, the contents of the capsules may be given by gastric tube or gastrostomy to dysphagic (e.g. E.N.T. cancer) patients who can benefit from the analgesia obtained from an extended release preparation. It is recommended that the internal diameter of the tube is at least 2.5 mm and the procedure for a tube with a dead volume must be strictly followed according to the instructions for each tube. In addition the tube's composition is important as the material needs to allow the microgranules to slide through and this property has to be

determined for each tube. Some tubes are not suitable for use with this formulation and compatibility will need to be discerned from the manufacturer's data.

4.3 Contraindications

- Co-ingestion with alcohol (in the presence of alcohol, dose-dumping of opioid to potentially fatal plasma levels may occur, even in opioid-tolerant patients)
- Respiratory depression especially in the presence of cyanosis and excessive bronchial secretion, obstructive airways disease, known morphine sensitivity or acute hepatic disease.
- Acute alcoholism, severe cirrhosis, delirium tremens.
- Severe CNS depression.
- Convulsive disorders (may lower the seizure threshold).
- Head injuries, brain tumours and other conditions in which cerebrospinal or intracranial pressure is raised (may cause marked exaggeration of cerebrospinal fluid pressure and mask the clinical course).
- Acute attacks of bronchial asthma.
- Heart failure secondary to chronic lung disease, cor pulmonale.
- Cardiac arrhythmias.
- Hypotension.
- Surgical anastomosis (narcotics may cause increase in intraluminal pressure).
- Concurrent administration with or within 2 weeks of discontinuation of monoamine oxidase inhibitors (MAOIs).
- Patients with paralytic ileus, acute abdomen, or delayed gastric emptying.
- Patients with phaeochromocytoma as morphine appears to increase catecholamine levels.
- m-Eslon SR is not to be used as a pre-operative medication.
- Children under the age of 6 months.
- Patients with chronic pain of non-malignant origin who have a prior history of substance abuse.

4.4 Special warnings and precautions for use

m-Eslon SR capsules must NOT be taken with alcohol.

m-Eslon SR has not been compared to any modified-release morphine preparation on the New Zealand market, and therefore it is not interchangeable with other formulations.

Tolerance, dependence and withdrawal

Neuroadaptation of the opioid receptors to repeated administration of opioids can produce tolerance and physical dependence. Tolerance is the need for increasing doses to maintain analgesia. Tolerance may occur to both the desired and undesired effects of the opioid.

There is potential for abuse of the drug and for development of strong psychological dependence. m-Eslon SR capsules should therefore be prescribed and handled with the high degree of caution appropriate to the use of a drug with strong abuse potential. Drug abuse is not, however, a problem in patients with severe pain in which morphine is appropriately indicated. In these patients, an increase in the doses for pain management does not necessarily reflect a development of dependence. On the other hand, in the absence of a clear indication for a strong opioid analgesic, drug-seeking behaviour must be suspected and resisted, particularly in patients with a history of, or propensity for drug abuse.

Physical dependence, which can occur after several days to weeks of continued opioid usage, results in withdrawal symptoms if the opioid is ceased abruptly or the dose is significantly reduced.

Withdrawal symptoms can also occur following the administration of an opioid antagonist (e.g. naloxone) or partial agonist (e.g. buprenorphine). Withdrawal can result in some or all of the following symptoms: dysphoria, restlessness/agitation, lacrimation, rhinorrhoea, yawning, sweating, chills, myalgia, mydriasis, irritability, anxiety, increasing pain, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, increased blood pressure, increased respiratory rate and increased heart rate.

When discontinuing m-Eslon SR in a person who may be physically-dependent, the drug should not be ceased abruptly but withdrawn by tapering the dose gradually (see *Ceasing opioids and section 4.2 Dose and Method of Administration*).

Infants born to mothers who are physically dependent upon opioid analgesics may also be physically dependent and may exhibit withdrawal symptoms such as generalized tremors, hypertonicity, hyperalertness, sleeplessness, excessive crying, vomiting, diarrhoea, yawning, and occasional fever. These infants may have respiratory depression at birth.

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 m-Eslon SR within 24 hours of the procedure.

Precautions

m-Eslon SR capsules should be given with caution or in reduced doses to elderly or debilitated patients and in patients presenting adrenocortical insufficiency, impaired kidney or liver function, prostatic hypertrophy or urethral stricture, hypopituitarism, anemia, severe malnutrition, fulminant ulcerative colitis, hypothyroidism or untreated myxedema, shock. Cautions should also be exercised in its administration to patients presenting CNS depression, toxic psychosis, severe kyphoscoliosis, myasthenia gravis, patients about to undergo biliary tract surgery and patients with acute pancreatitis secondary to biliary disease.

m-Eslon SR should not be given to patients with gastrointestinal obstruction as there is a risk of the medication remaining in the stomach for an extended period and the subsequent bolus of morphine when normal gut motility is restored.

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

Other special risk patients

Morphine may also lead to acute retention of urine by causing spasm of the sphincter of the bladder especially in men with prostatism. Monitoring of patients at risk is recommended. Use with caution in patients with atrial flutter and other supraventricular tachycardia.

Respiratory depression

Serious, life-threatening or fatal respiratory depression can occur with the use of opioids even when used as recommended. It can occur at any time during the use of m-Eslon SR but the risk is greatest during initiation of therapy or following an increase in dose. Patients should be monitored closely for respiratory depression at these times.

The risk of life-threatening respiratory depression is also higher in elderly, frail, or debilitated patients and in patients with existing impairment of respiratory function (e.g. chronic obstructive pulmonary disease; asthma). For patients suffering from conditions accompanied by hypoxia or hypercapnia, even moderate therapeutic doses may significantly decrease pulmonary ventilation. Opioids should be used with caution and with close monitoring in these patients (see *section 4.2 Dose and method of administration*). The use of opioids is contraindicated in patients with severe respiratory disease, acute respiratory disease and respiratory depression (see *section 4.3 Contraindications*).

Morphine should be used with caution in patients presenting chronic pulmonary disease, substantially decreased respiratory reserve, hypoxia, hypercapnia or pre-existing respiratory depression. Such patients are often less sensitive to the stimulatory effects of carbon dioxide on the respiratory centre and therapeutic doses of morphine may increase airway resistance and decrease respiratory drive to the point of apnoea. Severe pain antagonizes the respiratory depressant effects of morphine.

The respiratory depressant effects of morphine with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure may be exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. 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 to be essential.

It is important to reduce the doses of morphine when other analgesic treatments are prescribed simultaneously, as such combinations enhance the risk of sudden occurrence of respiratory failure. The risk of respiratory depression is greater with the use of high doses of opioids, especially high potency and modified release formulations, and in opioid naïve

patients. Initiation of opioid treatment should be at the lower end of the dosage recommendations with careful titration of doses to achieve effective pain relief. Careful calculation of equianalgesic doses is required when changing opioids or switching from immediate release to modified release formulations, (see *section 4.2 Dose and method of administration*).

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper.

Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol

Concomitant use of opioids and benzodiazepines or other CNS depressants, including alcohol, may result in sedation, respiratory depression, hypotension, coma and death. Because of these risks, concomitant prescribing of m-Eslon SR with CNS depressant medicines, such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics and other CNS depressants, should be reserved for patients for whom other treatment options are not possible. If a decision is made to prescribe m-Eslon SR concomitantly with any of the medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible. Patients should be followed closely for signs and symptoms of respiratory depression and sedation. Patients and their caregivers should be made aware of these symptoms. Patients and their caregivers should also be informed of the potential harms of consuming alcohol while taking m-Eslon SR.

Hypotensive effect

Morphine may cause severe hypotension in patients whose blood pressure has already been compromised by reduced blood volume or concurrent administration of medicines such as phenothiazines or certain anaesthetics. Morphine may cause a decrease in systemic vascular resistance in patients with myocardial infarction. A transient fall in systemic arterial pressure may result, leading to severe hypotension. Administered in large doses, morphine may cause severe hypotension even in the supine patient and may induce orthostatic hypotension in ambulatory patients. Morphine should be administered with caution to patients in circulatory shock as its vasodilatory effects may further reduce cardiac output and blood pressure.

Competitive sports people should be made aware that morphine may produce a positive reaction to anti-doping tests.

Hazardous and harmful use

m-Eslon SR contains the opioid morphine and is a potential drug of abuse, misuse and addiction. Addiction can occur in patients appropriately prescribed m-Eslon SR at recommended doses.

The risk of addiction is increased in patients with a personal or family history of substance abuse (including alcohol and prescription and illicit drugs) or mental illness. The risk also

increases the longer the drug is used and with higher doses. Patients should be assessed for their risks for opioid abuse or addiction prior to being prescribed m-Eslon SR.

All patients receiving opioids should be routinely monitored for signs of misuse and abuse. Opioids are sought by people with addiction and may be subject to diversion. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the safe storage and proper disposal of any unused drug (see *section 6.4 Special precautions for storage and section 6.6 Special precautions for disposal*). Caution patients that abuse of oral or transdermal forms of opioids by parenteral administration can result in serious adverse events, which may be fatal.

Patients should be advised not to share m-Eslon SR with anyone else.

Use of opioids in chronic (long-term) non-cancer pain (CNCP)

Opioid analgesics have an established role in the treatment of acute pain, cancer pain and palliative and end-of-life care. Current evidence does not generally support opioid analgesics in improving pain and function for most patients with chronic non-cancer pain. The development of tolerance and physical dependence and risks of adverse effects, including hazardous and harmful use, increase with the length of time a patient takes an opioid. The use of opioids for long-term treatment of CNCP is not recommended.

The use of an opioid to treat CNCP should only be considered after maximised non-pharmacological and non-opioid treatments have been tried and found ineffective, not tolerated or otherwise inadequate to provide sufficient management of pain. Opioids should only be prescribed as a component of comprehensive multidisciplinary and multimodal pain management.

Opioid therapy for CNCP should be initiated as a trial in accordance with clinical guidelines and after a comprehensive biopsychosocial assessment has established a cause for the pain and the appropriateness of opioid therapy for the patient (see *Hazardous and harmful use, above*). The expected outcome of therapy (pain reduction rather than complete abolition of pain, improved function and quality of life) should be discussed with the patient before commencing opioid treatment, with agreement to discontinue treatment if these objectives are not met.

Owing to the varied response to opioids between individuals, it is recommended that all patients be started at the lowest appropriate dose and titrated to achieve an adequate level of analgesia and functional improvement with minimum adverse reactions. Immediate-release products should not be used to treat chronic pain, but may be used for a short period in opioid-naïve patients to develop a level of tolerance before switching to a modified-release formulation. Careful and regular assessment and monitoring is required to establish the clinical need for ongoing treatment. Discontinue opioid therapy if there is no improvement of pain and/or function during the trial period or if there is any evidence of misuse or abuse. Treatment should only continue if the trial has demonstrated that the pain is opioid responsive and there has been functional improvement. The patient's condition should be reviewed regularly and the dose tapered off slowly if opioid treatment is no longer appropriate (see *Ceasing Opioids*).

Accidental ingestion/exposure

Accidental ingestion or exposure of m-Eslon SR, especially by children, can result in a fatal overdose of morphine. Patients and their caregivers should be given information on safe storage and disposal of unused m-Eslon SR (see *section 6.4 Special precautions for storage and section 6.6 Special precautions for disposal*).

Hyperalgesia

Hyperalgesia may occur with the use of opioids, particularly at high doses. Hyperalgesia may manifest as an unexplained increase in pain, increased levels of pain with increasing opioid dosages or diffuse sensitivity not associated with the original pain. Hyperalgesia should not be confused with tolerance (see *Tolerance, dependence and withdrawal*). If opioid induced hyperalgesia is suspected, the dose should be reduced and tapered off if possible. A change to a different opioid may be required.

Ceasing opioids

Abrupt discontinuation or rapid decreasing of the dose in a person physically dependent on an opioid may result in serious withdrawal symptoms and uncontrolled pain (see *Tolerance, dependence and withdrawal*). Such symptoms may lead the patient to seek other sources of licit or illicit opioids. Opioids should not be ceased abruptly in a patient who is physically dependent but withdrawn by tapering the dose slowly. Factors to take into account when deciding how to discontinue or decrease therapy include the dose and duration of the opioid the patient has been taking, the type of pain being treated and the physical and psychological attributes of the patient. A multimodal approach to pain management should be in place before initiating an opioid analgesic taper. During tapering, patients require regular review and support to manage any increase in pain, psychological distress and withdrawal symptoms.

There are no standard tapering schedules suitable for all patients and an individualised plan is necessary. In general, tapering should involve a dose reduction of no more than 10 percent to 25 percent every 2 to 4 weeks (see *section 4.2 Dose and Method of Administration*). If the patient is experiencing increased pain or serious withdrawal symptoms, it may be necessary to go back to the previous dose until stable before proceeding with a more gradual taper.

When ceasing opioids in a patient who has a suspected opioid use disorder, the need for medication assisted treatment and/or referral to a specialist should be considered.

4.5 Interaction with other medicines and other forms of interaction**General considerations**

The depressant effects of morphine may be enhanced by other CNS depressants such as alcohol, anaesthetics, hypnotics and sedatives, tricyclic antidepressants, phenothiazines and antipsychotics. Concurrent use may result in potentiation of respiratory depression, hypotension, profound sedation or coma and death may occur. If used concurrently with CNS depressants, dosage adjustment may be required.

Antihistamines, beta-blockers and skeletal muscle relaxants may also enhance the depressant effects of morphine.

The action of morphine may in turn affect the activities of other compounds; for example its gastrointestinal effects may delay absorption as with mexilitine or may be counteractive as with cisapride, domperidone or metoclopramide.

Agonist/antagonist analgesics e.g. buprenorphine should not be administered to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic. The analgesic effect may be reduced or withdrawal symptoms may occur.

Specific interactions

Other medicines and drugs

Alcohol

In vitro data have shown that in the presence of alcohol there is an increased rate of morphine release from the microgranules in the capsule. Co-ingestion with alcohol is contraindicated. Patients should be instructed against taking m-Eslon SR capsules with alcohol as this may lead to the rapid release and absorption of a potentially toxic dose of morphine.

Amphetamines

Amphetamines potentiate the analgesic effect of morphine.

Anticholinergics

The concomitant use of anticholinergics with opioid analgesics, including morphine, may result in an increased risk of severe constipation and urinary retention. For example, concomitant administration of morphine with tricyclic antidepressants may increase the likelihood of adverse effects such as confusion and constipation.

Cimetidine

Cimetidine inhibits the metabolism of morphine. There is a report of confusion and severe respiratory depression when a patient receiving haemodialysis was administered morphine and cimetidine. Caution is therefore advised when administering morphine with cimetidine.

Cyclizine

Cyclizine may counteract the haemodynamic benefits of opioid analgesics.

Diuretics

Morphine reduces the efficacy of diuretics by inducing the release of anti-diuretic hormone.

MAO inhibitors

Morphine should not be given to patients receiving MAOIs or within 14 days of their discontinuation. Non-selective MAOIs intensify the effects of morphine and other opioids which can cause anxiety, confusion and significant depression of respiration sometimes leading to coma.

Narcotic antagonists

Concomitant use of narcotic antagonists may result in reversal of analgesia, and may precipitate withdrawal symptoms in patients who are physically dependent on opioids.

Oral anticoagulants

Morphine may increase the anti-coagulant activity of coumarin and other anti-coagulants.

Ritonavir

Ritonavir may increase the activity of glucuronyl transferases and co-administration with morphine may result in decreased morphine serum levels and possible loss of analgesic activity.

Skeletal muscle relaxants

Morphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Zidovudine

Morphine may competitively inhibit the hepatic glucuronidation of zidovudine thus reducing its clearance. Concurrent use of morphine and zidovudine should be avoided because the toxicity of either or both medicines may be potentiated.

Food

The bioavailability of morphine is not significantly affected by food.

4.6 Fertility, pregnancy, and lactation

Fertility

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

Pregnancy

m-Eslon SR is not recommended for use in pregnancy. Morphine is assigned Category C in the Australian Categorisation of risk system. Category C refers to medicines 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. Accompanying texts should be consulted for further details. Opioid analgesics may cause respiratory depression in the newborn infant. Withdrawal symptoms in newborn infants have been reported with prolonged use of this class of drugs.

Lactation

Morphine is excreted in human milk and breast-feeding is not recommended while a patient is receiving morphine. Withdrawal symptoms have been observed in breast-fed infants when maternal administration of morphine is stopped.

4.7 Effects on ability to drive and use machines

Morphine may impair the mental and/or physical abilities needed for driving a car or operating machinery. Patients should be cautioned accordingly.

4.8 Undesirable effects

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

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

The adverse effects listed below are classified by body system according to their incidence: common (1 in 100 or more); uncommon (< 1 in 100).

Gastrointestinal

Common: Abdominal pain, anorexia, constipation, dry mouth, dyspepsia, nausea, vomiting.

Uncommon: biliary pain, gastrointestinal disorders, ileus, taste perversion.

Central Nervous System

Common: Asthenia, confusion, headache, insomnia, involuntary muscle contractions, somnolence, thought abnormalities.

Uncommon: Agitation, dysphoria, euphoria, hallucinations, malaise, mood changes, respiratory depression, seizure, paresthesia, vertigo, vision abnormalities, withdrawal syndrome.

Genitourinary

Uncommon: Amenorrhea, decreased libido, impotence, urinary retention, hypogonadism.

Cardiovascular

Uncommon: Hypotension, syncope

Metabolic and nutritional

Uncommon: Peripheral edema, pulmonary edema

Respiratory

Common: Bronchospasm, cough decreased, respiratory depression.

Dermatological

Common: Rash

Uncommon: Urticaria

General

Common: Chills, pruritus, sweating.

Uncommon: Allergic reaction, anaphylactic/anaphylactoid reactions, drug dependence, facial flushing, hypertonia, miosis, tolerance.

Withdrawal Syndrome

Chronic use of opioid analgesics may be associated with the development of physical dependence. Withdrawal symptoms may occur when opioid administration is abruptly discontinued or opioid antagonists administered. Withdrawal symptoms include body aches, diarrhoea, piloerection, anorexia, nervousness or restlessness, rhinorrhoea, sneezing, tremors or shivering, abdominal colic, nausea, sleep disturbances, unusual increase in sweating and yawning, weakness, tachycardia and unexplained fever. With appropriate dose adjustments and gradual withdrawal these symptoms are usually mild.

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

Serious morphine overdosage is characterised by the following signs: pinpoint pupils; respiratory depression (manifested as reduced respiratory rate and/or tidal volume; Cheyne-Stokes respiration; cyanosis); extreme somnolence progressing to stupor or coma; flaccidity of skeletal muscle; cold or clammy skin; sometimes hypotension and bradycardia. Severe overdosage may result in apnoea, circulatory collapse, cardiac arrest and death. Convulsions may occur in young children. Dilation of pupils occurs as hypoxia develops.

Immediate attention should be given to the re-establishment of adequate respiratory exchange through provision of a patient airway and institution of assisted or controlled ventilation. In patients physically dependent on opioids, respiratory support is the first line of treatment. In these patients, the use of naloxone is potentially dangerous. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated.

The opioid antagonist, naloxone, is a specific antidote against respiratory depression which may result from overdosage or unusual sensitivity to opioids. The recommended adult dose of naloxone for the treatment of severe opiate induced respiratory depression is 0.4 to 2mg intravenously every 2 to 3 minutes as necessary, simultaneously with assisted respiration.

For children, the initial dose recommended is 0.01 mg/kg naloxone. A response should be seen after 2 to 3 doses. Note the duration of action of naloxone is usually shorter than that of morphine and thus the patient should be carefully observed for signs of CNS depression returning.

If the response to naloxone is suboptimal or not sustained, additional naloxone may be administered as needed, or given by continuous intravenous infusion to maintain alertness and respiratory function. There is no information about the cumulative dose of naloxone that may be safely administered.

Naloxone should be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdosage.

Naloxone should be administered cautiously to persons who are known or suspected to be physically dependent on morphine. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. If it is necessary to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care and by titration with smaller than usual doses of the antagonist.

Morphine toxicity may be a result of overdosage but because of the large inter-individual variation in sensitivity to opioids, it is difficult to assess the exact dose of any opioid that is toxic or lethal. The toxic effects of morphine tend to be overshadowed by the presence of pain or tolerance. Patients having chronic morphine therapy have been known to take in excess of 3,000 mg/day with no apparent toxic effects being present.

The contents of m-Eslon SR capsules remaining in the intestinal tract will continue to release and add to the morphine load for up to 12 hours after ingestion and management of the morphine overdosage should be modified accordingly. Fluid and electrolyte levels must be maintained.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: N02AA01: member of N02AA – natural opium alkaloids, a subset of N02A – opioids.

Morphine is an opioid analgesic which exerts an agonist effect at specific, saturable opioid receptors in the central nervous system (CNS) and on smooth muscle. In man, morphine produces a variety of pharmacological effects including analgesia, constipation from decreased gastrointestinal motility, suppression of the cough reflex, respiratory depression from reduced responsiveness of the respiratory centre to carbon dioxide, nausea and vomiting via stimulation of the chemoreceptor trigger zone (CTZ), changes in mood including euphoria and dysphoria, sedation, mental clouding, and alterations of the endocrine and autonomic nervous systems.

The psychological effects are of longer duration than that of analgesia. Morphine-induced analgesia is relatively selective in that other sensory modalities (touch, vision, hearing) are not affected. Moderate doses of morphine are effective in relieving clinical (pathological) pain and increasing pain threshold to tolerate pain. The capacity to perceive the sensation of pain may be relatively unaltered. The analgesic effects of morphine are due to its CNS action, i.e., limbic system, hypothalamus, and centrally induced endocrinological effect. At present, the exact mechanism by which the opiates exert their effects remains unknown.

Oral morphine is as efficacious as parenteral morphine when it is used at three times the parenteral dose.

m-Eslon SR capsules release morphine from microgranules that are specially coated enabling twice daily administration to control pain when opiate medication is required. The capsules may be swallowed whole or separated and the contents mixed with soft foods and consumed immediately or given through a compatible feeding tube.

5.2 Pharmacokinetic properties

m-Eslon SR capsules produce peak morphine levels at steady state in approximately 3 to 4 hours following administration. In human pharmacokinetic studies, they have been shown to have an extended release action, when compared to oral morphine sulphate syrup, as characterized by a flatter peak serum concentration curve which took longer to attain; the elimination half-life was significantly lengthened. Therapeutic levels are maintained over a period of 12 hours.

Summary of pharmacokinetic parameters (mean \pm SD) in cancer patients presenting severe pain (n=25) who received morphine sulphate 60 to 300 mg/day for 6 days as syrup or as modified release capsules from Gillette et al, Clin Drug Invest 14:suppl. 1 pp.22-27 (1997).

Parameter	Morphine syrup	m-Eslon SR capsules
C _{max} (mcg/l)	49.52 \pm 28.38	48.13 \pm 30.67
AUC 0-12h	308.41 \pm 203.81	323.17 \pm 201.69
t _{max} (h)	1.18 \pm 0.93	3.60 \pm 1.95

m-Eslon SR has not been compared to any modified-release morphine preparation on the New Zealand market, and therefore it is not interchangeable with other formulations.

Absorption

Morphine is readily absorbed from the gastrointestinal tract and after subcutaneous or intramuscular injection. Due to extensive first-pass metabolism in the liver and gut, the effect of an oral dose is less than after parenteral administration. With repeated regular dosing, orally administered morphine is about one-third as potent as when given by intramuscular injection. Enterohepatic circulation probably occurs.

As the rate of morphine release from m-Eslon SR formulation is independent of pH over the range 1.5 to 7.2, it does not limit the absorption of morphine to any part of the gastrointestinal tract. Following oral administration of morphine, the extent of absorption is essentially the same for immediate or extended release formulations, whether the latter are given once or twice a day. This means that morphine can be absorbed all along the GI tract, including the colon. Diarrhoea may reduce morphine absorption.

There is no clinical evidence of dose dumping in either the fed or fasting state. However, the consumption of fatty food with m-Eslon SR capsules may affect the morphine release properties resulting in a higher and delayed C_{max}.

Distribution

Morphine is widely distributed throughout the body but mainly in the kidneys, liver, lungs and spleen with lower concentrations in the brain and muscles. Volume of distribution is about 3 to 5 litres/kg and 20 to 35% is bound to plasma proteins.

Morphine crosses the blood-brain barrier less readily than more lipid soluble opioids, but it has been detected in the cerebrospinal fluid as have its highly polar metabolites morphine-3-glucuronide and morphine-6-glucuronide. Morphine diffuses across the placenta and residual levels also appear in breast milk and sweat.

Biotransformation

Morphine is mostly conjugated to morphine-3-glucuronide and morphine-6-glucuronide which then undergo renal excretion. These metabolites are also excreted in bile and may be subject to hydrolysis and subsequent reabsorption.

Elimination

The elimination half-life of morphine is 2 to 3 hours with great interpatient variability. About 90% of total morphine is excreted in 24 hours with traces in urine for 48 hours or more.

Special patient groups

Because morphine-6-glucuronide has been observed to accumulate in patients with renal disease, caution should be exercised in patients with clinically significant impairment of the renal function.

5.3 Preclinical safety data

No data available.

6. PHARMACEUTICAL PARTICULARS**6.1 List of Excipients**

Capsule shells	Microgranules
<ul style="list-style-type: none"> • Gelatin (animal source) • Erythrosine • Iron oxide, black (ink) • Quinolone yellow • Sunset yellow • Titanium dioxide 	<ul style="list-style-type: none"> • Dibutyl sebecate • Ethylcellulose • Macrogol 4000 • Maize starch • Sugar • Talc

6.2 Incompatibilities

No information available.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

Blister strips of 10 capsules within cardboard carton.

Not all strengths may be marketed.

6.6 Special precautions for disposal

None.

7. MEDICINE SCHEDULE

Class B1 Controlled Drug

8. SPONSOR

Multichem NZ Limited

Private Bag 93527

Takapuna

Auckland 0740

Telephone: (09) 488 0330

9. DATE OF FIRST APPROVAL

22 August 2002

10. DATE OF REVISION OF THE TEXT

01 July 2021

SUMMARY TABLE OF CHANGES

Section	Details of Change
All	Formatting changes to improve readability
4.4	Addition of new safety warnings for opioids as requested by Medsafe.