NM-ESLON®
(Morphine Sulfate)
10 mg, 15 mg, 30 mg, 60 mg, 100 mg, 200 mg Extended Release Capsules

Narcotic Analgesic

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^M-ESLON® (morphine sulfate) Product Monograph
July 15, 2015
ACTIONS

Morphine is a narcotic analgesic which exerts an agonist effect at specific, saturable opioid receptors in the CNS and other tissues. In man, morphine produces a variety of effects including analgesia, constipation from decreased gastrointestinal motility, suppression of the cough reflex, respiratory depression from reduced responsiveness of the respiratory centre to CO₂, nausea and vomiting via stimulation of the 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.

Morphine is readily absorbed from the gastrointestinal tract and after s.c. or i.m. injection. Due to first-pass metabolism in the liver, 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 i.m. injection. Morphine is primarily excreted in the urine as morphine-3-glucuronide. About 7 to 10% of a dose of morphine is excreted in the feces via the bile.

M-ESLON Capsules (Morphine Sulfate Extended Release 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 sulfate 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.

This product has not been compared to any slow-release morphine preparation on the Canadian market, and therefore is not interchangeable.

INDICATIONS AND CLINICAL USE

Adults:

M-ESLON (Morphine Sulfate Extended Release Capsules) is indicated for the management of pain severe enough to require daily, continuous, long-term opioid treatment, and:

- that is opioid-responsive; and
- for which alternative options are inadequate.

M-ESLON is not indicated as an as-needed (prn) analgesic.
Geriatrics (> 65 years of age):
In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or other drug therapy.

Pediatrics (< 18 years of age):
The safety and efficacy of M-ESLON has not been studied in the pediatric population. Therefore, the use of M-ESLON is not recommended in patients under 18 years of age.

CONTRAINDICATIONS

M-ESLON (Morphine Sulfate Extended Release Capsules) is contraindicated in:

- Patients who are hypersensitive to the active substance (morphine sulfate) or other opioid analgesics or to any ingredient in the formulation. For a complete listing, see the PHARMACEUTICAL INFORMATION - COMPOSITION section of the Product Monograph.
- In patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction, strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).
- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis).
- Patients with surgical anastomosis (narcotics may cause increase in intraluminal pressure).
- Patients who had surgery of the biliary tract.
- Patients with mild, intermittent or short duration pain that can be managed with other pain medications.
- The management of acute pain.
- Patients with acute asthma or other obstructive airway, and status asthmaticus.
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood, and cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, head injury or brain tumor (may cause marked exaggeration of cerebrospinal fluid pressure and mask the clinical course).
- Patients with cardiac arrhythmias or hypotension.
- Patients with severe cirrhosis.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).
- Women who are breast-feeding, pregnant, or during labour and delivery.
Patients who consume alcohol, or any medication containing alcohol. Co-ingestion of M-ESLON and alcohol can potentially result in rapid increases in opioid plasma concentrations, which may be fatal, even in opioid tolerant patients.

SERIOUS WARNINGS AND PRECAUTIONS

Limitations of Use
Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, M-ESLON should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics), or would be otherwise inadequate to provide sufficient management of pain (e.g., immediate-release opioids) (see DOSAGE AND ADMINISTRATION).

Addiction, Abuse, and Misuse
M-ESLON poses risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Each patient’s risk should be assessed prior to prescribing M-ESLON, and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS). M-ESLON should be stored securely to avoid theft or misuse.

Life-threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of M-ESLON. Patients should be monitored for respiratory depression, especially during initiation of M-ESLON or following a dose increase. M-ESLON should be swallowed whole; crushing, chewing, or dissolving M-ESLON Capsules can cause rapid release and absorption of a potentially fatal dose of morphine sulfate (see WARNINGS AND PRECAUTIONS).

Accidental Exposure
Accidental consumption of even one dose of M-ESLON, especially by children, can result in a fatal overdose of (active opioid) (see DOSAGE AND ADMINISTRATION subsection Disposal, for instructions on proper disposal).

Neonatal Opioid Withdrawal Syndrome
Prolonged maternal use of M-ESLON during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see WARNINGS AND PRECAUTIONS).

WARNINGS AND PRECAUTIONS

General
This product has not been compared to any slow-release morphine preparation on the Canadian market, and therefore is not interchangeable.
Morphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

**Addiction, Abuse and Misuse**
M-ESLON is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, M-ESLON should be prescribed and handled with caution.

Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse and abuse.

Opioids, such as M-ESLON, should be used with particular care in patients with a history of alcohol and illicit/prescription drug abuse. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

**Cardiovascular**
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 anesthetics.

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.

**Dependence/Tolerance**
As with other opioids, tolerance and physical dependence may develop upon repeated administration of M-ESLON and there is a potential for development of psychological dependence.

Physical dependence and tolerance reflect the neuroadaptation of the opiate receptors to chronic exposure to an opiate, and are separate and distinct from abuse and addiction. Tolerance, as well as physical dependence, may develop upon repeated administration of opioids, and are not by themselves evidence of an addictive disorder or abuse.

Patients on prolonged therapy should be tapered gradually from the drug if it is no longer required for pain control. Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist.
### Neurologic

**Interactions with Central Nervous System Depressants (Including Alcohol):**

M-ESLON should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics, general anesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, benzodiazepines, centrally-active anti-emetics and other CNS depressants. Respiratory depression, hypotension and profound sedation, coma or death may result. When such combination therapy is contemplated, a substantial reduction in the dose of one or both agents should be considered and patients should be carefully monitored. M-ESLON should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS**).

### Head Injury:

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

### Neonatal Opioid Withdrawal Syndrome (NOWS)

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

Use of M-ESLON is contraindicated in pregnant women (see **CONTRAINDICATIONS**).

### Perioperative Considerations

Patients who are scheduled for cordotomy or other interruption of pain transmission pathways should not receive M-ESLON Capsules within 24 hours of the procedure.

### Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Carbon dioxide (CO₂) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of M-ESLON, the risk is greatest during the initiation of therapy or following a dose increase.

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Patients should be closely monitored for respiratory depression when initiating therapy with M-ESLON and following dose increases.

To reduce the risk of respiratory depression, proper dosing and titration of M-ESLON are essential (see DOSAGE AND ADMINISTRATION). Overestimating the M-ESLON dose when converting patients from another opioid product can result in fatal overdose with the first dose.

Morphine should be used with extreme caution in patients with chronic pulmonary disease; substantially decreased respiratory reserve, preexisting respiratory depression, hypoxia or hypercapnia. Such patients are often less sensitive to the stimulatory effects of carbon dioxide on the respiratory center and the respiratory depressant effects of morphine may reduce respiratory drive to the point of apnea.

**Special Population**

**Pregnant Women**

Animals studies indicate that morphine may be teratogenic at high doses in mice (see TOXICOLOGY), and may cause an increased incidence of abortions and reduced birth weight in rabbits. In humans, it is not known whether morphine can cause fetal harm when administered during pregnancy or can affect reproductive capacity. M-ESLON Capsules should not be given to pregnant patients.

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening (see WARNINGS AND PRECAUTIONS – Neonatal Opioid Withdrawal Syndrome).

**Special Risk Groups**

Morphine should be administered with caution, and 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, hypopituitarism, anemia, severe malnutrition, fulminant ulcerative colitis, untreated myxedema.

**Labor/Delivery and Lactation**

Morphine crosses the placental barrier and its administration during labor can produce respiratory depression in the neonate. M-ESLON is contraindicated in women during labour and delivery. Morphine has been detected in human breast milk. M-ELSON is contraindicated in nursing mothers.

**Occupational Hazards**

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.
DRUG INTERACTIONS

Generally, the effects of morphine may be antagonized by acidifying agents and potentiated by alkalinizing agents.

**Anticholinergics**
The concomitant use of anticholinergics with narcotics, including morphine, may result in an increased risk of severe constipation and urinary retention.

**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 narcotics.

**CNS Depressants**
CNS depressants, such as other opioids, alcohol, anesthetics, antihistamines, barbiturates, beta-blockers, chloral hydrate, glutethimide, hypnotics, MAO inhibitors, phenothiazines, pyrazolidone, sedatives, skeletal muscle relaxants and tricyclic antidepressants may enhance the depressant effects of morphine. Concurrent use may result in potentiation of CNS depression and death may occur. If used concurrently with CNS depressants, dosage adjustment may be required.

**Amphetamines**
Amphetamines potentiate the analgesic effect of morphine.

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

**Drug-Lifestyle Interaction**
The concomitant use of alcohol should be avoided (see CONTRAINDICATIONS).

ADVERSE REACTIONS

The major hazards associated with morphine, as with other narcotic 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 narcotic 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 3 to 5 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 realized. If it is necessary to reduce the dose, it can be carefully increased again after 3 or 4 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 in the younger age group.

**Nausea and Vomiting**
Nausea and vomiting occur frequently after single doses of narcotics or as an early unwanted effect of regular narcotic therapy. When instituting prolonged therapy for chronic pain the routine prescription of antiemetic should be considered. Patients taking the equivalent of a single dose of 20 mg or more of morphine every 4 hours (60 mg of M-ESLON Capsules (Morphine Sulfate Extended Release Capsules) every 12 hours) 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**
Practically all patients become constipated while taking narcotics on a persistent basis. 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 narcotic therapy. Softeners, laxatives and other appropriate measures should be used as required.

**CNS**
Euphoria, dysphoria, weakness, insomnia, dizziness, headache, agitation, tremor, uncoordinated muscle movements, visual disturbances, confusional symptoms and occasionally hallucinations.

**Gastrointestinal**
Dry mouth, anorexia, constipation, cramps, taste alterations and biliary tract spasm.

**Genitourinary**
Urinary retention or hesitance, reduced libido or potency.

**Cardiovascular**
Supraventricular tachycardia, postural hypotension, palpitations, faintness and syncope.

**Endocrine**
A syndrome of inappropriate antidiuretic hormone secretion characterized by hyponatremia secondary to decreased free-water excretion may be prominent (monitoring of electrolytes may be necessary).

**Allergic**
Pruritus, urticaria, other skin rashes and edema.

**Withdrawal (Abstinence) Syndrome**
Physical dependence with or without psychological dependence tends to occur on chronic administration. An abstinence syndrome may be precipitated when narcotic administration is discontinued or narcotic antagonists administered. The following withdrawal symptoms may be observed after narcotics are discontinued: body aches, diarrhea, gooseflesh, loss of appetite, nervousness or restlessness, runny nose, sneezing, 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 narcotics and gradual withdrawal from the drug, these symptoms are usually mild.

**OVERDOSAGE**

**Symptoms**
Serious morphine overdosage is characterized by respiratory depression (reduced respiratory rate and/or tidal volume; Cheyne-Stokes respiration; cyanosis), extreme somnolence progressing to stupor or coma, flaccidity of skeletal muscle, cold or clammy skin, and sometimes hypotension and bradycardia. Severe overdosage may result in apnea, circulatory collapse, cardiac arrest and death. Convulsions may occur in young children.

**Treatment**
Primary attention should be given to the establishment of adequate respiratory exchange through provision of a patent airway and controlled or assisted ventilation. The narcotic antagonist naloxone is a specific antidote against respiratory depression due to overdosage or as a result of unusual sensitivity to morphine. An appropriate dose of this antagonist should therefore be administered, preferably by the i.v. route. The usual initial 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 extended 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, i.v. fluids, vasopressors and other supportive measures should be used as indicated.

**Note**
In an individual physically dependent on narcotics, the administration of the usual dose of narcotic 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 narcotic antagonists in such individuals should be avoided if possible. If a narcotic 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.
Evacuation of gastric contents may be useful in removing unabsorbed drug, particularly when an extended release formulation has been taken.

**DOSAGE AND ADMINISTRATION**

M-ESLON should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics), or would be otherwise inadequate to provide sufficient management of pain (e.g., immediate-release opioids).

M-ESLON should be swallowed whole; crushing, chewing, or dissolving M-ESLON Capsules can cause rapid release and absorption of a potentially fatal dose of morphine sulfate (see SERIOUS WARNINGS AND PRECAUTIONS Box and WARNINGS AND PRECAUTIONS – Respiratory Depression).

This product has not been compared to any slow-release morphine preparation on the Canadian market, and therefore is not interchangeable.

Administration and dosing of morphine should be individualized 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 narcotic 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 narcotics 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.

For essential information on the important details of the management of cancer pain, the reader may wish to consult the following resource: Cancer Pain: A Monograph on the Management of Cancer Pain. Health and Welfare Canada.

The capsules may be opened, and the microgranules given mixed with soft food, liquids or by gastric tube or gastrotomy to dysphagic (e.g. E.N.T. cancer) patients who can benefit from the analgesia obtained from an extended release preparation.

**Recommended Dose and Dosage Adjustment**

Individual dosing requirements vary considerably based on each patient's age, weight, severity of pain, and medical and analgesic history.

The most frequent initial dose is 30 mg M-ESLON Capsules (Morphine Sulfate Extended Release Capsules) every 12 hours.
The capsules may be opened, and the microgranules given mixed with soft food, liquids or 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.

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

Patients currently receiving other oral morphine immediate release formulations may be transferred
to M-ESLON Capsules at the same total daily morphine dosage, equally divided into two 12-hourly
M-ESLON doses.

For patients who are receiving an alternate narcotic, the "oral morphine 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 dosage that should provide equivalent analgesia. This total daily oral
morphine dosage should then be equally divided in two 12 hourly M-ESLON doses.

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<th>Narcotics: Approximate Analgesic Equivalences*</th>
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<tr>
<td>DRUG</td>
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<tr>
<td>Agonists</td>
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<tr>
<td>Morphine sulfate</td>
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<tr>
<td>Codeine phosphate</td>
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<tr>
<td>Hydromorphone (Dilaudid®)</td>
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<tr>
<td>Levorphanol (Levo-Dromoran®)</td>
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<td>Oxycodone (Percodan®, Percocet®)</td>
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<td>Anileridine (Leritine®)</td>
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<td>Meperidine (pethidine, Demerol®)</td>
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<td>Oxymorphone (Numorphan®)</td>
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<td>Methadone</td>
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<td>Heroin</td>
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<tr>
<td>Agonist-Antagonists</td>
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<tr>
<td>Pentazocine (Talwin®)</td>
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<tr>
<td>Nalbuphine (Nubain®)</td>
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<td>Butorphanol</td>
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Dose titration is the key to success with morphine therapy. Proper optimization of doses scaled to the relief of the individual's pain should aim at the regular administration of the lowest dose of morphine which will maintain the patient free of pain at all times. Dose adjustments should be based on the patient's clinical response. Higher doses may be justified in some patients to cover periods of physical activity.

Because of the extended release properties of M-ESLON Capsules, dosage adjustments should generally be separated by 48 hours. If dose increments turn out to be required, they should be proportionately greater at the lower dose level (in terms of percentage of previous dose), than when adjusting a higher dose. The usual recommended dose (every 12 hours) increments are 30, 60, 90, 120, 150, 180, 200 mg. Above the 200 mg/dose (400 mg/day) increments should be by 30 to 60 mg/dose.

M-ESLON Capsules (Morphine Sulfate Extended Release Capsules) are designed to allow 12-hourly dosing. If "breakthrough" pain repeatedly occurs at the end of a dose interval, it is generally an indication for a dosage increase, not more frequent administration. However, where judged necessary for optimization of drug effects, the product may be administered every 8 hours. More frequent (than every 8 hours) administration is not recommended.

**Adjustment or reduction of dosage**

During the first 2 or 3 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 patient exhausted by pain. 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. Some of these are: concomitant sedative medications, hepatic or renal failure, exacerbated respiratory failure, higher doses than tolerated by an older patient, or the patient is actually more severely ill than realized. 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.

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

Narcotic agents do not relieve effectively dysesthetic pain, post-herpetic neuralgia, stabbing pains, activity-related pain, and some forms of headache. This is not to say that patients with advanced
cancer suffering from some of these forms of pain should not be given an adequate trial of opiate analgesics, but it may be necessary to refer such patients at an early time for other forms of pain therapy. Pain without nociception does not respond to narcotics.

**Disposal**

M-ESLON should be kept in a safe place, out of the sight and reach of children before, during and after use. M-ESLON should not be used in front of children, since they may copy these actions.

Unused or expired M-ESLON should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets. If temporary storage is required before disposal, a sealed child-proof container, such as a biohazard waste container or a lockable medication box could be obtained from a pharmacy.

**M-ESLON should never be disposed of in household trash.** Disposal via a pharmacy take back program is recommended.
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper (common) name
Morphine Sulfate

Chemical name
Morphinan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl, (5α,6α)-, sulfate (2:1) (salt), pentahydrate;

Structural formula

\[
\text{\text{M}} \quad \text{\text{H}} \quad \text{\text{C}} \quad \text{\text{N}} \quad \text{\text{O}} \\
\text{\text{H}} \quad \text{\text{C}} \quad \text{\text{H}} \quad \text{\text{C}} \\
\text{\text{H}} \quad \text{\text{O}} \quad \text{\text{H}} \quad \text{\text{H}} \\
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\[\text{\text{H}_2\text{SO}_4 \cdot \text{5H}_2\text{O}}\]

Molecular formula: \((\text{C}_{17}\text{H}_{19}\text{NO}_3)_2 \text{H}_2\text{SO}_4\cdot\text{5H}_2\text{O}\)

Molecular Weight: 758.83

Description
Pentahydrate, white, fine odorless acicular crystals or powder, or cubical masses. Odourless or almost odourless. One gram dissolves in 15.5 mL water at 25°C, 0.7 mL water at 80°C, 565 mL alcohol, 240 mL alcohol at 60°C; insoluble in chloroform, ether.

COMPOSITION

Each hard gelatin capsule of M-ESLON (Morphine Sulfate Extended Release Capsules) contains 10, 15, 30, 60, 100 or 200 mg of morphine sulfate in the form of extended release microgranules.

Non-medicinal ingredients (all strengths)
Dibutyl sebacate, maize starch, polyethylene glycol 4000, polymeric dispersion of ethylcellulose, sucrose, talc; capsule shell contains gelatin and coloring agent (10 mg : titanium dioxide, 15 mg : titanium dioxide, quinoline yellow WS (D&C Yellow No. 10), 30 mg : titanium dioxide, erythrosine (FD&C Red No. 3), 60 mg : titanium dioxide, sunset yellow FCF (FD&C Yellow No. 6), 100 mg : titanium dioxide, black iron oxide, 200 mg : titanium dioxide, allura red AC (FD&C Red No. 40), brilliant blue FCF (FD&C Blue No. 1). Tartrazine-free.
STABILITY AND STORAGE RECOMMENDATIONS

Store at room temperature (15°C to 30°C).

AVAILABILITY

M-ESLON (Morphine Sulfate Extended Release Capsules) is a drug listed under the Narcotic Act and Regulations, and may only be sold under the authority of the written prescription of a qualified practitioner.

Available in cartons containing blister packs of 20 hard gelatin capsules of the following strengths:

10 mg (#4 capsule printed with "M-ESLON" and "10" in black; opaque white cap and body).

15 mg (#4 capsule printed with "M-ESLON" and "15" in black; opaque yellow cap and transparent natural body).

30 mg (#4 capsule printed with "M-ESLON" and "30" in black; opaque pink cap and transparent natural body).

60 mg (#3 capsule printed with "M-ESLON" and "60" in black; opaque orange cap and transparent natural body).

100 mg (#2 capsule printed with "M-ESLON" and "100" in white; opaque gray cap and transparent natural body).

200 mg (#0 capsule printed with "M-ESLON" and "200" in white; opaque red cap and transparent natural body).

Also available in white, opaque polypropylene bottles of 50 capsules, with tamper-evident polyethylene caps.
PHARMACOLOGY

Animal Pharmacology
Morphine reduces the contractile response and the quantity of acetylcholine released by the longitudinal muscle of isolated guinea pig ileum.

In vivo, morphine raises the pain perception threshold, modifies reaction to pain, suppresses responses to mechanical, thermal and electrical stimuli and, at high doses, induces catatonia in most species (Straub tail). In cats, subcutaneous administration causes excitation, fright, aggressiveness, motor incoordination and circling movements (morphine mania). In general, morphine increases locomotor activity.

At a dose of 20 mg/kg, morphine causes a three-fold increase in hot plate reaction time in the mouse. In rodents, analgesia is dose-related.

At low doses, morphine increases respiratory rate; at higher doses, respiration is slowed. A 35% decrease in respiratory rate has been observed in mice. In the rat, a dose of 10 mg/kg causes an 86% decrease in oxygen consumption after 120 minutes. Finally, in rabbits and dogs, periodic respiration occurs as a result of the reduced reaction of the bulbar respiratory centre to CO₂, its physiological excitant.

In rodents, morphine induces a biphasic change in body temperature (primarily hypothermia). In rats and other species, naloxone blocks this hypothermic effect, and the analgesic action of morphine.

In the dog, as in man, morphine induces miosis; in cats, it causes mydriasis. These effects are of central origin.

Repeated administration of morphine causes characteristic signs of tolerance, addiction and withdrawal syndromes. Monkeys, dogs and rats show the major characteristics of the dependence syndrome observed in man.

TOXICOLOGY

Single dose studies
The LD₅₀ values given in the Registry of toxic effects of chemical substances are shown in the following table:
<table>
<thead>
<tr>
<th>Species</th>
<th>Route of administration</th>
<th>LD&lt;sub&gt;50&lt;/sub&gt; in mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>Oral</td>
<td>461</td>
</tr>
<tr>
<td></td>
<td>Intravenous</td>
<td>70</td>
</tr>
<tr>
<td>Mouse</td>
<td>Oral</td>
<td>670</td>
</tr>
<tr>
<td></td>
<td>Intravenous</td>
<td>200</td>
</tr>
<tr>
<td>Dog</td>
<td>Intravenous</td>
<td>316</td>
</tr>
</tbody>
</table>

The symptoms of acute toxicity vary from one animal species to another. In the mouse, the symptoms are pronounced excitation and cramps, while the rat shows akinesia and paralysis. In the dog, the signs of toxicity are vomiting, diarrhea and tachycardia. Acute toxicity is age-dependent. The ratio of the LD<sub>50</sub> in mice aged 30 days and 1 day is 6.2.

A study to redetermine the LD<sub>50</sub> of morphine sulfate raw material administered by the oral route was conducted in parallel with the M-ESLON Capsules (Morphine Sulfate Extended Release Capsules) microgranules. The results are shown in the table which appears below:

<table>
<thead>
<tr>
<th>SPECIES</th>
<th>STRAIN</th>
<th># of animals and sex/group</th>
<th>Route of administration</th>
<th>Product administered</th>
<th>Observation Period</th>
<th>LD&lt;sub&gt;50&lt;/sub&gt; (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOUSE</td>
<td>Swiss</td>
<td>10 females 10 males</td>
<td>oral oral</td>
<td>Morphine sulfate</td>
<td>14 days 14 days</td>
<td>1000 1100</td>
</tr>
<tr>
<td>RAT</td>
<td>Wistar</td>
<td>10 females 10 males</td>
<td>oral oral</td>
<td>Morphine sulfate</td>
<td>14 days 14 days</td>
<td>675 700</td>
</tr>
<tr>
<td>MOUSE</td>
<td>Swiss</td>
<td>10 females 10 males</td>
<td>oral oral</td>
<td>Microgranules containing 364 mg morphine sulfate/g</td>
<td>14 days 14 days</td>
<td>1164 1310</td>
</tr>
<tr>
<td>RAT</td>
<td>Wistar</td>
<td>10 females 10 males</td>
<td>oral oral</td>
<td>Microgranules containing 364 mg morphine sulfate/g</td>
<td>14 days 14 days</td>
<td>764 910</td>
</tr>
</tbody>
</table>
*Calculated by Lichfield and Wilcoxon method (J Pharmacol Exp Ther 1949, 96: 99-113)

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

NM-ESLON®
Morphine Sulfate Extended Release Capsules

Read this carefully before you start taking M-ESLON and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about M-ESLON.

Serious Warnings and Precautions

- Even if you take M-ESLON as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to overdose and death.

- Life-threatening breathing problems can happen while taking M-ESLON, especially if not taken as directed.

- Never give anyone your M-ESLON. They could die from taking it. If a person has not been prescribed M-ESLON, taking even one dose can cause a fatal overdose. This is especially true for children.

- Babies born to mothers who have taken M-ESLON (for short or long periods, in small or large doses) during their pregnancy can suffer life-threatening withdrawal symptoms. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has breathing changes (weak, difficult or fast), is unusually difficult to comfort, has tremors (shakiness), or has increased stools, sneezing, yawning, vomiting, or fever, seek immediate medical help for your baby.

What is M-ESLON used for?

M-ESLON is used for the long-term management of pain, when:

- the pain is severe enough to require daily, around-the-clock painkillers
- the doctor determines that other treatment options are not able to effectively treat your pain

M-ESLON is NOT used (“as needed”) to treat pain that you only have once in a while.
How does M-ESLON work?
M-ESLON is a painkiller belonging to the class of medicines known as opioids. It relieves pain by acting on specific nerve cells of the spinal cord and brain.

What are the ingredients in M-ESLON?
Medicinal ingredients: morphine sulfate
Non-medicinal ingredients: dibutyl sebacate, maize starch, polyethylene glycol 4000, polymeric dispersion of ethylcellulose, sucrose, talc; capsule shell contains gelatin and coloring agent (10 mg: titanium dioxide, 15 mg: titanium dioxide, quinoline yellow WS (D&C Yellow No. 10), 30 mg: titanium dioxide, erythrosine (FD&C Red No. 3), 60 mg: titanium dioxide, sunset yellow FCF (FD&C Yellow No. 6), 100 mg: titanium dioxide, black iron oxide, 200 mg: titanium dioxide, allura red AC (FD&C Red No. 40), brilliant blue FCF (FD&C Blue No. 1).

M-ESLON comes in the following dosage forms:
M-ESLON is available in six capsule strengths:

10 mg (capsule printed with "M-ESLON" and "10" in black; opaque white cap and body).

15 mg (capsule printed with "M-ESLON" and "15" in black; opaque yellow cap and transparent natural body).

30 mg (capsule printed with "M-ESLON" and "30" in black; opaque pink cap and transparent natural body).

60 mg (capsule printed with "M-ESLON" and "60" in black; opaque orange cap and transparent natural body).

100 mg (capsule printed with "M-ESLON" and "100" in white; opaque gray cap and transparent natural body).

200 mg (capsule printed with "M-ESLON" and "200" in white; opaque red cap and transparent natural body).

Do not use M-ESLON if:
- you are allergic to morphine sulfate or any of the other ingredients of M-ESLON
- your pain can be controlled by the occasional use of painkillers including those available without a prescription
- you have severe asthma, trouble breathing, or any heart problems
- you have bowel blockage or narrowing of the stomach or intestines
- you have a head injury or other risks for seizures
- you suffer from alcoholism
- you are pregnant or plan to become pregnant, breastfeeding, or in labour
- you have a surgical connection between tubular structures, such as blood vessels or loops of intestine.
• you have severe cirrhosis
• you had surgery of the biliary tract
• you are under 18 years of age

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take M-ESLON. Talk about any health conditions or problems you may have, including if you:

• have a history of illicit or prescription drug or alcohol abuse
• have severe kidney or liver disease
• have low blood pressure
• have past or current depression
• suffer from chronic or severe constipation
• are going to have, or recently had, a planned surgery
• have problems with your thyroid, adrenal or prostate gland

Other warnings you should know about:

Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to M-ESLON. Drowsiness, dizziness, or lightheadedness, can especially occur after the first dose and when the dose is increased.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with M-ESLON:

• alcohol, including prescription and non-prescription medications containing alcohol. Do not drink alcohol while taking M-ESLON. This can lead to drowsiness, depressed breathing, serious side effects or a fatal overdose
• other sedative drugs which may enhance the drowsiness caused by M-ESLON
• other opioid analgesics (for pain)
• general anesthetics (used during surgery)
• drugs used to help you sleep or to reduce anxiety
• antidepressants (for depression and mood disorders). Do not take M-ESLON with monamine oxidase inhibitors (MAOIs) or if you have taken MAOIs in the last 14 days before treatment with M-ESLON.
• drugs used to treat serious mental or emotional disorders such as schizophrenia
• antihistamines (for allergies)
• anti-emetics (for prevention of vomiting)
• drugs used to treat muscle spasms and back pain
• warfarin and other coumarin anticoagulants (for prevention/treatment of blood clots)
• anti-retroviral, anti-fungal and antibiotic drugs
• some heart medications (beta-blockers)

How to take M-ESLON:

Swallow whole, or the capsules may be opened and the contents sprinkled on your food. Do not break, chew, dissolve or crush the capsule contents as it can cause rapid release and absorption of a potentially fatal dose of morphine sulfate.

M-ESLON must be taken regularly every 12 hours (with 120 to 180 mL of water) to prevent pain all day and night. If your pain worsens, making you uncomfortable, contact your doctor immediately and she/he may decide that it is necessary to adjust your daily dosage of M-ESLON.

Your starting dosage of M-ESLON will be clearly labeled on the medication bottle. Be sure to follow these directions on the label exactly; this is very important. If your dosage is changed, be sure to write it down at the time your doctor calls you or sees you. And follow the new directions exactly.

Usual Adult Starting Dose:
Dosage is individualized. Be sure to follow your doctor’s dosing instructions exactly.

Overdose:

Signs of overdose may include abnormally slow or weak breathing, dizziness, confusion or extreme drowsiness.

If you think you have taken too much M-ESLON, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss one dose, take it as soon as possible. However, if it is almost time for your next dose, then skip the missed dose. Do not take two doses at once. If you miss several doses in succession, talk to your doctor before restarting your medication.

Refilling Prescriptions for M-ESLON:

A new written prescription is required from your doctor each time you need more M-ESLON. Therefore, it is important to contact your doctor before your current supply runs out.

What are possible side effects from using M-ESLON?

These are not all the possible side effects you may feel when taking M-ESLON. If you experience
any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Drowsiness, insomnia
- Dizziness, fainting
- Nausea, vomiting, poor appetite, dry mouth
- Headache
- Problems with vision
- Weakness, uncoordinated muscle movement
- Itching
- Sweating
- Constipation

Talk with your doctor or pharmacist about ways to prevent constipation when you start using M-ESLON.

<table>
<thead>
<tr>
<th>Serious side effects and what to do about them</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom / effect</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>RARE</strong></td>
</tr>
<tr>
<td>Overdose: hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone, cold and clammy skin.</td>
</tr>
<tr>
<td><strong>Respiratory Depression:</strong></td>
</tr>
<tr>
<td>Slow, shallow or weak breathing.</td>
</tr>
<tr>
<td><strong>Allergic Reaction:</strong></td>
</tr>
<tr>
<td>rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing.</td>
</tr>
<tr>
<td><strong>Bowel Blockage (impaction):</strong></td>
</tr>
<tr>
<td>abdominal pain, severe constipation, nausea.</td>
</tr>
<tr>
<td><strong>Withdrawal:</strong></td>
</tr>
<tr>
<td>nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating.</td>
</tr>
<tr>
<td><strong>Fast, Slow or Irregular Heartbeat:</strong></td>
</tr>
<tr>
<td>heart palpitations.</td>
</tr>
<tr>
<td><strong>Low Blood Pressure:</strong></td>
</tr>
</tbody>
</table>
If you have troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

**Reporting Side Effects**
We encourage you to report serious or unexpected side effects to Health Canada. The information is used to check for new safety concerns about health products. As a consumer, your report contributes to the safe use of health products for everyone.

**3 ways to report:**
- Online at [MedEffect](#);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at [MedEffect](#).

*NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.*

**Storage:**

Store at room temperature (15°C to 30°C).

**Keep unused or expired M-ESLON in a secure place to prevent theft, misuse or accidental exposure.**

**Keep out of sight and reach of children and pets.**

**Disposal:**

M-ESLON should never be thrown into household trash, where children and pets may find it. It should be returned to a pharmacy for proper disposal.

**If you want more information about M-ESLON:**
- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this patient medication information by visiting the [Health Canada website](#); or by calling Ethypharm Inc. at 1-800-347-1675.

This leaflet was prepared by Ethypharm Inc.

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