

## PRODUCT MONOGRAPH

<sup>N</sup>**M-ESLON**<sup>®</sup>

(Morphine Sulfate)

10 mg, 15 mg, 30 mg, 60 mg, 100 mg, 200 mg  
Extended Release Capsules

Narcotic Analgesic

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## 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 CO<sub>2</sub>, 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 (see **SERIOUS WARNINGS AND PRECAUTIONS** and **WARNINGS AND PRECAUTIONS**).
- 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: OVERDOSE**

Serious, life-threatening, or fatal respiratory depression may occur with use of M-ESLON. Infants exposed in-utero or through breast milk are at risk of life-threatening respiratory depression upon delivery or when nursed. Patients should be monitored for respiratory depression, especially during initiation of M-ESLON or following a dose increase.

M-ESLON should be swallowed whole, or the contents of the capsule mixed with soft food and swallowed immediately without chewing. Cutting, breaking, crushing, chewing, or dissolving M-ESLON can lead to rapid release and absorption of a potentially fatal dose of morphine sulfate (see WARNINGS AND PRECAUTIONS). Further, instruct patients of the hazards related to taking opioids including fatal overdose.

### **Accidental Exposure**

Accidental consumption of even one dose of M-ESLON, especially by children, can result in a fatal overdose of morphine (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).

### **Interaction with Alcohol**

The co-ingestion of alcohol with M-ESLON should be avoided as it may result in dangerous additive effects, causing serious injury or death (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

### **Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants**

**Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see WARNINGS AND PRECAUTIONS, Neurologic and DRUG INTERACTIONS).**

- **Reserve concomitant prescribing of M-ESLON and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

## **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.

Hyperalgesia that does not respond to a further dose increase of morphine may occur in particular in high doses. A morphine dose reduction or change in opioid may be required.

### **Abuse and Misuse**

M-ESLON (Morphine Sulfate Extended Release Capsules) 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 (see **DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage**). Some of the symptoms that may be associated with abrupt withdrawal of an opioid analgesic include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, anxiety, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning (see **ADVERSE REACTIONS, Withdrawal (Abstinence) Syndrome**).

### **Use in Drug and Alcohol Addiction**

Patients with a history of addiction to drugs or alcohol may be at higher risk of becoming addicted to M-ESLON unless used under extreme caution and awareness.

### **Endocrine**

#### **Adrenal Insufficiency:**

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

## **Neurologic**

### **Interactions with Central Nervous System Depressants (Including benzodiazepines and 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**).

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (see **DRUG INTERACTIONS**). If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when M-ESLON is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see **DRUG INTERACTIONS**).

M-ESLON should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS**).

Severe pain antagonizes the subjective and respiratory depressant actions of opioid analgesics. Should pain suddenly subside, these effects may rapidly become manifest.

**Serotonin Syndrome:** M-ESLON could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs (e.g. anti-depressants, migraine medications). Treatment with the serotonergic drug should be discontinued if such events (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic



instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated. M-ESLON should not be used in combination with MAO inhibitors or serotonin-precursors (such as L-tryptophan, oxitriptan) and should be used with caution in combination with other serotonergic drugs (triptans, certain tricyclic antidepressants, lithium, tramadol, St. John's Wort) due to the risk of serotonergic syndrome (see **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**

#### **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 (CO<sub>2</sub>) 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. 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.

**Acute chest syndrome (ACS) in patients with sickle cell disease (SCD):**

Due to a possible association between ACS and morphine use in SCD patients treated with morphine during a vaso-occlusive crisis, close monitoring for ACS symptoms is warranted.

**Sexual Function/Reproduction**

Long-term use of opioids may be associated with decreased sex hormone levels, increased prolactin and symptoms such as low libido, erectile dysfunction, infertility, impotence, or amenorrhea (see **ADVERSE REACTIONS, Post-Marketing Experience**).

**Special Populations**

**Pregnant Women**

Animal 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.

**Labour, Delivery and Nursing Women**

M-ESLON is contraindicated during labour, delivery, pregnancy and in nursing mothers. Morphine can cross the placental barrier and is also excreted in breast milk. Life-threatening respiratory depression may occur in the infant if opioids are administered to the mother. Naloxone, a drug that counters the effects of opioids, should be readily available if M-ESLON is used in this population.

### **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**

### **Overview**

#### **Interactions with Central Nervous System (CNS) Depressants (including benzodiazepines and alcohol):**

Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants (e.g. other opioids, sedatives/hypnotics, antidepressants, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, phenothiazines, neuroleptics, antihistamines, antiemetics, and alcohol) and beta-blockers, increases the risk of respiratory depression, profound sedation, coma, and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see **WARNINGS AND PRECAUTIONS, Neurologic, Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol) and Psychomotor Impairment**).

M-ESLON (Morphine Sulfate Extended Release Capsules) should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

#### **Drug-Drug Interactions**

Generally, the effects of morphine may be antagonized by acidifying agents and potentiated by alkalinizing agents. The analgesic effect of morphine is potentiated by amphetamines, chlorpromazine and methocarbamol.

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

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

**Administration with Mixed Activity Agonist/Antagonist Opioids:** Mixed agonist/antagonist opioid analgesics (i.e., pentazocine, nalbuphine, butorphanol, and buprenorphine) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as morphine. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of morphine and/or may precipitate withdrawal symptoms in these patients.

**MAO Inhibitors:** Monoamine oxidase inhibitors intensify the effects of opioid drugs which can cause anxiety, confusion and decreased respiration. M-ESLON is contraindicated in patients receiving MAO Inhibitors or who have taken them within the previous 14 days (see **CONTRAINDICATIONS**).

**Serotonergic Agents:** Coadministration of morphine sulfate with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor or a Serotonin Norepinephrine Re-uptake Inhibitor, may increase the risk of serotonin syndrome, a potentially life-threatening condition (see **WARNINGS AND PRECAUTIONS, Neurologic**).

**Rifampicin:** Plasma concentrations of morphine may be reduced by rifampicin. The analgesic effect of morphine should be monitored and doses of morphine adjusted during and after treatment with rifampicin.

#### **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.

### **Central Nervous System**

Euphoria, dysphoria, weakness, insomnia, dizziness, headache, agitation, tremor, uncoordinated muscle movements, visual disturbances, confusion, occasional hallucinations, and hyperalgesia or allodynia that does not respond to an increase in morphine dose.

### **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, anaphylactic reaction, anaphylactoid reaction.

### **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, anxiety, runny nose, sneezing, tremors or shivering, stomach cramps, nausea, trouble with sleeping, unusual increase in sweating, palpitations, and yawning, weakness, tachycardia and unexplained fever. With appropriate medical use of narcotics and gradual withdrawal from the drug, these symptoms are usually mild.

### **Post-Marketing Experience**

**Androgen deficiency:** Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency and increase in serum prolactin that may manifest as low

libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

## OVERDOSAGE

### **Symptoms**

Serious morphine overdose is characterized by respiratory depression (reduced respiratory rate and/or tidal volume; Cheyne-Stokes respiration; cyanosis), pneumonia aspiration, extreme somnolence progressing to stupor or coma, flaccidity of skeletal muscle, cold or clammy skin, and sometimes hypotension and bradycardia. Severe overdose 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 overdose 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 (Morphine Sulfate Extended Release Capsules) 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).**

All doses of opioids carry an inherent risk of fatal or non-fatal adverse events. This risk is increased with higher doses. For the management of chronic non-cancer, non-palliative pain, it is recommended that 90 mg (90 morphine milligram equivalent) of M-ESLON not be exceeded. Each patient should be assessed for their risk prior to prescribing M-ESLON, as the likelihood of experiencing serious adverse events can depend upon the type of opioid, duration of treatment, level of pain as well as the patient's own level of tolerance. In addition, the level of pain should be assessed routinely to confirm the most appropriate dose and the need for further use of M-ESLON (see **DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage**).

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 gastrostomy 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 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.

**Opioid Rotation:** Conversion ratios for opioids are subject to variations in kinetics governed by genetics and other factors. When switching from one opioid to another, consider reducing the calculated dose by 25-50% to minimize the risk of overdose. Subsequently, up-titrate the dose, as required, to reach the appropriate maintenance dose.



**Table 1: Opioid Conversion Table<sup>a</sup>**

| Opioids       | To convert to oral morphine equivalent                | To convert from oral morphine multiply by | Daily 90 mg MED <sup>b</sup> |
|---------------|---|---|------------------------------|
| Morphine      | 1   | 1   | 90 mg/d                      |
| Codeine       | 0.15  | 6.67                                      | 600 mg/d                     |
| Hydromorphone | 5   | 0.2                                       | 18 mg/d                      |
| Oxycodone     | 1.5   | 0.667                                     | 60 mg/d                      |
| Tapentadol    | 0.3-0.4   | 2.5-3.33                                  | 300 mg/d                     |
| Tramadol      | 0.1-0.2   | 6   | ***                          |
| Methadone     | Morphine dose equivalence is not reliably established |   |                              |

\*\*\* The maximum recommended daily dose of tramadol is 300 mg - 400 mg depending on the formulation.

a. Adapted from the 2017 Canadian guideline for opioids for chronic non-cancer pain. McMaster University; 2017

b. MED: Morphine Equivalent Dose

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.

Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including M-ESLON. Withdrawal (abstinence) symptoms may occur following abrupt discontinuation of therapy. These symptoms may include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, anxiety, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning.

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. Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal for the drug, these symptoms are usually mild (see **WARNINGS AND PRECAUTIONS**). Tapering should be individualized and carried out under medical supervision.

Patient should be informed that reducing and/or discontinuing opioids decreases their tolerance to these drugs. If treatment needs to be re-initiated, the patient must start at the lowest dose and titrate up to avoid overdose.

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

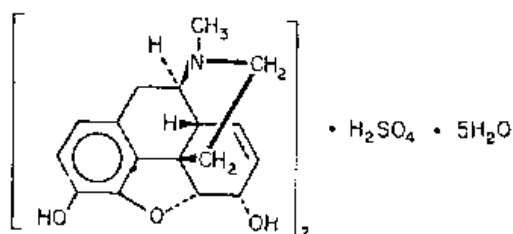
Proper (common) name

Morphine Sulfate

Chemical name

Morphinan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl, (5 $\alpha$ ,6 $\alpha$ )-, sulfate (2:1) (salt), pentahydrate;

Structural formula



Molecular formula: (C<sub>17</sub>H<sub>19</sub>NO<sub>3</sub>)<sub>2</sub> H<sub>2</sub>SO<sub>4</sub>·5H<sub>2</sub>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).

Also available in white, opaque polypropylene bottles of 50 capsules, with tamper-evident polyethylene caps. The 200 mg strength is only available in bottles of 50 capsules:

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

## 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 CO<sub>2</sub>, 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.

In male rats, reduced fertility and chromosomal damage in gametes have been reported.

## TOXICOLOGY

### Single dose studies

The LD<sub>50</sub> values given in the Registry of toxic effects of chemical substances are shown in the following table:

| Species | Route of administration | LD <sub>50</sub> in mg/kg |
|---------|-------------------------|---------------------------|
| Rat     | Oral                    | 461                       |
|         | Intravenous             | 70                        |
| Mouse   | Oral                    | 670                       |
|         | Intravenous             | 200                       |
| Dog     | Intravenous             | 316                       |

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:

| Species | Strain | # of animals and sex/group | Route of administration | Product administered                               | Observation Period | LD <sub>50</sub> (mg/kg) |
|---------|--------|----------------------------|-------------------------|--|--------------------|--------------------------|
| Mouse   | Swiss  | 10 females<br>10 males     | oral<br>oral            | Morphine sulfate                                   | 14 days<br>14 days | 1000<br>1100             |
| Rat     | Wistar | 10 females<br>10 males     | oral<br>oral            | Morphine sulfate                                   | 14 days<br>14 days | 675<br>700               |
| Mouse   | Swiss  | 10 females<br>10 males     | oral<br>oral            | Microgranules containing 364 mg morphine sulfate/g | 14 days<br>14 days | 1164<br>1310             |
| Rat     | Wistar | 10 females<br>10 males     | oral<br>oral            | Microgranules containing 364 mg morphine sulfate/g | 14 days<br>14 days | 764<br>910               |

\*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**

**<sup>N</sup>M-ESLON<sup>®</sup>**

**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. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.**
- **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.**
- **If you took M-ESLON while you were pregnant, whether for short or long periods of time or in small or large doses, your baby can suffer life-threatening withdrawal symptoms after birth. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has any of the following symptoms:**
  - **has changes in their breathing (such as weak, difficult or fast breathing)**
  - **is unusually difficult to comfort**
  - **has tremors (shakiness)**
  - **has increased stools, sneezing, yawning, vomiting, or fever****Seek immediate medical help for your baby.**
- **Taking M-ESLON with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.**

## **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 contains morphine which is a pain medication belonging to the class of medicines known as opioids which includes codeine, fentanyl, morphine and oxycodone. 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:**

- your doctor did not prescribe it for you
- you are allergic to morphine sulfate, other opioids, or any of the other ingredients of M-ESLON
- you have mild or short term pain that can be controlled by the occasional use of pain medications, including those available without a prescription
- you have severe asthma, trouble breathing, or other lung problems
- you have a condition where the small bowel does not work properly (paralytic ileus) or you have severe pain in your abdomen
- you have gallbladder disease, bile duct disease or problems with your pancreas
- 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
- you are taking, or have taken within the past 2 weeks, a monoamine oxidase inhibitor medication (e.g., phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline)
- you are going to have, or recently had, a planned surgery

**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, liver or lung disease
- have heart 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
- suffer from migraines
- suffer from sickle cell disease

**Other warnings you should know about:**

**Opioid dependence and addiction:** There are important differences between physical dependence and addiction. It is important that you talk to your doctor if you have questions or concerns about abuse, addiction or physical dependence.

**Pregnancy, nursing, labour and delivery:** Do not use M-ESLON while pregnant, nursing, during labour or delivery. Opioids can be transferred to your baby through breast milk, or while still in the womb. M-ESLON can then cause life-threatening breathing problems in your unborn baby or nursing infant.

**Driving and using machines:** Before you do tasks which may require special attention, you should wait until you know how you react to M-ESLON. M-ESLON can cause:

- drowsiness
- dizziness or
- light headedness

This can usually occur after you take your first dose and when your dose is increased.

**Disorder of the adrenal gland:** You may develop a disorder of the adrenal gland called adrenal insufficiency. This means that your adrenal gland is not making enough of certain hormones. You may experience symptoms such as:

- nausea, vomiting
- feeling tired, weak or dizzy
- decreased appetite

You may be more likely to have problems with your adrenal gland if you have been taking opioids for longer than one month. Your doctor may do tests, give you another medication, and slowly take you off M-ESLON.

**Serotonin Syndrome:** M-ESLON can cause Serotonin Syndrome, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop Serotonin Syndrome if you take M-ESLON with certain anti-depressants or migraine medications.

Serotonin Syndrome symptoms include:

- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

**Sexual function/reproduction:** Long term use of **M-ESLON** may lead to sexual and reproductive problems such as:

- decreases in sexual desire,
- difficulty getting or keeping an erection,
- infertility or
- missing your menstrual period for 3 months or more in a row.



**Increased sensitivity to pain:** You may experience more pain despite already taking high doses of M-ESLON. Your doctor will decide whether you need to change your dose or change your medication.

**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, unusually slow or weak 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)
- St. John's Wort
- rifampicin (an antibiotic)

**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. Do not increase or decrease your dose without consulting your doctor. Taking higher doses can lead to more side effects and a greater chance of overdose.

Review your pain regularly with your doctor to determine if you still need M-ESLON. Be sure to use M-ESLON only for the condition for which it was prescribed.

Should your pain increase or any other complaint develop as a result of taking M-ESLON, tell your doctor immediately.

**Stopping your Medication:**

You should not stop taking M-ESLON all at once if you have been taking it for more than a few days.

Your doctor will monitor and guide you on how to slowly stop taking M-ESLON. You should do it slowly to avoid uncomfortable symptoms such as having:

- body aches
- diarrhea
- goosebumps
- loss of appetite
- nausea
- feeling nervous or restless
- runny nose
- sneezing
- tremors or shivering
- stomach cramps
- rapid heart rate (tachycardia)
- having trouble with sleeping
- an unusual increase in sweating
- heart palpitations
- an unexplained fever
- weakness
- yawning.

By reducing or stopping your opioid treatment, your body will become less used to opioids. If you start treatment again, you will need to start at the lowest dose. You may overdose if you restart at the last dose you took before you slowly stopped taking M-ESLON.

### **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 that you contact your doctor before your current supply runs out.

Only obtain prescriptions for this medicine from the doctor in charge of your treatment. Do not seek prescriptions from other doctors unless you switch to another doctor for your pain management.

### **Overdose:**

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.

Signs of overdose may include:

- unusually slow or weak breathing
- dizziness
- confusion
- extreme drowsiness

Overdose can result in lung infection, loss of consciousness and death.

### **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 a row, talk to your doctor before restarting your medication.

### **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
- Low sex drive, impotence (erectile dysfunction), infertility
- Confusion
- Light-headedness
- Sleepiness

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

| <b>Serious side effects and what to do about them</b>   |                                      |              |   |
|---|--------------------------------------|--------------|---|
| Symptom / effect  | Talk to your healthcare professional |              | Stop taking drug and get immediate medical help |
|   | Only if severe                       | In all cases |   |
| <b>RARE</b>   |                                      |              |   |
| <b>Overdose:</b> hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone, cold and clammy skin. |                                      |              | √   |
| <b>Respiratory Depression:</b> Slow, shallow or weak breathing.   |                                      |              | √   |
| <b>Allergic Reaction:</b> rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing.  |                                      |              | √   |
| <b>Bowel Blockage (impaction):</b> abdominal pain, severe constipation, nausea.   |                                      |              | √   |
| <b>Withdrawal:</b> nausea, vomiting, diarrhea, anxiety, shivering, cold and   |                                      | √            |   |

| <b>Serious side effects and what to do about them</b>   |                                      |              |   |
|---|--------------------------------------|--------------|---|
| Symptom / effect  | Talk to your healthcare professional |              | Stop taking drug and get immediate medical help |
|   | Only if severe                       | In all cases |   |
| clammy skin, body aches, loss of appetite, sweating.  |                                      |              |   |
| <b>Fast, Slow or Irregular Heartbeat:</b> heart palpitations.   |                                      | √            |   |
| <b>Low Blood Pressure:</b> dizziness, fainting, light-headedness.   | √                                    |              |   |
| <b>Serotonin Syndrome:</b> agitation or restlessness, loss of muscle control or muscle twitching, tremor, diarrhea. |                                      |              | √   |
| <b>UNKNOWN</b><br>Increased response to pain and/or burning sensation.  |                                      | √            |   |

If you have a 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

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

### Storage:

- **Keep unused or expired M-ESLON in a secure place to prevent theft, misuse or accidental exposure.**
- Store at room temperature (15°C - 30°C).
- **Keep M-ESLON under lock, out of sight and reach of children and pets.**
- **Never take medicine in front of small children as they will want to copy you. Accidental ingestion by a child is dangerous and may result in death. If a child accidentally takes M-ESLON, get emergency help right away.**

**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 Ethypharm Inc. website at [www.ethypharm.com/ethypharm-canada/](http://www.ethypharm.com/ethypharm-canada/), or by calling Ethypharm Inc. at 1-800-347-1675.

This leaflet was prepared by Ethypharm Inc.

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