PRESCRIBING INFORMATION

INCLUDING PATIENT MEDICATION INFORMATION

^{N}M-EDIAT®

Morphine Sulfate Immediate Release Capsules
5 mg, 10 mg, 20 mg and 30 mg

Opioid Analgesic

NOT A PRODUCT MONOGRAPH

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Immediate Release Capsules / 5 mg, 10 mg, 20 mg and 30 mg	Hypromellose, maize starch, sucrose, talc; capsule shell contains gelatin and colouring agent (5 mg capsule – indigo carmine; 10 mg capsule – azorubine; 20 mg capsule – allura red AC (FD&C Red No. 40), brilliant blue FCF (FD&C Blue No. 1); 30 mg capsule – indigo carmine, quinoline yellow WS (D&C Yellow No. 10)).

INDICATIONS AND CLINICAL USE

Adults
M-EDIAT (morphine sulfate immediate release capsules) is indicated for the symptomatic relief of severe pain.

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 and titrated slowly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or other drug therapy (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics**).

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

CONTRAINDICATIONS

- Patients who are hypersensitive to the active substance (morphine) or other opioid analgesics or to any ingredient in the formulation. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Prescribing Information.
- 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 mild pain that can be managed with other pain medications.
- Patients with acute or severe bronchial asthma, chronic obstructive airway, and status asthmaticus.
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood, and cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe central nervous system (CNS) depression, increased cerebrospinal or intracranial pressure, brain tumour and/or head injury.
- Patients with cardiac arrhythmias.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).
- Women who are breast-feeding, pregnant, or during labour and delivery (see **SERIOUS WARNINGS and PRECAUTIONS**, and **WARNINGS and PRECAUTIONS**).

WARNINGS AND PRECAUTIONS

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 risks of overdose and death with immediate release opioid formulations, M-EDIAT (morphine sulfate immediate release capsules) should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide appropriate management of pain (see DOSAGE AND ADMINISTRATION).

Addiction, Abuse, and Misuse

M-EDIAT 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-EDIAT, and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS). M-EDIAT 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-EDIAT. 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-EDIAT or following a dose increase.

M-EDIAT must be swallowed whole or the capsules may be opened and the contents sprinkled on food. Cutting, breaking, crushing, chewing, or dissolving M-EDIAT can lead to dangerous adverse events including death (see WARNINGS AND PRECAUTIONS). Further, instruct patients of the hazards related to taking opioids including fatal overdose.

Accidental Exposure

Accidental ingestion of even one dose of M-EDIAT, especially by children, can result in a fatal overdose of morphine (see DOSAGE AND ADMINISTRATION, Disposal, for instructions on proper disposal).

Neonatal Opioid Withdrawal Syndrome

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

Interaction with Alcohol

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

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

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

- **Reserve concomitant prescribing of M-EDIAT 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.**

General

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

M-EDIAT 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.

Patients should be cautioned not to consume alcohol while taking M-EDIAT, as it may increase the chance of experiencing dangerous side effects, including death.

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

Abuse and Misuse

Like all opioids, M-EDIAT is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, M-EDIAT 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-EDIAT, should be used with particular care in patients with a history of alcohol and illicit/prescription drug abuse. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.
M-EDIAT is intended for oral use only. The capsules should be swallowed whole, or the capsules may be opened and the contents sprinkled on food, and not chewed or crushed. Abuse of oral dosage forms can be expected to result in serious adverse events, including death.

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.

Cardiovascular

Morphine administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of such drugs as phenothiazines 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-EDIAT.

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

Dependence/Tolerance
As with other opioids, tolerance and physical dependence tend to develop upon repeated administration of morphine and there is potential for abuse of the drug and for development of psychological dependence.

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.

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

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

Use in Drug and Alcohol Addiction
M-EDIAT is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission is for the management of pain requiring opioid analgesia. Patients with a history of addiction to drugs or alcohol may be at higher risk of becoming addicted to M-EDIAT; extreme caution and awareness is warranted to mitigate the risk.

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

Gastrointestinal Effects
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 **CONTRAINDICATIONS**).

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-EDIAT is contraindicated in pregnant women (see **CONTRAINDICATIONS**).

Neurologic
Interactions with CNS Depressants (including benzodiazepines and alcohol): Morphine should be used only with caution and in a reduced dosage during concomitant administration of other opioid analgesics, general anesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, benzodiazepines, centrally-active anti-emetics and other CNS depressants. Respiratory depression, hypotension and profound sedation, coma, or death may result.

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

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

overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see **DRUG INTERACTIONS**).

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

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

Serotonin Syndrome: M-EDIAT 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-EDIAT should not be used in combination with MAO inhibitors or serotonin- precursors (such as L-tryptophan, oxitriptan) and should be used with caution in combination with other serotonergic drugs (triptans, certain tricyclic antidepressants, lithium, tramadol, St. John's Wort) due to the risk of serotonergic syndrome (see **DRUG INTERACTIONS**).

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

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

Peri-Operative Considerations

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

In the case of planned chordotomy or other pain-relieving operations, patients should not be treated with M-EDIAT for at least 24 hours before the operation and M-EDIAT should not be used in the immediate post-operative period.

Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. Thereafter, if M-EDIAT is to be continued after the patient recovers from the post-operative period, a new dosage should be administered in accordance with the changed need for pain relief. The risk of withdrawal in opioid-tolerant patients should be addressed as clinically indicated.

The administration of analgesics in the peri-operative period should be managed by healthcare providers with adequate training and experience (e.g., by an anesthesiologist).

Morphine and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common post-operative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in post-operative patients receiving opioids. Standard supportive therapy should be implemented.

M-EDIAT should not be used in the early post-operative period (12 to 24 hours post-surgery) unless the patient is ambulatory and gastrointestinal function is normal.

Psychomotor Impairment

M-EDIAT 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.

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. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Morphine should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia (see **CONTRAINDICATIONS**).

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of M-EDIAT, 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-EDIAT and following dose increases.

Life-threatening respiratory depression is more likely to occur in the elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

To reduce the risk of respiratory depression, proper dosing and titration of M-EDIAT are essential. Overestimating the M-EDIAT dose when converting patients from another opioid product can result in a fatal overdose with the first dose. In these patients, the use of non-opioid analgesics should be considered, if feasible (see **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Special Risk Groups**, and **DOSAGE AND ADMINISTRATION**).

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-EDIAT, as in these patients,

even usual therapeutic doses of M-EDIAT 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-EDIAT is contraindicated in patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see **CONTRAINDICATIONS**).

Patient Counselling Information

The patient information leaflet should be provided when M-EDIAT capsules are dispensed to the patient.

Patients receiving M-EDIAT should be given the following instructions by the physician:

1. Patients should be informed that accidental ingestion or use by individuals (including children) other than the patient for whom it was originally prescribed, may lead to severe, even fatal, consequences.

2. Patients should be advised that M-EDIAT contains morphine, an opioid pain medicine.

3. Patients should be advised that M-EDIAT should only be taken as directed. The dose of M-EDIAT should not be adjusted without consulting with a physician.

4. M-EDIAT must be swallowed whole or the capsules may be opened and the contents sprinkled on food. Do not cut, break, chew, dissolve or crush due to the risk of fatal morphine overdose.

5. Patients should be advised to report episodes of pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.

6. Patients should not combine M-EDIAT with alcohol or other central nervous system depressants (sleep aids, tranquilizers) because dangerous additive effects may occur resulting in serious injury or death.

7. Patients should be advised to consult their physician or pharmacist if other medications are being used or will be used with M-EDIAT.

8. Patients should be advised that if they have been receiving treatment with M-EDIAT and cessation of therapy is indicated, it may be appropriate to taper the M-EDIAT dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms.

9. Patients should be advised of the most common adverse reactions that may occur while taking M-EDIAT: constipation, dizziness, hyperhidrosis, nausea, sedation and vomiting.

10. Patients should be advised that M-EDIAT may cause drowsiness, dizziness, or light-headedness and may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery). Patients started on M-

EDIAT or patients whose dose has been adjusted should be advised not to drive a car or operate machinery unless they are tolerant to the effects of M-EDIAT.

11. Patients should be informed that M-EDIAT could cause seizures if they are at risk for seizure or have epilepsy. Such patients should be advised to use M-EDIAT with care. Patients should be advised to stop taking M-EDIAT if they have a seizure while taking M-EDIAT and seek medical help immediately.

12. Patients should be advised that M-EDIAT is a potential drug of abuse. They should protect it from theft or misuse.

13. Patients should be advised that M-EDIAT should never be given to anyone other than the individual for whom it was prescribed.

14. Women of childbearing potential who become or are planning to become pregnant should be advised to consult a physician prior to initiating or continuing therapy with M-EDIAT. Women who are breast-feeding or pregnant should not use M-EDIAT.

Sexual Function/Reproduction

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

Special Populations

Special Risk Groups: Morphine should be administered with caution to patients with a history of alcohol, seizures, and drug abuse and in a reduced dosage to elderly or debilitated patients, patients with reduced hepatic function or severe renal dysfunction, and in patients with severely impaired pulmonary function, Addison's disease, biliary tract disorders, hypotension with hypovolemia, hypothyroidism, myxedema, toxic psychosis, prostatic hypertrophy or urethral stricture.

Pregnant Women: Studies in humans have not been conducted. M-EDIAT crosses the placental barrier and is contraindicated in pregnant women (see **CONTRAINDICATIONS**).

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal Opioid Withdrawal Syndrome (NOWS), unlike opioid withdrawal syndrome in adults, can be life-threatening (see **WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome (NOWS), ADVERSE REACTIONS, Post-marketing Experience**).

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.

Labour/Delivery and Nursing Women: Since opioids can cross the placental barrier and are excreted in breast milk, M-EDIAT is contraindicated in nursing women during labour and delivery. Life-threatening respiratory depression can occur in the infant if opioids are administered to the mother. Naloxone, a drug that counters the effects of opiates, should be readily available if M-EDIAT is used in this population.

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

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 and titrated slowly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Geriatrics**).

Patients over the age of 50 years of age tend to require much lower doses of morphine than in the younger age group. Morphine should be administered with caution and in a reduced dosage to elderly or debilitated patients. The initial dose should be one half the usual recommended dose.

Patients with Hepatic Impairment: Dosage reduction is recommended in severe hepatic impairment due to the risk of toxicity (see **ACTION AND CLINICAL PHARMACOLOGY Special Populations and Conditions**, **Hepatic Impairment).**

Patients with Renal Impairment: Dosage reduction is recommended in severe renal impairment due to the risk of toxicity (see **ACTION AND CLINICAL PHARMACOLOGY Special Populations and Conditions**, **Renal Impairment).**

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse effects of M-EDIAT (morphine sulfate immediate release capsules) are similar to those of other opioid analgesics, and represent an extension of pharmacological effects of the drug class. The major hazards associated with opioids include respiratory and central nervous system depression and, to a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest.

The most frequently observed side effects of M-EDIAT are constipation, dizziness, hyperhidrosis, nausea, sedation, and vomiting.

Sedation: Sedation is a common side effect of opioid analgesics, especially in opioid naïve individuals. Sedation may also occur partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Most patients develop tolerance to the sedative effects of opioids within three to five days and, if the sedation is not severe, will not require any

treatment except reassurance. If excessive sedation persists beyond a few days, the dose of the opioid should be reduced and alternate causes investigated. Some of these are: concurrent CNS depressant medication, hepatic or renal dysfunction, brain metastases, hypercalcemia and respiratory failure. If it is necessary to reduce the dose, it can be carefully increased again after three or four days if it is obvious that the pain is not being well controlled. Dizziness and unsteadiness may be caused by postural hypotension particularly in elderly or debilitated patients, and may be alleviated if the patient lies down. Because of the slower clearance in patients over 50 years of age, an appropriate dose in this age group may be as low as half or less the usual dose in the younger age group.

Nausea and Vomiting: Nausea is a common side effect on initiation of therapy with opioid analgesics and is thought to occur by activation of the chemoreceptor trigger zone, stimulation of the vestibular apparatus and through delayed gastric emptying. The prevalence of nausea declines following continued treatment with opioid analgesics. When instituting therapy with an opioid for chronic pain, the routine prescription of an antiemetic should be considered. In the cancer patient, investigation of nausea should include such causes as constipation, bowel obstruction, uremia, hypercalcemia, hepatomegaly, tumor invasion of celiac plexus, and concurrent use of drugs with emetogenic properties. Persistent nausea which does not respond to dosage reduction may be caused by opioid-induced gastric stasis and may be accompanied by other symptoms including anorexia, early satiety, vomiting and abdominal fullness. These symptoms respond to chronic treatment with gastrointestinal prokinetic agents.

Constipation: Practically all patients become constipated while taking opioids on a persistent basis. In some patients, particularly the elderly or bedridden, fecal impaction may result. 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. Stimulant laxatives, stool softeners, and other appropriate measures should be used as required. As fecal impaction may present as overflow diarrhea, the presence of constipation should be excluded in patients on opioid therapy prior to initiating treatment for diarrhea.

The following adverse effects occur with M-EDIAT and opioid analgesics. The reactions are categorized by body system and frequency according to the following definitions: Very common (≥ 1/10); (Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥ 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: asthenia, fatigue, malaise, pruritus, weakness, sedation
Uncommon: peripheral edema
Not known: drug tolerance, drug withdrawal syndrome, drug withdrawal syndrome neonatal

Cardiac Disorders:
Rare: faintness, palpitations
Unknown: supraventricular tachycardia, bradycardia

Ear and Labyrinth Disorders:
Uncommon: vertigo

Endocrine Disorders:
Unknown: 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)

Eye Disorders:
Uncommon: visual disturbance
Not known: miosis

Gastrointestinal Disorders:
Very common: constipation, nausea
Common: abdominal pain, anorexia, dry mouth, vomiting
Uncommon: dyspepsia, ileus, taste perversion

Hepato-Biliary Disorders:
Uncommon: increased hepatic enzyme
Not known: biliary pain, exacerbation of pancreatitis

Immune System Disorders:
Uncommon: hypersensitivity
Not known: anaphylactic reaction, anaphylactoid reaction

Nervous System Disorders:
Common: dizziness, headache, involuntary muscle contractions, somnolence
Uncommon: convulsions, hypertonia, paraesthesia, syncope, myoclonus
Not known: hyperalgesia

Psychiatric Disorders:
Common: confusion, insomnia
Uncommon: agitation, euphoria, 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: amenorrhoea, decreased libido, erectile dysfunction

Skin and Subcutaneous Tissue Disorders:
Common: hyperhidrosis, rash
Uncommon: urticaria

Vascular Disorders:
Uncommon: facial flushing, hypotension
Not known: hypertension

Post-Marketing Experience
Androgen Deficiency: Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency 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 INTERACTIONS

Overview

Interaction with Benzodiazepines and Other CNS Depressants: Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants (e.g. other opioids, sedatives/hypnotics, antidepressants, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, phenothiazines, neuroleptics, antihistamines, antiemetics, and alcohol) and beta-blockers, increases the risk of respiratory depression, profound sedation, coma, and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see **WARNINGS AND PRECAUTIONS, Neurologic, Interactions with CNS Depressants (including benzodiazepines and alcohol) and Psychomotor Impairment**). M-EDIAT (morphine sulfate immediate release capsules) should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

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

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

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-EDIAT is contraindicated in patients receiving MAO Inhibitors or who have taken them within the previous 14 days (see **CONTRAINDICATIONS**).

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

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions
The concomitant use of alcohol should be avoided (see **WARNINGS AND PRECAUTIONS, General**).

DOSAGE AND ADMINISTRATION

For acute pain, it is recommended that M-EDIAT be used for a maximum of 7 days at the lowest dose that provides adequate pain relief.

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 of M-EDIAT (morphine sulfate immediate release capsules) not be exceeded. Each patient should be assessed for their risk prior to prescribing M-EDIAT, 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-EDIAT (see DOSAGE AND ADMINISTRATION - Adjustment or Reduction of Dosage).

M-EDIAT should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics).

M-EDIAT must be swallowed whole or the capsules may be opened and the contents sprinkled on food. Cutting, breaking, crushing, chewing, or dissolving M-EDIAT can lead to dangerous adverse events including death (see WARNINGS AND PRECAUTIONS).

Dosing Considerations

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 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-EDIAT (morphine sulfate immediate release capsules) should be used with caution within 12 hours pre-operatively and within the first 12-24 hours post-operatively (see **WARNINGS AND PRECAUTIONS, Peri-operative Considerations**).

M-EDIAT is not indicated for rectal administration.

M-EDIAT capsules may be taken with a glass of water.

Recommended Dose and Dosage Adjustment

Adults: 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 10 mg orally, every 4 hours as needed for acute pain and every 4 hours around-the-clock for chronic pain, or as directed by a physician.

M-EDIAT capsules may be opened, and the microgranules given mixed with soft food or liquids.

Patients Not Receiving Opioids at the Time of Initiation of Morphine Treatment: The usual initial adult dose of M-EDIAT for patients who have not previously received opioid analgesics is 5 mg or 10 mg, orally, every 4 hours.

Patients Currently Receiving Opioids: For patients who are receiving an alternate opioid, the "oral morphine sulfate equivalent" of the analgesic presently being used, should be determined. Having determined the total daily dosage of the present analgesic, Table 1 can be used to calculate the approximate daily oral morphine sulfate dosage that should provide equivalent analgesia. It is usually appropriate to treat a patient with only one opioid at a time. Further dose reductions should be considered due to incomplete cross-tolerance between opioids.

Use with Non-Opioid Medications: If a non-opioid analgesic is being provided, it may be continued. If the non-opioid is discontinued, consideration should be given to increasing the opioid dose to compensate for the non-opioid analgesic. M-EDIAT can be safely used concomitantly with usual doses of other non-opioid analgesics.

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
Codeine	0.15	6.67	600 mg
Hydromorphone	5	0.2	18 mg
Oxycodone	1.5	0.667	60 mg
Tapentadol	0.3-0.4	2.5-3.33	300 mg
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

Patients over the age of 50: Patients over 50 years of age tend to require much lower doses of morphine than in the younger age group. An appropriate dose in this age group may be as low as half or less than the usual dose in the younger age group.

Debilitated patients: In debilitated patients and those with impaired respiratory function or

significantly decreased hepatic and/or renal function, the initial dose should be one half the usual recommended dose.

Geriatrics: 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. M-EDIAT should be initiated at the low end of the dosing range and slowly titrated (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

Dose Titration: Dose titration is the key to success with opioid analgesic therapy. **Proper optimization of doses scaled to the relief of the individual's pain should aim at 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.

Adjustment or Reduction of Dosage: Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including M-EDIAT. 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, 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 may become feasible due to a change in the patient's condition or improved mental state. Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal for the drug, these symptoms are usually mild (see **WARNINGS AND PRECAUTIONS**). Tapering should be individualised 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 analgesics may only be partially effective in relieving dysesthetic pain, post-herpetic neuralgia, stabbing pains, activity-related pain, and some forms of headache. This is not to say that patients with advanced cancer suffering from some of these forms of pain should not be given an adequate trial of opiate analgesics, but it may be necessary to refer such patients at an early time for other forms of pain therapy.

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.

Disposal

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

M-EDIAT should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired M-EDIAT should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets. M-EDIAT 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.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Symptoms: Serious overdosage with morphine may be characterized by respiratory depression (respiratory rate and/or tidal volume; Cheyne-Stokes respiration; cyanosis), dizziness, confusion, extreme somnolence progressing to stupor or coma, pneumonia aspiration, miosis, rhabdomyolysis progressing to renal failure, hypotonia, cold and clammy skin, and sometimes bradycardia and hypotension. 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. Severe overdose may result in apnea, circulatory collapse, cardiac arrest and death.

Treatment: Primary attention should be given to the establishment of adequate respiratory exchange through the provision of a patent airway and controlled or assisted ventilation. The opioid antagonist naloxone hydrochloride is a specific antidote against respiratory depression due to overdosage or as a result of unusual sensitivity to morphine. An appropriate dose should therefore be administered, preferably by the intravenous route. The usual initial intravenous 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 may exceed that of the antagonist, the patient should be under continued surveillance and doses of the antagonist should be repeated as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated.

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.

ACTION AND CLINICAL PHARMACOLOGY

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 CO_2, 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.

Pharmacodynamics

Morphine is an opioid agonist. Adequate doses will relieve even the most severe pain. Clinically however, dosage limitations are imposed by the adverse effects, primarily respiratory depression, nausea and vomiting, which can result from high doses.

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 man, 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 CO_2 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 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.

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-EDIAT must be individualized (see **DOSAGE AND ADMINISTRATION**) because the effective analgesic dose for some patients will be too high to be tolerated by other patients.

Pharmacokinetics

Absorption: Morphine is readily absorbed when given orally, rectally or by subcutaneous or intramuscular injection.

Distribution: Once absorbed, morphine is distributed to skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen, and brain. The volume of distribution of morphine is approximately 3 to 4 L/kg. Morphine is 30 to 35% reversibly bound to plasma proteins. Although the primary site of action of morphine is in the CNS, only small quantities pass the blood-brain barrier. Morphine also crosses the placental membranes (see **WARNINGS AND PRECAUTIONS**) and has been found in breast milk.

Metabolism: Due to first-pass metabolism in the liver, the effect of an oral dose is less than after parenteral administration. With repeated regular dosing, oral morphine is about 1/3 as potent as when given by intramuscular injection. Major pathways of morphine metabolism

include glucuronidation in the liver to produce metabolites including morphine-3-glucuronide, M3G (about 50%) and morphine-6-glucuronide, M6G (about 5 to 15%) and sulfation in the liver to produce morphine-3etheral sulfate. A small fraction (less than 5%) of morphine is demethylated. M3G has no significant contribution to the analgesic activity. Although M6G does not readily cross the blood-brain barrier, it has been shown to have opioid agonist and analgesic activity in humans.

Excretion: Morphine is primarily excreted in the urine as morphine-3-glucuronide. Formation of glucuronidated metabolites is less following rectal administration compared to oral administration. About 7% to 10% of a dose of morphine is excreted in the feces via the bile.

Special Populations and Conditions

Pediatrics: Individuals under 18 years of age should not take M-EDIAT capsules.

Geriatrics: 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, and of concomitant disease or other drug therapy.

Hepatic Impairment: The pharmacokinetics of morphine was found to be significantly altered in individuals with alcoholic cirrhosis. The clearance was found to decrease with a corresponding increase in half-life. M3G and M6G to morphine plasma AUC ratios also decreased in these patients, indicating a decrease in metabolic activity. Adequate studies of the pharmacokinetics of morphine in patients with severe hepatic impairment have not been conducted.

Renal Impairment: The pharmacokinetics of morphine are altered in patients with renal failure. The AUC is increased and clearance is decreased. Metabolites, M3G and M6G, accumulate several-fold in patients with renal failure compared to healthy subjects. Adequate studies of the pharmacokinetics of morphine in patients with severe renal impairment have not been conducted.

STORAGE AND STABILITY

Store at room temperature (15°-30°C). Keep in a dry place.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms:

5 mg: Light blue transparent cap and body capsule with "5 mg" printed in white, containing off-white to yellowish spherical microgranules.

10 mg: Standard red transparent cap and body capsule with "10 mg" printed in white, containing off-white to yellowish spherical microgranules.

20 mg: Standard blue transparent cap and body capsule with "20 mg" printed in white, containing off-white to yellowish spherical microgranules.

30 mg: Dark green transparent cap and body capsule with "30 mg" printed in white, containing off-white to yellowish spherical microgranules.

Composition:

Each capsule of M-EDIAT (morphine sulfate immediate release capsules) contains 5 mg, 10 mg, 20 mg or 30 mg of morphine sulfate.

M-EDIAT (morphine sulfate immediate release capsules) contains the following nonmedicinal ingredients (all strengths): hypromellose, maize starch, sucrose, talc; capsule shell contains gelatin and colouring agent (5 mg capsule – indigo carmine; 10 mg capsule – azorubine; 20 mg capsule – allura red AC (FD&C Red No. 40), brilliant blue FCF (FD&C Blue No. 1); 30 mg capsule – indigo carmine, quinoline yellow WS (D&C Yellow No. 10)). Tartrazine-free.

Packaging:

M-EDIAT is available in blister packs of 20 and bottles of 50 hard gelatin capsules.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

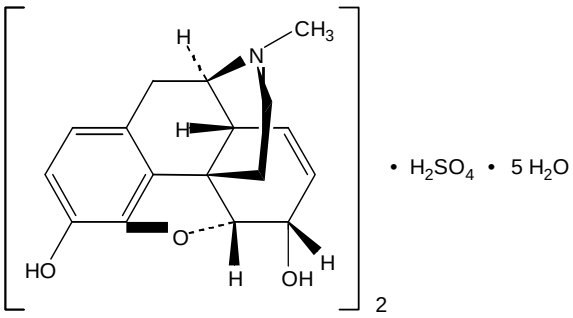
Proper name: morphine sulfate

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

Molecular formula: $(C_{17}H_{19}NO_3) \cdot H_2SO_4 \cdot 5H_2O$

Molecular mass: 758.8 g/mol (pentahydrate)
668.8 g/mol (anhydrous)

Structural formula:



Physicochemical Properties: Morphine is a phenanthrene alkaloid obtained from opium.

Physical Description: White, odourless crystalline powder or needlelike crystals.

Solubility: Soluble 1:21 in water and 1:1000 in ethanol. It is practically insoluble in ether or chloroform.

Melting Point: Approximately 250°C (decomposes when anhydrous).

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

[N]M-EDIAT®
Morphine Sulfate Immediate Release Capsules

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

Serious Warnings and Precautions

- **Even if you take M-EDIAT as prescribed you are at a risk for opioid addiction, abuse and misuse. This can lead to overdose and death.**
- **When you take M-EDIAT it 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.**
- **You may get life-threatening breathing problems while taking M-EDIAT. This is less likely to happen if you take it as prescribed by your doctor. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.**
- **You should never give anyone your M-EDIAT. They could die from taking it. If a person has not been prescribed M-EDIAT, taking even one dose can cause a fatal overdose. This is especially true for children.**
- **If you took M-EDIAT 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-EDIAT with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.**

What is M-EDIAT used for?

M-EDIAT is a medicine used to manage your pain.

How does M-EDIAT work?

M-EDIAT contains morphine which is a pain medication belonging to the class of drugs known as opioids which includes codeine, fentanyl, hydromorphone and oxycodone. It relieves pain by acting on specific nerve cells of the spinal cord and brain.

What are the ingredients in M-EDIAT?

Medicinal ingredient: Morphine sulfate
Non-medicinal ingredients: Hypromellose, maize starch, sucrose, talc; capsule shell contains gelatin and colouring agent (5 mg capsule – indigo carmine; 10 mg capsule – azorubine; 20 mg capsule – allura red AC (FD&C Red No. 40), brilliant blue FCF (FD&C Blue No. 1); 30 mg capsule – indigo carmine, quinoline yellow WS (D&C Yellow No. 10)).

M-EDIAT comes in the following dosage forms:

M-EDIAT capsules are available in 4 strengths:
5 mg (light blue capsule with "5 mg" printed in white)
10 mg (red capsule with "10 mg" printed in white)
20 mg (blue capsule with "20 mg" printed in white)
30 mg (dark green capsule with "30 mg" printed in white)

Do not use M-EDIAT if:

- your doctor did not prescribe it for you
- you are allergic to morphine, or any of the other ingredients in M-EDIAT
- you can control your pain by the occasional use of other pain medications. This includes those available without a prescription
- you have severe asthma, trouble breathing, or other breathing problems
- you have any heart problems
- you have bowel blockage or narrowing of the stomach or intestines
- you have severe pain in your abdomen
- you have a head injury
- you are at risk for seizures
- you have a brain tumor
- you suffer from alcoholism
- 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)
- you are going to have, or recently had, a planned surgery
- you are pregnant or planning to become pregnant or you are in labour
- you are breastfeeding

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

- have a history of illicit or prescription drug or alcohol abuse
- have severe kidney, liver or lung disease
- have heart disease

- have low blood pressure
- have past or current depression
- suffer from chronic or severe constipation
- have problems with your thyroid, adrenal or prostate gland
- have, or had in the past hallucinations or other severe mental problems
- suffer from migraines
- are planning to become pregnant

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

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

If you are pregnant and are taking M-EDIAT, 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 doctor will monitor and guide you on how to slowly stop taking M-EDIAT. 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-EDIAT. M-EDIAT can cause:
- drowsiness
- dizziness or
- lightheadedness

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

Disorder of the adrenal gland: You may develop a disorder of the adrenal gland called adrenal insufficiency. This means that your adrenal gland is not making enough of certain hormones. You may experience symptoms such as:
- nausea, vomiting
- feeling tired, weak or dizzy
- decreased appetite

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

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

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

Sexual Function/Reproduction: Long term use of 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.

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

The following may interact with M-EDIAT:

- Alcohol. This includes prescription and non-prescription medications that contain alcohol. **Do not** drink alcohol while you are taking M-EDIAT. It can lead to:
    - drowsiness
    - unusually slow or weak breathing
    - serious side effects or
    - a fatal overdose
- other sedative drugs which may enhance the drowsiness caused by M-EDIAT
- other opioid analgesics (drugs used to treat pain)
- general anesthetics (drugs used during surgery)
- benzodiazepines (drugs used to help you sleep or that help reduce anxiety)
- antidepressants (for depression and mood disorders). **Do not** take M-EDIAT with MAO inhibitors (MAOI) or if you have taken MAOI's in the last 14 days.
- drugs used to treat serious mental or emotional disorders (such as schizophrenia)
- anticonvulsants (used to treat seizures)
- antihistamines (drugs used to treat allergies)
- anti-emetics (drugs used for the prevention of vomiting)
- drugs used to treat muscle spasms and back pain
- some heart medications (such as beta blockers)
- anticoagulants (blood thinners)
- drugs used to treat migraines (e.g. triptans)
- St. John's Wort

How to take M-EDIAT:

Take M-EDIAT capsules:

- regularly, usually every 4 to 6 hours, as directed by your doctor.
- with a full glass of water

Swallow 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.

Usual Adult Starting Dose:

Your dose is tailored/personalized just for you. Be sure to follow your doctor's dosing instructions exactly. Do not increase or decrease your dose without consulting your doctor.

Your doctor will prescribe the lowest dose that works to control your pain. It is recommended that you only take M-EDIAT for up to 7 days. If you need to take M-EDIAT for longer, your doctor will determine the best dose for you to lower the risk of side effects and overdose. Higher doses can lead to more side effects and a greater chance of overdose.

Review your pain regularly with your doctor to determine if you still need M-EDIAT. Be sure to use M-EDIAT 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-EDIAT, tell your doctor immediately.

Stopping your Medication

If you have been taking M-EDIAT for more than a few days you should not stop taking it all of a sudden. Your doctor will monitor and guide you on how to slowly stop taking M-EDIAT. 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-EDIAT.

Refilling your Prescription for M-EDIAT:
A new written prescription is required from your doctor each time you need more M-EDIAT. Therefore, it is important that you contact your doctor before your current supply runs out.

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

Overdose:

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

Signs of overdose may include:

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

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

What are possible side effects from using M-EDIAT?

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

Side effects may include:

- Drowsiness
- Insomnia
- Dizziness
- Fainting
- Nausea, vomiting, or a poor appetite
- Dry mouth
- Headache
- Problems with vision
- Weakness, uncoordinated muscle movement
- Itching
- Sweating
- Constipation
- Low sex drive, impotence (erectile dysfunction), infertility

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

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

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

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

3 ways to report:

- Online at MedEffect: https://www.canada.ca/en/health-canada/services/drugs-healthproducts/medeffect-canada.html
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html).

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

Storage:

- Store capsules at room temperature (15˚ - 30˚C). Keep in a dry place.
- **Keep unused or expired M-EDIAT in a secure place to prevent theft, misuse or accidental exposure.**
- **Keep M-EDIAT 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 accidently takes M-EDIAT, get emergency help right away.**

Disposal:

M-EDIAT 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-EDIAT:

- Talk to your healthcare professional
- Find the full prescribing information that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drugproduct-database.html); the manufacturer's website www.ethypharm.com/ethypharm-canada/ or by contacting Ethypharm Inc. at: 1-800-347-1675.

This leaflet was prepared by Ethypharm Inc.

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