PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[N]MS•IR®

Morphine Sulfate Immediate Release Tablets

Tablets, 5 mg, 10 mg, 20 mg and 30 mg, Oral

Purdue Pharma Standard

Opioid Analgesic

N02AA01

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M2H3S7

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RECENT MAJOR LABEL CHANGES

2 CONTRAINDICATIONS	06/2022
7 WARNINGS AND PRECAUTIONS, General, Addiction, Abuse and Misuse	06/2022
7 WARNINGS AND PRECAUTIONS, General, Addiction, Abuse and Misuse	07/2022
7 WARNINGS AND PRECAUTIONS, Neurologic, Opioid-induced hyperalgesia	06/2022
7 WARNINGS AND PRECAUTIONS, Respiratory, Acute Chest Syndrome (ACS) in Patients with Sickle Cell Disease (SCD)	06/2022
7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance and Hepatic/Biliary/Pancreatic	12/2023

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

MS•IR (morphine sulfate) tablets are indicated for the symptomatic relief of severe pain in adults.

1.1 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of MS•IR have not been studied in the pediatric population. Therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

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 10.3 Pharmacokinetics, Special Populations and Conditions, Geriatrics).

2 CONTRAINDICATIONS

MS•IR is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- 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 with hypoxia and/or hypercapnia, and cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe 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 3 SERIOUS WARNINGS AND PRECAUTIONS BOX; 7.1.1 Pregnant Women, and 7.1.2 Breast-feeding).

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 risks of overdose and death with immediate release opioid formulations, MS•IR (morphine sulfate) tablets 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 4.1 Dosing Considerations).

Addiction, Abuse, and Misuse
MS•IR 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 MS•IR, and all patients should be monitored regularly for the development of these behaviours or conditions (see 7 WARNINGS AND PRECAUTIONS,General, Addiction, Abuse and Misuse). MS•IR 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 MS•IR. 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 MS •IR or following a dose increase 7 WARNINGS AND PRECAUTIONS, Respiratory, Respiratory Depression).

MS•IR must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving MS•IR can lead to dangerous adverse events including death. Further, instruct patients of the hazards related to taking opioids including fatal overdose.

Accidental Exposure
Accidental ingestion of even one dose of MS•IR, 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 MS•IR during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see 7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential, Teratogenic Risk, Neonatal Opioid Withdrawal Syndrome (NOWS)).

Interaction with Alcohol
The co-ingestion of alcohol with MS•IR should be avoided as it may result in dangerous additive effects, causing serious injury or death (see 7 WARNINGS AND PRECAUTIONS, General and 9.2 Drug Interactions Overview, Interactions with Central Nervous Systems (CNS) Depressants (including benzodiazepines and alcohol)).

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 WARNINGS AND PRECAUTIONS, Neurologic, Interactions with CNS Depressants (including benzodiazepines and alcohol), and 9.2 Drug Interactions Overview, Interactions with Central Nervous Systems (CNS) Depressants (including benzodiazepines and alcohol)).

- Reserve concomitant prescribing of MS•IR 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

For acute pain, it is recommended that MS•IR 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 daily of MS•IR not be exceeded. Each patient should be assessed for their risk prior to prescribing MS•IR, 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 MS•IR (see 4.2 Recommended Dose and Dosage Adjustment).

MS•IR should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, or not tolerated or would be otherwise inadequate to provide appropriate management of pain.

MS•IR tablets must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving MS•IR can lead to dangerous adverse events including death (see 7 WARNINGS AND PRECAUTIONS, General, Addiction, Abuse and Misuse).

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.

MS•IR tablets should be used with caution within 12 hours pre-operatively and within the first 12-24 hours post-operatively (see 7 WARNINGS AND PRECAUTIONS, Peri-operative Considerations).

MS•IR is not indicated for rectal administration.

4.2 Recommended Dose and Dosage Adjustment

Pediatrics (<18 years of age): Health Canada has not authorized an indication for pediatric use (see 1.1 Pediatrics).

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 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.

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 as or less than the usual dose in 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 and slowly titrated, 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 WARNINGS AND PRECAUTIONS, Respiratory, Respiratory Depression and 10.3 Pharmacokinetics, Special Populations and Conditions, Geriatrics).

Patients Not Receiving Opioids at the Time of Initiation of MS•IR Treatment

The usual initial adult dose of MS•IR for patients who have not previously received opioid analgesics is 5 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 (below) 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.

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

Debilitated Patients

In debilitated patients and those with impaired respiratory function or significantly decreased hepatic and/or renal function, morphine should be administered with caution and at one half of the usual recommended dose (see 7.1 Special Populations and 10.3 Pharmacokinetics, Special Populations and Conditions).

Patients with Hepatic Impairment

Dosage reduction is recommended in severe hepatic impairment due to the risk of toxicity (see 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency).

Patients with Renal Impairment

Dosage reduction is recommended in severe renal impairment due to the risk of toxicity (see 10.3 Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency).

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. MS•IR can be safely used concomitantly with usual doses of other non-opioid analgesics.

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 MS•IR. 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 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance). Tapering should be individualized and carried out under medical supervision.

Patients 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 opioid analgesics, but it may be necessary to refer such patients at an early time for other forms of pain therapy.

4.4 Administration

MS•IR tablets may be taken with a glass of water.

4.5 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 centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

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, skeletal muscle flaccidity, hypotonia, cold and clammy skin, toxic leukoencephalopathy, delayed post-hypoxic leukoencephalopathy 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.

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	Immediate Release Tablets / 5, 10, 20 and 30 mg	Croscarmellose sodium, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400

Dosage Forms

MS•IR 5 mg are round, scored, white tablets imprinted with 5 on one side and PF on the other.

MS•IR 10 mg are round, scored, white tablets imprinted with 10 on one side and PF on the other.

MS•IR 20 mg are round, scored, white tablets imprinted with 20 on one side and PF on the other.

MS•IR 30 mg are round, scored, white tablets imprinted with 30 on one side and PF on the other.

Packaging
Tablets are supplied in opaque plastic bottles of 60 and Control Packs of 25 tablets.

7 WARNINGS AND PRECAUTIONS

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

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

MS•IR 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.

Patients should be cautioned not to consume alcohol while taking MS•IR, 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 sulfate may occur in particular in high doses. A morphine sulfate dose reduction or change in opioid may be required.

Addiction, Abuse and Misuse
Like all opioids, MS•IR is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, MS•IR 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 MS•IR, 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.

MS•IR is intended for oral use only. The tablets should be swallowed whole, 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 tablet excipients, especially talc, 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.

Patient Counselling Information
A patient information sheet should be provided to patients when MS•IR is dispensed to them.

Patients receiving MS•IR 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 MS•IR contains morphine, an opioid pain medicine.
3. Patients should be advised that MS•IR should only be taken as directed. The dose of MS•IR should not be adjusted without consulting with a physician. MS•IR must be swallowed whole (not cut, broken, chewed, dissolved or crushed) due to the risk of fatal morphine overdose.
4. 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.
5. Patients should not combine MS•IR with alcohol or other central nervous system depressants (sleep aids, tranquilizers) because dangerous additive effects may occur resulting in serious injury or death.
6. Patients should be advised to consult their physician or pharmacist if other medications are being used or will be used with MS•IR.
7. Patients should be advised that if they have been receiving treatment with MS•IR and cessation of therapy is indicated, it may be appropriate to taper the MS•IR dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms.
8. Patients should be informed that MS•IR could cause seizures if they are at risk for seizure or have epilepsy. Patients should be advised not to take MS•IR if they have seizure disorders Patients should be advised to stop taking MS•IR if they have a seizure while taking MS•IR and seek medical help immediately.
9. Patients should be advised of the most common adverse reactions that may occur while taking MS•IR: constipation, dizziness, hyperhidrosis, nausea, sedation and vomiting. If symptoms worsen, seek immediate medical attention.
10. Patients should be advised that MS•IR 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 MS•IR 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 MS•IR.
11. Patients should be advised that MS•IR is a potential drug of abuse. They should protect it from theft or misuse.
12. Patients should be advised that MS•IR should never be given to anyone other than the individual for whom it was prescribed.
13. 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 MS•IR. Women who are breast-feeding or pregnant should not use MS•IR.

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 MS•IR.

The use of MS•IR 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, physical and psychological dependence and opioid use disorder (OUD) tend to develop upon repeated administration of MS.IR.

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.

Abuse or intentional misuse of MS.IR 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).

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. 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 and 4.2 Recommended Dose and Dosage Adjustment).

Use in Drug and Alcohol Addiction
MS•IR 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 MS•IR; extreme caution and awareness is warranted to mitigate the risk.

Driving and Operating Machinery
MS•IR 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 CONTRAINDICATIONS) and is also contraindicated in patients with paralytic ileus, and appendicitis (see 2 CONTRAINDICATIONS and 8.1 Adverse Reaction Overview, Nausea and Vomiting, and 8.1 Adverse Reaction Overview ,Constipation).

Hepatic/Biliary/Pancreatic

Morphine can cause spasm of the sphincter of Oddi and an increase in intrabiliary pressure. 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 biliary tract disorders. Monitor patients for worsening symptoms related to biliary tract disease, including acute pancreatitis. Morphine is contraindicated in pancreatitis (see 2 CONTRAINDICATION).

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. 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. MS•IR should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects (see 9.2 Drug Interactions Overview, Interactions with Central Nervous Systems (CNS) Depressants (including benzodiazepines and alcohol)).

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 9.2 Drug Interactions Overview, Interactions with Central Nervous Systems (CNS) Depressants (including benzodiazepines and alcohol)). 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 MS•IR 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.

MS•IR should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see 2 CONTRAINDICATIONS; 8.1 Adverse Reaction Overview, Sedation, and 9.2 Drug Interactions Overview, Interactions with Central Nervous Systems (CNS) Depressants (including benzodiazepines and alcohol)).

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 MS•IR 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 toxicity / Serotonin syndrome

Serotonin toxicity also known as serotonin syndrome is a potentially life-threatening condition and has been reported with morphine, including MS•IR, particularly during combined use with other serotonergic drugs (see 9.4 Drug-Drug Interactions, Serotonergic Agents).

Serotonin toxicity is characterised by neuromuscular excitation, autonomic stimulation (e.g. tachycardia, flushing) and altered mental state (e.g. anxiety, agitation, hypomania). In accordance with the Hunter Criteria, serotonin toxicity diagnosis is likely when, in the presence of at least one serotonergic agent, one of the following is observed:

- Spontaneous clonus
- Inducible clonus or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature >38°C and ocular clonus or inducible clonus.

If concomitant treatment with MS•IR and other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see 9.4 Drug-Drug Interactions, Serotonergic Agents). If serotonin toxicity is suspected, discontinuation of the serotonergic agents should be considered.

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. Opioid analgesics, including 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
MS•IR 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 MS•IR for at least 24 hours before the operation and MS•IR should not be used in the immediate post-operative period.

Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. Thereafter, if MS•IR 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 has 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.

MS•IR 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.

Reproductive Health: Female and Male Potential

- **Fertility**

  Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (see 8.5 Post-Market Adverse Reactions).

- **Teratogenic Risk**

  - Neonatal Opioid Withdrawal Syndrome (NOWS)

    Prolonged maternal use of opioid 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 MS CONTIN 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. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. Morphine should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia (see 2 CONTRAINDICATIONS).

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of MS•IR, 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 MS•IR 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 MS•IR are essential. Overestimating the MS•IR 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 7.2 Special Populations, Special Risk Groups, 4.2 Recommended Dose and Dosage Adjustment).

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 MS•IR, as in these patients, even usual therapeutic doses of MS•IR 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 MS•IR 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 4.2 Recommended Dose and Dosage Adjustment).

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.

7.1 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 hypovolaemia, hypothyroidism, myxedema, toxic psychosis, prostatic hypertrophy or urethral stricture.

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 Pregnant Women

Studies in humans have not been conducted. MS•IR 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 (NOWS), unlike opioid withdrawal syndrome in adults, can be life-threatening (see 7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential, Teratogenic Risk, Neonatal Opioid Withdrawal Syndrome (NOWS), and 8.5 Post-Market Adverse Reactions).

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 Breast-feeding

Since opioids can cross the placental barrier and are excreted in breast milk, MS•IR 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 MS•IR is used in this population.

7.1.3 Pediatrics (<18 years of age)

The safety and efficacy of MS•IR have not been studied in the pediatric population. Therefore, Health Canada has not authorized an indication for pediatric use.

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 and titrated slowly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see 4.2 Recommended Dose and Dosage Adjustment and 10.3 Pharmacokinetics, 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.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Adverse effects of MS•IR 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 MS•IR 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.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates

observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful for identifying and approximating rates of adverse drug reactions in real-world use.

The following adverse effects occur with MS•IR 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 hyponatraemia 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, sphincter of Oddi dysfunction

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: allodynia, hyperalgesia, obstructive sleep apnea syndrome

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

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).

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.

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

There have also been post-marketing reports of Neonatal Opioid Withdrawal Syndrome (NOWS) in patients treated with hydromorphone (see 7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential, Teratogenic Risk, Neonatal Opioid Withdrawal Syndrome (NOWS)).

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 WARNINGS AND PRECAUTIONS, Neurologic, Interactions with CNS Depressants (including benzodiazepines and alcohol)).
  - Reserve concomitant prescribing of MS•IR 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. MS•IR 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. Monitor patients closely for signs of respiratory depression and sedation (see 7 WARNINGS AND PRECAUTIONS, Neurologic, Interactions with CNS Depressants (including benzodiazepines and alcohol) and Driving and Operating Machinery). MS•IR should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

9.3 Drug-Behavioural Interactions

The concomitant use of alcohol should be avoided (see 7 WARNINGS AND PRECAUTIONS, General and 7 WARNINGS AND PRECAUTIONS, Neurologic, Interactions with CNS Depressants (including benzodiazepines and alcohol)).

9.4 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.

Warfarin and Other Coumarin Anticoagulants: 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 (MAO) intensify the effects of opioid drugs which can cause anxiety, confusion and decreased respiration. MS•IR is contraindicated in patients receiving MAO Inhibitors or who have taken them within the previous 14 days (see 2 CONTRAINDICATIONS).

Serotonergic Agents: Coadministration of morphine sulfate with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI), may increase the risk of serotonin syndrome, a potentially life-threatening condition (see 7 WARNINGS AND PRECAUTIONS, Neurologic, Serotonin toxicity/Serotonin syndrome).

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 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.

10.2 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 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 (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, 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 MS•IR must be individualized (see 4 DOSAGE AND ADMINISTRATION) because the effective analgesic dose for some patients will be too high to be tolerated by other patients.

10.3 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 7.1.1 Pregnant Women, and 7.1.2 Breast-feeding) 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.

Elimination: 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 (<18 years of age): Individuals under 18 years of age should not take MS·IR.

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, and of concomitant disease or other drug therapy (see 7.1.4 Geriatrics).

Hepatic Insufficiency: 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 (see 4.2 Recommended Dose and Dosage Adjustment, Patients with Hepatic Impairment and 7.1 Special Populations).

Renal Insufficiency: 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 (see 4.2 Recommended Dose and Dosage Adjustment, Patients with Renal Impairment and 7.1 Special Populations).

11 STORAGE, STABILITY AND DISPOSAL

Store MS•IR tablets at room temperature (15º - 30° C). Keep in a dry place.

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

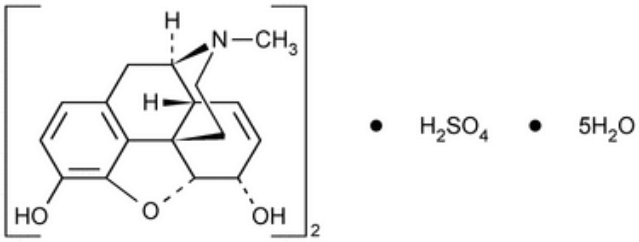
12 SPECIAL HANDLING INSTRUCTIONS

MS•IR 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. MS•IR should not be used in front of children, since they may copy these actions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Morphine Sulfate
Chemical name:	7,8-didehydro-4,5 α-epoxy-17-methyl-morphinan-3, 6α-diol sulfate (2:1) (salt) pentahydrate
Molecular formula and molecular mass:	$(C_{17}H_{19}NO_3) \cdot H_2SO_4 \cdot 5H_2O$ 758.8 (pentahydrate) 668.8 (anhydrous)
Structural formula:	
Physicochemical properties:	Morphine is a phenanthrene alkaloid obtained from opium.

Product Characteristics

Physical Description:	White, odourless crystalline powder or needle-like 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).

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

General Toxicology:

Animal

Table 3 – Morphine lethal dose toxicity values in animals

Acute	Oral LD50
Mice	650 mg/kg
Rats	460 mg/kg
Guinea Pigs	1000 mg/kg

Morphine toxicity varies considerably from species to species. In some species, relatively low doses of morphine cause hypothermia and gross excitation. In the rat, for example, doses suitable for analgesia also affect a continually restless and seemingly frightened state. These effects are antagonized by naloxone and are prevented by phenytoin.

Human

Morphine toxicity may result from overdosage but because of the great inter-individual variation in sensitivity to opioids it is difficult to determine an exact dose of any opioid that is toxic or lethal.

The presence of pain or tolerance tends to diminish the toxic effects of morphine. Published data suggests that in a morphine naive, pain-free individual, the lethal oral dose would be in excess of 120 mg. Patients on chronic oral morphine therapy have been known to take in excess of 3000 mg/day with no apparent toxicity.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

ᴺMS•IR®
(Morphine Sulfate Immediate Release Tablets)

Read this carefully before you start taking MS•IR 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 MS•IR.

Serious Warnings and Precautions

- Even if you take MS•IR 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 prescriber (e.g., healthcare professional).
- When you take MS•IR ~~it~~ tablets they must be swallowed whole. Do not cut, break, crush, chew, or dissolve the tablet. This can be dangerous and can lead to death or seriously harm you.
- Life-threatening breathing problems can happen while taking MS•IR, 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 MS•IR. They could die from taking it. If a person has not been prescribed MS•IR, taking even one dose can cause a fatal overdose. This is especially true for children.
- If you took MS•IR 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 MS•IR 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 MS•IR used for?
MS•IR is a medicine used to manage your pain

How does MS•IR work?
MS•IR is a painkiller belonging to the class of medicine known as opioids. It relieves pain by acting on specific nerve cells of the spinal cord and brain.

What are the ingredients in MS•IR?

Medicinal ingredient: morphine sulfate
Non-medicinal ingredients: croscarmellose sodium, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose and polyethylene glycol 400.

MS•IR comes in the following dosage forms:
Immediate Release Tablets: 5 mg, 10 mg, 20 mg and 30 mg.

Do not use MS•IR if:
- your healthcare professional did not prescribe it for you
- you are allergic to morphine, or any of the other ingredients in MS•IR
- 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 (for example, from appendicitis or pancreatitis)
- you have increased pressure in your skull, have a head injury or a brain tumour.
- you have or have a had a history of epilepsy
- you suffer from alcoholism or alcohol withdrawal
- 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 a surgery or operation, or have had a surgery in the last 24 hours you are pregnant or planning to become pregnant or you are in labour or delivery
- you are breastfeeding

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take MS•IR. 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 kidney or liver problems.
- have sickle cell disease.
- have a sleep disorder which causes pauses in breathing or shallow breathing while sleeping (sleep apnea).
- have low blood pressure.
- have or have had problems with your mood (such as depression or anxiety), hallucinations, or other mental health problems.
- suffer from chronic or severe constipation.
- have a history of pancreas or gall bladder problems.
- have problems with your thyroid, adrenal or prostate gland.
- have difficulty urinating.
- are over 50 years of age.
- have a condition that causes weakness or frailty.
- have circulatory problems (e.g. body does not get enough oxygen and nutrients to function properly due to lack of blood flow).
- are planning on drinking alcohol. Drinking alcohol while taking MS•IR may cause dangerous side effects, including death. Do not drink alcohol while taking MS•IR.
- take hypnotics, centrally acting analgesics, opioids, or psychotropic medicines. Ask your healthcare professional if you are unsure.

Other warnings you should know about:

Opioid dependence and addiction
Like any opioid, MS IR may cause mental and physical dependence. Morphine sulfate also has the potential to cause addiction. 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 addiction, physical dependence, or tolerance. Your healthcare professional should prescribe and administer MS IR 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 MS•IR while pregnant, nursing, during labour or delivery. Opioids can be transferred to your baby through breast milk, or while still in the womb. MS•IR can then cause life-threatening breathing problems in your unborn baby or nursing infant.

If you are pregnant and are taking MS•IR, 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 MS•IR. 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 MS•IR. MS•IR can cause:
- drowsiness
- dizziness or
- light headedness

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

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

You may be more likely to have problems with your adrenal gland if you have been taking opioids for longer than one month. Your healthcare professional may do tests, give you another medication, and slowly take you off MS•IR.

Serotonin toxicity (also known as serotonin syndrome): MS•IR 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 MS•IR with certain anti-depressants or migraine medications.

Serotonin syndrome symptoms include:

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

Sexual Function/Reproduction

Long term use of 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.

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.

Worsened 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 doctor if you notice a change like this in your pain while you are taking MS•IR.

Testing and check-ups: Your healthcare professional will regularly monitor you for signs of misuse and abuse.

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

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 MS•IR include:

- benzodiazepines used to help you sleep or that help 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 anaesthetics 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 MS•IR. It can lead to drowsiness, usually slow or weak breathing, serious side effects, or a fatal overdose.

- monoamine oxidase inhibitors (MAOIs) used to treat depression. Do not take MS•IR with MAOIs or if you have taken MAOIs in the last 14 days.

The following may also interact with MS•IR:
- anticonvulsants (used to treat seizures)
- anticoagulants, used to thin the blood and prevent blood clots (e.g., warfarin and other couratins)
- drugs used to treat migraines (e.g. triptans)

If you are unsure about the medications you are taking, ask your healthcare professional.

How to take MS•IR:
Take MS·IR tablets:
- regularly, usually every 4 to 6 hours, as directed by your healthcare professional
- with a full glass of water

Swallow whole. Do not cut, break, crush, chew or dissolve the tablet. This can be dangerous and can lead to death or seriously harm you.

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

Your healthcare professional will prescribe the lowest dose that works to control your pain. It is recommended that you only take MS•IR for up to 7 days. If you need to take MS•IR for longer, your healthcare professional 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 healthcare professional to determine if you still need MS•IR. Be sure to use MS•IR only for the condition for which it was prescribed.

If your pain increases or you develop any side effect as a result of taking MS•IR, tell your healthcare professional immediately.

Stopping your Medication
If you have been taking MS•IR 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 MS•IR. 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 MS•IR.

Refilling your Prescription for MS•IR:
A new written prescription is required from your healthcare professional each time you need more MS•IR. Therefore, it is important that you contact your healthcare professional 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 healthcare professional for your pain management.

Overdose:

If you think you, or a person you are caring for, have taken too much MS•IR, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no symptoms.

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

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.

What are possible side effects from using MS•IR?
These are not all the possible side effects you may feel when taking MS•IR. 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 healthcare professional or pharmacist about ways to prevent constipation when you start using MS•IR.

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	
UNCOMMON			
Seizures (fits): uncontrollable shaking with or without loss of consciousness.			✓
Hallucinations: seeing or hearing things that are not there.			✓
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.		✓	
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.		✓	

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

Reporting Side Effects

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

- Visiting the Web page on Adverse Reaction Reporting (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 health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- **Keep unused or expired MS•IR in a secure place to prevent theft, misuse or accidental exposure.**
- Store tablets at room temperature (15˚- 30˚C). Keep in a dry place.
- **Keep MS•IR 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 MS•IR, get emergency help right away.**

Disposal:

MS•IR 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 MS•IR:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website www.purdue.ca, or by calling 1-800-387-4501.

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