

Product Monograph
Including Patient Medication Information

^NM-ESLON[®]

Morphine Sulfate
10 mg, 15 mg, 30 mg, 60 mg, 100 mg, 200 mg
Extended-Release Capsules

Opioid Analgesic

Ethypharm Inc.
1200 avenue McGill College, Suite 1500
Montréal, Québec
H3B 4G7

Date of Initial Authorization:
December 31, 1993

Control No.: 303535

Date of Revision:
SEP 17, 2026

RECENT MAJOR LABEL CHANGES

2 CONTRAINDICATIONS	09/2026
4 DOSAGE AND ADMINISTRATION, 4.1 Dosing Considerations	09/2026
4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment	09/2026
7 WARNINGS AND PRECAUTIONS, General, Addiction, Abuse and Misuse	09/2026
7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance	09/2026
7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic	09/2026
7 WARNINGS AND PRECAUTIONS, Neurologic	09/2026
7 WARNINGS AND PRECAUTIONS, Respiratory, Sleep Apnea	09/2026
7 WARNINGS AND PRECAUTIONS, Respiratory, Acute Chest Syndrome (ACS) in Patients with Sickle Cell Disease (SCD)	09/2026
7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance and Hepatic/Biliary/Pancreatic	09/2026
7 WARNINGS AND PRECAUTIONS, Skin	09/2026
7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women	09/2026

Part 1: Healthcare Professional Information	5
1 Indications	5
1.1 Pediatrics (< 18 years of age)	5
1.2 Geriatrics (> 65 years of age)	5
2 Contraindications	5
3 Serious Warnings and Precautions Box	6
4 Dosage and Administration	7
4.1 Dosing Considerations	7
4.2 Recommended Dose and Dosage Adjustment	8
4.3 Administration	11
4.4 Missed Dose	11
5 Overdosage	11
6 Dosage Forms, Strengths, Composition, and Packaging.....	12
7 Warnings and Precautions	13
General	13
Abuse and Misuse.....	13
Carcinogenesis and Genotoxicity	13
Cardiovascular	14
Use in Drug and Alcohol Addiction	15
Driving and Operating Machinery.....	15
Gastrointestinal.....	15
Hepatic/Biliary/Pancreatic	15
Neurologic.....	15
Use in Patients with Convulsive or Seizure Disorders	16
Serotonin Syndrome	16
Head Injury	16

Opioid-induced hyperalgesia	17
Peri-Operative Considerations	17
Sexual Function/Reproduction	17
Neonatal Opioid Withdrawal Syndrome (NOWS)	17
Respiratory	17
Use in Patients with Chronic Pulmonary Disease	18
Sleep Apnea	18
Acute Chest Syndrome (ACS) in Patients with Sickle Cell Disease (SCD)	18
Skin	18
7.1 Special Populations	18
7.1.1 Pregnancy	19
7.1.2 Breastfeeding	19
7.1.3 Pediatrics (< 18 years of age)	19
7.1.4 Geriatrics (> 65 years of age)	19
8 Adverse Reactions	19
8.1 Adverse Reaction Overview	19
8.2 Clinical Trial Adverse Reactions	20
8.5 Post-Market Adverse Reactions	22
9 Drug Interactions.....	23
9.1 Serious Drug Interactions	23
9.2 Drug Interactions Overview	23
9.3 Drug-Behaviour Interactions	23
9.4 Drug-Drug Interactions	23
9.5 Drug-Food Interactions	24
9.6 Drug-Herb Interactions	24
9.7 Drug-Laboratory Test Interactions	24

10 Clinical Pharmacology	24
10.1 Mechanism of Action.....	24
10.2 Pharmacodynamics	24
10.3 Pharmacokinetics	26
11 Storage, Stability and Disposal.....	26
Disposal.....	26
12 Special Handling Instructions.....	26
Part 2: Scientific Information	28
13 Pharmaceutical Information	28
14 Clinical Trials	28
15 Microbiology	28
16 Non-Clinical Toxicology	28
Patient Medication Information	31

Part 1: Healthcare Professional Information

1 Indications

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.

1.1 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.

1.2 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.

2 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 6.
- 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 (opioids 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 or severe asthma or other obstructive airway (COPD), and status asthmaticus.
- Patients with acute respiratory depression with hypoxia and/or elevated carbon dioxide levels in the blood (hypercapnia), 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 3, 7.1.1 Pregnancy, 7.1.2 Breastfeeding).

- 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.

3 Serious Warnings and Precautions Box

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 4.1 Dosing Considerations).

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 7 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 7). 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 11 Storage, Stability and 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 7 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 7 and 9).

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 7, **Neurologic** and 9 Drug Interactions⁹).

- 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.

4 Dosage and Administration

4.1 Dosing Considerations

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).

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 4.2 Recommended Dose and Dosage Adjustment).

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

M-ESLON should not be used for post-operative pain, unless the patient is already receiving M-ESLON prior to surgery (see 7 Warnings and Precautions, Peri-Operative Considerations).

M-ESLON is not indicated for rectal administration.

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.

4.2 Recommended Dose and Dosage Adjustment

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.

Adults (≥ 18 years of age):

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 :

Patients over the age of 50 tend to require much lower doses of morphine than the younger age group.

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.

Respiratory depression has occurred in the elderly following administration of large initial doses of opioids to patients who were not opioid-tolerant or when opioids were co-administered with other agents that can depress respiration (see 7 , Respiratory, Respiratory Depression).

Patients Currently Receiving Opioids :

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 opioid, 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^a

Opioids	To Convert to Oral Morphine Equivalent	To Convert From Oral Morphine Multiply By	Daily 90 mg MED^b
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

Debilitated patients

In debilitated patients and those with impaired respiratory function, morphine should be administered with caution and at one half of the usual recommended dose (see 7 Warnings and Precautions, 7.1 **Special Populations**, Special Risk Groups).

Patients with Hepatic Impairment

Dosage reduction is recommended in severe hepatic impairment due to the risk of toxicity (see 7 Warnings and Precautions, 7.1 **Special Populations**, Special Risk Groups).

Patients with Renal Impairment

Dosage reduction is recommended in severe renal impairment due to the risk of toxicity (see 7 Warnings and Precautions, 7.1 **Special Populations**, Special Risk Groups).

Dose Titration

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 which will achieve the overall treatment goal of satisfactory pain relief with acceptable side effects. 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 opioid dose should be made. Smaller doses or complete discontinuation of the opioid analgesic may become feasible due to a change in the patient's condition or improved mental state. 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 7 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.

Opioid 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 opioid 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 opioids.

Treatment Goals and Discontinuation

Before initiating treatment with M-ESLON, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust the dose, if needed. When the benefits of continuing treatment with M-ESLON no longer outweigh the risks, taper the dose gradually to prevent symptoms of withdrawal. In the absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see 7).

Duration of Treatment

M-ESLON should not be used longer than necessary.

4.3 Administration

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 3 and 7 Warnings and Precautions, Respiratory Depression).

4.4 Missed Dose

If the patient forgets to take one or more doses, they should take their next dose at the next scheduled time and in the normal amount.

5 Overdosage

For management of a suspected drug overdose, contact your regional poison control center or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

Symptoms

Serious morphine overdose is characterized by respiratory depression (reduced respiratory rate and/or tidal volume; Cheyne-Stokes respiration; cyanosis), dizziness, confusion, pneumonia aspiration, extreme somnolence progressing to stupor or coma, miosis, rhabdomyolysis progressing to renal failure, flaccidity of skeletal muscle, hypotonia, cold or clammy skin, toxic leukoencephalopathy, delayed post-hypoxic leukoencephalopathy 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 opioid 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 opioids, the administration of the usual dose of opioid antagonist will precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of antagonist administered. The use of opioid antagonists in such individuals should be avoided if possible. If an opioid antagonist must be used to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care by using dosage titration, commencing with 10 to 20% of the usual recommended initial dose.

Evacuation of gastric contents may be useful in removing unabsorbed drug, particularly when an extended release formulation has been taken.

6 Dosage Forms, Strengths, Composition, and Packaging

Table 2 – Dosage Forms, Strengths, Composition and Packaging		
Route of Administration	Dosage Form / Strength/ Composition	Non-medicinal Ingredients
Oral	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.	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.

Dosage Forms

- 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

Packaging

M-ESLON is available in blister packs of 20 hard gelatin capsules and bottles of 50 hard gelatin capsules with tamper-evident polyethylene caps.

M-ESLON 200 mg is only available in bottles of 50 capsules.

7 Warnings and Precautions

Please see the 3 Serious Warnings and Precautions Box at the beginning of Part 1: Healthcare Professional Information.

General

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

Patients should be instructed not to give M-ESLON to anyone other than for whom it was prescribed, as such, inappropriate use may have severe medical consequences, including death. M-ESLON should be stored securely to avoid theft or misuse.

M-ESLON should only be prescribed by healthcare professionals who are knowledgeable in the continuous administration of potent opioids, in the management of patients receiving potent opioids for the treatment of pain, and in the detection and management of respiratory depression, including the use of opioid antagonists.

In diseases, such as malignant cancers, where pain control is the primary focus, opioid administration at very high doses is associated with seizures and myoclonus.

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

Like all opioids, 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 and other mental health disorders including, but not limited to, major depression and anxiety. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

With parenteral abuse, the capsule excipients can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury, which may also be fatal.

Carcinogenesis and Genotoxicity

Include human data where there is evidence that the drug is carcinogenic or genotoxic. In the absence of human data, include pertinent animal data with a cross-reference to 16 Non-clinical Toxicology.

Cardiovascular

Hypotension

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 and other tranquilizers, sedative/hypnotics, tricyclic antidepressants or general anesthetics. These patients should be monitored for signs of hypotension after initiating or titrating the dose of M-ESLON.

The use of M-ESLON in patients with circulatory shock should be avoided as it may cause vasodilation that can further reduce cardiac output and blood pressure.

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 and/or Abuse Liability 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 and opioid use disorder (OUD).

Physical dependence and tolerance reflect the neuroadaptation of the opioid receptors to chronic exposure to an opioid 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. 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.

In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes.

Abuse or intentional misuse of M-ESLON may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g., major depression, anxiety and personality disorders).

Before initiating treatment with M-ESLON and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see 4 Dosage and Administration Treatment Goals and Discontinuation).

Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician.

Patients will require monitoring for signs of drug-seeking behaviour (e.g., too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

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 4 Dosage and Administration, 4.2 Recommended Dose and Dosage Adjustment). 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 8 Adverse Reactions, General Disorders and Administration Site Conditions).

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.

Driving and Operating Machinery

Morphine may impair the mental and/or physical abilities needed for certain potentially hazardous activities such as driving a car or operating machinery. Patients should be cautioned accordingly. Patients should also be cautioned about the combined effects of morphine with other CNS depressants, including other opioids, phenothiazines, sedative/hypnotics and alcohol.

Endocrine and Metabolism 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.

Gastrointestinal

Morphine and other morphine-like opioids have been shown to decrease bowel motility. Morphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions (see 2 Contraindications) and is also contraindicated in patients with paralytic ileus, and appendicitis (see 2 and 8 Nausea and Vomiting, and Constipation).

Hepatic/Biliary/Pancreatic

Morphine may cause dysfunction and spasm of the sphincter of Oddi and an increase in intrabiliary pressure and in the risk of biliary tract symptoms and pancreatitis. Other opioid related effects may include a reduction in biliary and pancreatic secretions or elevations in serum amylase. Morphine should be avoided in patients with hepatobiliary disorders. Monitor patients for worsening symptoms related to biliary tract disease, including acute pancreatitis.

Neurologic

Interactions with CNS 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, gabapentinoids, baclofen 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 2 Contraindications and 9).

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 9 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 9 Drug Interactions).

M-ESLON should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see 2 and 9).

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

Use in Patients with Convulsive or Seizure Disorders

The morphine in M-ESLON may aggravate convulsions in patients with convulsive disorders and may induce or aggravate seizures in some clinical settings. Therefore, morphine should not be used in these patients (see 2 Contraindications).

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

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 9 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 should not be used (see 2 Contraindications).

Opioid-induced hyperalgesia

Opioid induced hyperalgesia (OIH) is a paradoxical response to an opioid in which there is an increase in pain perception despite stable or increased opioid exposure. It differs from tolerance, in which higher opioid doses are required to achieve the same analgesic effect or treat recurring pain. Clinically, OIH may be associated with high opioid doses, long term opioid treatment, and intra-operative opioid use. OIH may manifest as an unexplained

increase in pain, more diffuse pain than pre-existing, or as pain from ordinary (i.e. non-painful) stimuli (allodynia) in the absence of disease progression. When OIH is suspected, the dose of opioid should be reduced or tapered off, if possible. It is reasonable to consider opioid rotation, or the use of a non-opioid strategy for pain control. There is currently no well-established treatment for OIH.

Peri-Operative Considerations

M-ESLON is not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative pain).

Patients who are scheduled for cordotomy or other interruption of pain transmission pathways should not receive M-ESLON within 24 hours of the procedure and M-ESLON should not be used in the immediate post-operative period.

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 8 , 8.5 Post-Market Adverse Reactions).

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 2 Contraindications).

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 (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. 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 4). Overestimating the M-ESLON dose when converting patients from another opioid product can result in fatal overdose with the first dose.

Use in Patients with Chronic Pulmonary Disease

Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression for

respiratory depression, particularly when initiating therapy and titrating with M-ESLON, as in these patients, even usual therapeutic doses of M-ESLON may decrease respiratory drive to the point of apnea. In these patients, use of alternative non-opioid analgesics should be considered, if possible. The use of M-ESLON is contraindicated in patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see 2 Contraindications).

Sleep Apnea

Opioids can cause sleep-related breathing disorders such as sleep apnea syndromes (including central sleep apnea [CSA]) and hypoxia (including sleep-related hypoxia). Opioid use increases the risk of CSA in a dose-dependent fashion. Evaluate patients on an ongoing basis for the onset of a new sleep apnea, or a worsening of an existing sleep apnea. In these patients, consider reducing or stopping the opioid treatment if appropriate, using best practices for tapering of opioids (see 4 Dosage and Administration)

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.

Skin

Severe Cutaneous Adverse Reactions (SCARs)

Acute Generalized Exanthematous Pustulosis (AGEP), which can be life-threatening or fatal, has been reported in association with morphine treatment. Most of these reactions occurred within the first 10 days of treatment. Patients should be informed about the signs and symptoms of AGEP and be advised to seek immediate medical care if they experience such symptoms.

If signs and symptoms suggestive of these skin reactions appear, morphine should be withdrawn and an alternative treatment considered.

7.1 Special Populations

Special Risk Groups

Morphine should be administered with caution to patients with a history of seizures, alcohol and drug abuse, acute generalized exanthematous pustulosis (AGEP), and Opioid Use Disorder (OUD). It should also be administered, at a reduced dose, to elderly or debilitated patients, to patients with reduced hepatic function or severe renal dysfunction, in patients with severely impaired pulmonary function, those with adrenocortical insufficiency (Addison's disease), hepatobiliary disorders, hypotension with hypovolaemia, hypothyroidism, myxedema (severe hypothyroidism), toxic psychosis, prostatic hypertrophy or urethral stricture, hypopituitarism, anemia, severe malnutrition, fulminant ulcerative colitis.

The administration of opioid analgesics, including morphine, may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Opioid analgesics including morphine should also be used with caution in patients about to undergo surgery of the biliary tract, since it may cause spasm of the sphincter of Oddi.

7.1.1 Pregnancy

Animal studies indicate that morphine may be teratogenic at high doses in mice (see 16 Non-Clinical 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 crosses the placental barrier and is contraindicated in pregnant women (see 2 Contraindications).

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 7 Warnings and Precautions– Neonatal Opioid Withdrawal Syndrome (NOWS)). 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.

Pregnant women using opioids should not discontinue their medication abruptly as this can cause pregnancy complications such as miscarriage or still-birth. Tapering should be slow and under medical supervision to avoid serious adverse events to the fetus.

7.1.2 Breastfeeding

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.

7.1.3 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.

7.1.4 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.

8 Adverse Reactions

8.1 Adverse Reaction Overview

Adverse effects of M-ESLON are similar to those of other opioid analgesics and represent an extension of pharmacological effects of the drug class. The major hazards associated with morphine, as with other opioid analgesics, include respiratory depression and central nervous system depression and, to a lesser degree, circulatory depression. Respiratory arrest, shock and cardiac arrest have occurred following oral or parenteral use of morphine.

Most Common Adverse Effects Requiring Medical Attention

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

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 opioids or as an early unwanted effect of regular opioid 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 opioid-induced gastric stasis. In such patients, metoclopramide is often useful.

Constipation

Practically all patients become constipated while taking opioids 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 opioid therapy. Softeners, laxatives and other appropriate measures should be used as required.

8.2 Clinical Trial Adverse Reactions

The following adverse effects occur with M-ESLON and opioid analgesics. The reactions are categorized by body system and frequency according to the following definitions: Very common ($\geq 1/10$); Common ($\geq 1/100$ to $< 1/10$); Uncommon ($\geq 1/1,000$ to $< 1/100$); Rare ($\geq 1/10,000$ to $< 1/1,000$); Very rare ($< 1/10,000$), Not known (cannot be estimated from the available data).

General Disorders and Administration Site Conditions

Common: weakness, asthenia, fatigue, malaise

Not known: drug tolerance, withdrawal syndrome, neonatal withdrawal syndrome

Cardiac disorders

Uncommon: palpitations

Rare: faintness

Not known: supraventricular tachycardia, bradycardia

Ear and Labyrinth Disorders

Uncommon: vertigo

Endocrine Disorders

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).

Not known: hypogonadism, androgen deficiency

Eye Disorders

Uncommon: visual disturbances

Not known: miosis

Gastrointestinal disorders

Very common: nausea, constipation

Common: dry mouth, anorexia, cramps (abdominal pain), vomiting

Uncommon: taste alterations, dyspepsia, ileus

Hepato-biliary Disorders

Uncommon: increased hepatic enzyme

Not known: biliary pain, biliary tract spasm, exacerbation of pancreatitis

Immune System Disorders

Not known: anaphylactic reaction, anaphylactoid reaction

Nervous System disorders

Common: dizziness, headache, drowsiness (somnolence), uncoordinated muscle movements

Uncommon: tremor, convulsions, hypertonia, paraesthesia, syncope, myoclonus

Not known: allodynia, hyperalgesia, central sleep apnea syndrome

Psychiatric Disorders

Common: confusion, insomnia

Uncommon: euphoria, agitation, hallucinations, mood altered

Not known: drug dependence, dysphoria, thinking disturbances

Renal and Urinary Disorders

Uncommon: urinary retention

Not known: ureteric spasm

Respiratory, Thoracic and Mediastinal Disorders:

Uncommon: bronchospasm, pulmonary edema, respiratory depression

Not known: cough decreased

Reproductive System and Breast Disorders

Not known: reduced libido or potency, impotence, erectile dysfunction, amenorrhea, infertility

Skin and Subcutaneous Tissue Disorders

Common: Pruritus, sweating, rash and edema

Uncommon: urticaria

Vascular Disorders

Uncommon: postural hypotension, facial flushing

Not known: hypertension

Investigations

Not known: serum prolactin increased

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post approval use of morphine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adrenal insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use (see 7 Warnings and Precautions, Endocrine and Metabolism Adrenal Insufficiency).

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.

Drug Dependence

Repeated use of M-ESLON can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see 3 Serious Warnings and Precautions Box, Dependence/Tolerance).

Neonatal Opioid Withdrawal Syndrome (NOWS)

Prolonged use of morphine sulfate during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated (see 7 , Neonatal Opioid Withdrawal Syndrome (NOWS)).

Serotonin Toxicity/Serotonin Syndrome

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Spasm of sphincter of Oddi

Acute Generalised Exanthematous Pustulosis (AGEP)

9 Drug Interactions

9.1 Serious Drug Interactions

Risks from concomitant use of opioids and benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see 7 , Neurologic, Interactions with CNS Depressants (including benzodiazepines and alcohol)).

Reserve concomitant prescribing of M-ESLON and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate

Consider dose reduction of CNS depressants in situations of concomitant prescribing
Follow patients for signs and symptoms of respiratory depression and sedation

MAO 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 used them within the previous 14 days.

9.2 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 gabapentin, pregabalin, baclofen, 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 7 Warnings and Precautions, Neurologic, Interactions with CNS 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.

9.3 Drug-Behaviour Interactions

The concomitant use of alcohol should be avoided (see 2 Contraindications).

9.4 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 opioids, 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 2).

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 7 , 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.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 Clinical Pharmacology

10.1 Mechanism of Action

Morphine is an opioid 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.

10.2 Pharmacodynamics

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 opioids exert their effects remains unknown.

Cardiovascular System

Morphine may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Central Nervous System

In humans, the principal pharmacological actions of morphine are in the CNS; analgesia, drowsiness, mood changes, mental clouding, respiratory depression, nausea or emesis and miosis.

Morphine produces respiratory depression by direct action on brain stem respiratory centres. The respiratory depression involves both a reduction in the responsiveness of the brain stem centres to increases in carbon dioxide (CO₂) tension and to electrical stimulation.

Morphine depresses the cough reflex by direct effect on the cough centre in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Morphine causes miosis, even in total darkness. Pinpoint pupils are a sign of narcotic overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of morphine overdose.

Endocrine System

Opioids, such as morphine sulfate, may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may be manifest from these hormonal changes.

Gastrointestinal Tract and Other Smooth Muscle

Morphine causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Hepatobiliary System

Opioids may induce spasm of the sphincter of Oddi.

Immune System

In vitro and animal studies indicate that opioids have a variety of effects on immune functions, depending on the context in which they are used. The clinical significance of these findings is unknown.

Concentration – Efficacy Relationships

Morphine induced analgesia is a result of increases in both the pain threshold and pain tolerance. Morphine alters the affective response to pain in that patients remain aware of its existence but are less distressed. Morphine relieves most types of pain but is more effective against dull constant pains than sharp intermittent ones.

Concentration – Adverse Reaction Relationship

There is a significant relationship between increasing morphine plasma concentrations and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related side effects.

The dose of M-ESLON must be individualized (see

4) because the effective analgesic dose for some patients will be too high to be tolerated by other patients.

10.3 Pharmacokinetics

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.

Absorption: Morphine is readily absorbed from the gastrointestinal tract and after s.c. or i.m. injection.

Distribution: 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.

Elimination: 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.

11 Storage, Stability and Disposal

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

Disposal

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 not be shared with others and steps should be taken to protect it from theft or misuse. The patient should speak to their pharmacist about temporary storage options, if required, until the medication can be returned to the pharmacy for safe disposal.

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

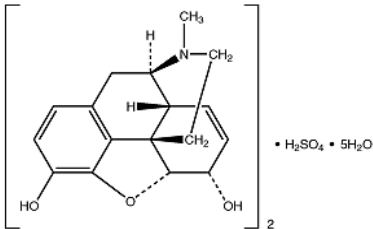
12 Special Handling Instructions

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.

Part 2: Scientific Information

13 Pharmaceutical Information

Drug Substance

Proper (common) name :	Morphine Sulfate
Chemical Name:	Morphinan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl, (5 α ,6 α)-, sulfate (2:1) (salt), pentahydrate;
Molecular Formula and molecular mass:	(C ₁₇ H ₁₉ NO ₃) • H ₂ SO ₄ • 5H ₂ O
Structural Formula:	 Morphine sulfate pentahydrate
Molecular Weight	758.83 (pentahydrate)
Product Characteristics:	Salt, Pentahydrate
Physical Description:	White, fine odorless acicular crystals or powder, or cubical masses. Odourless or almost odourless.
Solubility:	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.

14 Clinical Trials

The clinical trial data on which the original indication was authorized is not available.

15 Microbiology

No microbiological information is required for this drug product.

16 Non-Clinical Toxicology

16.1 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.

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

16.2 Single Dose Studies

The LD₅₀ values given in the Registry of toxic effects of chemical substances are shown in the following table:

Table 3. Morphine Lethal Dose Toxicity Values in Animals

Species	Route of Administration	LD ₅₀ 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 mouse, the symptoms are pronounced excitation and cramps, while the rat shows akinesia and paralysis. In dog, the signs of toxicity are vomiting, diarrhea and tachycardia. Acute toxicity is age dependent. The ratio of the LD₅₀ in mice aged 30 days and 1 day is 6.2.

A study to redetermine the LD₅₀ 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 4. M-ESLON Capsules (Morphine Sulfate Extended Release Capsules) Lethal Dose Toxicity Values in Animals

Species	Strain	# of animals and sex/group	Route of administration	Product administered	Observation Period	LD ₅₀ (mg/kg)
Mouse	Swiss	10 females	oral	Morphine sulfate	14 days	1000
		10 males	oral		14 days	1100
Rat	Wistar	10 females	oral	Morphine sulfate	14 days	675
		10 males	oral		14 days	700

Species	Strain	# of animals and sex/group	Route of administration	Product administered	Observation Period	LD ₅₀ (mg/kg)
Mouse	Swiss	10 females 10 males	oral oral	Microgranules containing 364 mg morphine sulfate/g	14 days 14 days	1164 1310
Rat	Wistar	10 females 10 males	oral oral	Microgranules containing 364 mg morphine sulfate/g	14 days 14 days	764 910

Calculated by Lichfield and Wilcoxon method (J Pharmacol Exp Ther 1949, 96: 99-113)

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

^NM-ESLON[®]

morphine sulfate extended release capsules

This Patient Medication Information is written for the person who will be taking **M-ESLON**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **M-ESLON**, talk to a healthcare professional.

Serious warnings and precautions box

- Even if you take M-ESLON as prescribed you are at risk for opioid addiction, abuse, and misuse. This can lead to overdose and death. To understand your risk of opioid addiction, abuse, and misuse you should speak to your healthcare professional.
- When you take M-ESLON capsules, they must be swallowed whole or the capsules may be opened and the contents sprinkled on food. Do not cut, break, crush, chew, or dissolve the capsules. This can be dangerous and can lead to death or seriously harm you.
- 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 M-ESLON is used for:

M-ESLON is used in adults to manage long-term pain, when:

- the pain is severe enough to require daily, around-the-clock pain medications; and
- the healthcare professional determines that other treatment options are not able to effectively manage your pain.

It is NOT used “as needed” to treat pain that you only have once in a while.

How M-ESLON works:

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.

The ingredients in M-ESLON are:

Medicinal ingredient: Morphine sulfate

Non-medicinal ingredients: Dibutyl sebacate, gelatin, maize starch, polyethylene glycol 4000, polymeric dispersion of ethylcellulose, sucrose, talc, and titanium dioxide.

The capsule shells contain the following additional ingredients:

- 15 mg: Quinoline yellow WS (D&C Yellow No. 10)
- 30 mg: Erythrosine (FD&C Red No. 3)
- 60 mg: Sunset yellow FCF (FD&C Yellow No. 6)
- 100 mg: Black iron oxide
- 200 mg: Allura red AC (FD&C Red No. 40), brilliant blue FCF (FD&C Blue No. 1)

M-ESLON comes in the following dosage form:

M-ESLON extended release capsules are available in 6 strengths:

- 10 mg (opaque white cap and body capsule with “M-ESLON” and “10” printed in black)
- 15 mg (opaque yellow cap and transparent natural body capsule with “M-ESLON” and “15” printed in black)
- 30 mg (opaque pink cap and transparent natural body capsule with “M-ESLON” and “30” printed in black)
- 60 mg (opaque orange cap and transparent natural body capsule with “M-ESLON” and “60” printed in black)
- 100 mg (opaque gray cap and transparent natural body capsule with “M-ESLON” and “100” printed in white)
- 200 mg (opaque red cap and transparent natural body capsule with “M-ESLON” and “200” printed in white)

Do not use M-ESLON if:

- your healthcare professional 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 painkillers, including those available without a prescription.
- you have severe asthma, trouble breathing, or other lung problems.
- you have an irregular heartbeat or low blood pressure.

- you have bowel blockage or narrowing of the stomach or intestines.
- you have a condition where the bowel does not work properly (ileus).
- you have severe pain in your abdomen (for example, from appendicitis or pancreatitis).
- you have increased pressure in your skull, have a head injury, or a brain tumour.
- you have gallbladder disease, bile duct disease or problems with your pancreas.
- you have or have had a history of epilepsy.
- you suffer from alcoholism or alcoholism withdrawal.
- you are pregnant or plan to become pregnant or are in labour and delivery.
- you are breast-feeding.
- you have a surgical connection between tubular structures, such as blood vessels or loops of intestine.
- you have severe cirrhosis of the liver.
- you had surgery of the biliary tract.
- you are taking or have taken within the past 2 weeks a monoamine oxidase inhibitor (MAOI) (such as phenelzine sulfate, tranylcypromine sulfate, moclobemide, or selegiline).

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 personal or family history of illicit or prescription drug or alcohol abuse.
- you are going to have, or recently had, a planned surgery;
- have been told that you have a low red blood cell count.
- have kidney or liver problems.
- have a sleep disorder which causes pauses in breathing or shallow breathing while sleeping (sleep apnea).
- suffer from chronic or severe constipation.
- have problems with your thyroid, adrenal or prostate gland.
- suffer from migraines.
- have or have had problems with your mood (such as depression or anxiety), hallucinations, or other mental health problems.
- have gastrointestinal (GI) problems.
- have a history of pancreas or gall bladder problems.
- are planning to breastfeed.
- are over 50 years of age.
- have circulatory problems (e.g., body does not get enough oxygen and nutrients to function properly due to lack of blood flow).
- have sickle cell disease.
- have difficulty urinating.
- have a condition that causes weakness or frailty.
- are planning on drinking alcohol. Drinking alcohol while taking M-ESLON may cause dangerous side effects, including death. Do NOT drink alcohol while taking M-ESLON.
- take hypnotics, centrally acting analgesics, opioids, or psychotropic medicines. Ask your healthcare professional if you are unsure.

Other warnings you should know about:

Taking M-ESLON can cause the following serious side effects:

- **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 healthcare professional may do tests, give you another medication, and slowly take you off M-ESLON.

- **Serotonin toxicity (also known as serotonin syndrome):** M-ESLON can cause serotonin toxicity, 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 toxicity if you take M-ESLON with certain anti-depressants or migraine medications. Serotonin toxicity 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.
- **Sleep apnea:** Opioids can cause a problem called sleep apnea (stopping breathing from time to time while sleeping). Tell your healthcare professional if you have a history of sleep apnea or if anyone notices that you stop breathing from time to time while sleeping.

See the **Serious side effects and what to do about them table** for more information on these and other serious side effects.

Opioid dependence and addiction: Like any opioid, M-ESLON may cause mental and physical dependence. Morphine sulfate also has the potential to cause addiction even at regular doses. There are important differences between physical dependence and addiction. Tolerance means that, over time, a higher dose may be needed to get the same level of pain relief. It is important that you talk to your healthcare professional if you have questions or concerns about abuse, addiction, physical dependence, or tolerance. Your healthcare professional should prescribe and administer M-ESLON with the same degree of caution appropriate to the use of other oral opioid medications. It is not recommended to use these products for a long period of time.

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.

If you are pregnant and are taking M-ESLON, it is important that you don't stop taking your medication all of a sudden. If you do, it can cause a miscarriage or a still-birth. Your healthcare professional will monitor and guide you on how to slowly stop taking M-ESLON. This may help avoid serious harm to your unborn baby.

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.

Sexual function and reproduction: Long term use of opioids may lead to a decrease in sex hormone levels. It may also lead to low libido (desire to have sex), erectile dysfunction or being infertile.

Worsening pain: Taking opioids for pain can sometimes have the unintended effect of making your pain feel worse (opioid-induced hyperalgesia) even though your opioid dose has been unchanged or increased. This can also include feeling pain in new places in your body, or feeling pain from something that would not normally hurt, for example, feeling pain from clothing touching your skin. Tell your healthcare professional if you notice a change like this in your pain while you are taking M-ESLON.

Testing and check-ups: Your healthcare professional will regularly monitor your health. This includes monitoring for signs of:

- misuse and abuse;
- sleep apnea (a sleep disorder which causes pauses in breathing or shallow breathing while sleeping);
- respiratory depression and sedation (e.g., slow, shallow, or weak breathing).

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

Serious drug interactions

Serious drug interactions with M-ESLON include:

- benzodiazepines used to help you sleep or to reduce anxiety
- central nervous system (CNS) depressants used to slow down the nervous system. These can include:
 - other opioids used to relieve pain (e.g., methadone, pentazocine, nalbuphine, butorphanol, buprenorphine);
 - hypnotics used to help with sleeping;
 - antidepressants used for depression and mood disorders (e.g., fluoxetine, citalopram, venlafaxine; tricyclic antidepressants such as amitriptyline, imipramine, maprotiline, paroxetine; serotonin norepinephrine re-uptake inhibitors [SNRIs]; and selective serotonin re-uptake inhibitors [SSRIs] such as St. John's Wort);
 - anxiolytics, tranquilizers, and phenothiazines used to treat mental or emotional disorders;
 - muscle relaxants used to treat muscle spasms and back pain (e.g., baclofen);
 - general anesthetics used during surgery;
 - antipsychotics and neuroleptics used to treat mental health disorders (e.g., chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone, and risperidone);
 - antihistamines used to treat allergies;
 - antiemetics used to prevent nausea or vomiting (e.g., domperidone, granisetron, dolasetron, and ondansetron);
 - sedatives which may enhance the drowsiness;
 - pregabalin, used to treat nerve pain;
 - gabapentin, used to prevent and control seizures in the treatment of epilepsy;
 - beta blockers used to lower blood pressure;
 - alcohol.; This includes prescription and non-prescription medications that contain alcohol. Do not drink alcohol while you are taking M-ESLON. It can lead to drowsiness, unusually slow or weak breathing, serious side effects, or a fatal overdose.
- monoamine oxidase inhibitors (MAOIs) used to treat depression. Do not take M-ESLON with

MAOIs or if you have taken MAOIs in the last 14 days.

The following may also interact with M-ESLON:

- rifampicin, used to treat bacterial infections
- anticoagulants, used to thin the blood and prevent blood clots (e.g., warfarin and other coumarin)
- drugs used to treat migraines (e.g., triptans)
- anti-retroviral, anti-fungal and antibiotic drugs

How to take M-ESLON:

- M-ESLON must be taken orally, by mouth. Do **NOT** administer the M-ESLON capsules via any other routes as this can cause serious harm, including death.
- Take M-ESLON every 12 hours as prescribed, with 120 mL to 180 mL of water.
- **Swallow whole. Do not break, crush, chew or dissolve the capsule. This can be dangerous and can lead to death or seriously harm you. The capsules may be opened and the contents sprinkled onto soft food or mixed in liquids or taken by specific feeding tubes if necessary.**
- M-ESLON should not be used longer than necessary.

Usual dose:

Your dose is tailored/personalized just for you. Take it exactly as your healthcare professional has told you to. Do not increase or decrease your dose without consulting your healthcare professional. Taking higher doses can lead to more side effects and a greater chance of overdose.

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

If your pain increases or you develop any side effect as a result of taking M-ESLON, tell your healthcare professional immediately.

Stopping your Medication:

If you have been taking M-ESLON for more than a few days, you should not stop taking it all of a sudden. Your healthcare professional 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 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 healthcare professional each time you need more M-ESLON. Therefore, it is important that you contact your healthcare professional before your current supply runs out.

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

Overdose:

If you think you, or a person you are caring for, have taken too much M-ESLON, contact a healthcare professional, hospital emergency department, regional Poison Control Centre or Health Canada's tollfree number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Signs of overdose with M-ESLON may include:

- unusually slow or weak breathing
- dizziness
- confusion
- extreme drowsiness
- shrinking of the pupils
- lack of muscle shape and tone
- cold and clammy skin
- slow heart rate
- low blood pressure
- muscle weakness, cramping, or aching
- toxic leukoencephalopathy (a brain disorder affecting the brain's white matter)

Missed dose:

It is important that you do not miss any doses. If you miss:

- **one dose:** skip the missed dose and take your next dose as scheduled. Do not take two doses at once to make up for a missed dose.
- **several doses in a row:** talk to your healthcare professional before restarting your medication.

Possible side effects from using M-ESLON:

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

Side effects with M-ESLON may include:

- Drowsiness
- Insomnia
- Dizziness
- Fainting
- Nausea, vomiting, or a poor appetite
- Dry mouth
- Headache
- Problems with vision
- Weakness, uncoordinated muscle movement
- Itching
- Rash
- Sweating
- Constipation. Talk with your healthcare professional about ways to prevent constipation when you start using M-ESLON.
- Low sex drive, impotence (erectile dysfunction), infertility
- Severe pain in your abdomen that comes and goes [e.g., spasm of the sphincter of Oddi (muscle that controls the flow of bile and pancreatic fluid into the intestine)]

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Uncommon			
Hallucinations: seeing or hearing things that are not there.			✓
Seizures (fits): uncontrollable shaking with or without loss of consciousness.			✓
Rare			
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.			✓
Respiratory Depression: slow, shallow or weak breathing.			✓
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing.			✓
Bowel Blockage (impaction): abdominal pain, severe constipation, nausea.			✓
Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and		✓	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
clammy skin, body aches, loss of appetite, sweating.			
Fast, Slow or Irregular Heartbeat: heart palpitations.		✓	
Hypotension (low blood pressure): dizziness, fainting, light-headedness.	✓		
Serotonin toxicity (also known as serotonin syndrome): a reaction which may cause feelings of agitation or restlessness, flushing, muscle twitching, involuntary eye movements, heavy sweating, high body temperature (>38°C), or rigid muscles.			✓
Unknown			
Disorder of the adrenal gland: nausea, vomiting, anorexia, fatigue, weakness, dizziness, or low blood pressure.			✓
Sleep apnea: stop breathing for short periods during your normal nightly sleep.		✓	
Severe Cutaneous Adverse Reactions (SCAR) (severe skin reactions that may also affect other organs): skin peeling, scaling, or blistering (with or without pus) which may also affect your eyes, mouth, nose or genitals, itching, severe rash, bumps under the skin, skin pain, skin color changes (redness, yellowing, purplish). Swelling and redness of eyes or face. Flu-like feeling, fever, chills, body aches, swollen glands, cough. Shortness of breath, chest pain or discomfort.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell 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 (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:

- Store capsules at room temperature (15°C - 30°C).
- Keep unused or expired M-ESLON in a secure place to prevent theft, misuse or accidental exposure.
- 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 the Patient Medication Information by visiting the Health Canada Drug Product Database website (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website at www.ethypharm.com/ethypharm-canada/; or by calling 1-800-347-1675.

This leaflet was prepared by Ethypharm Inc.

Date of Authorization: 2026-09-17