PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

ⓃMORPHINE HP 25

Morphine sulfate injection USP

25 mg/mL

ⓃMORPHINE HP 50

Morphine sulfate injection USP

50 mg/mL

Narcotic Analgesic

Sandoz Canada Inc.
110 rue de Lauzon
Boucherville, QC, Canada
J4B 1E6

Date of Revision: May 17, 2019

Submission Control No: 221205

Table of Contents

[N]MORPHINE HP 25 / [N]MORPHINE HP 50

Morphine sulfate injection USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Intramuscular, intravenous, and subcutaneous	Sterile solution / 25 mg/mL, and 50 mg/mL	Sodium chloride, sulfuric acid and/or sodium hydroxide and water for injection

INDICATIONS AND CLINICAL USE

Adults
Morphine HP 25 and Morphine HP 50 (morphine sulfate injection USP) used without dilution are indicated for the relief of severe pain in patients who require subcutaneously or intramuscularly administered narcotics in doses higher than those usually needed.

For the relief of severe pain, Morphine HP 25 and Morphine HP 50 may also be diluted and administered by intravenous infusion.

Morphine HP 25 and Morphine HP 50 are not indicated as an as-needed (prn) analgesic.

Geriatrics (> 65 years of age)
In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or other drug therapy.

Pediatrics (< 18 years of age)
The safety and efficacy of morphine sulfate have not been studied in the pediatric population. Therefore, the use of Morphine HP 25 and Morphine HP 50 are not recommended in patients under 18 years of age.

CONTRAINDICATIONS

- Patients who are hypersensitive to the active substance morphine sulfate or other opioid analgesics or to any ingredient in the formulation. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.

- In patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction or strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).
- Patients with suspected surgical abdomen, after biliary tract surgery or surgical anastomosis (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, or status asthmaticus.
- Heart failure secondary to chronic lung disease or cardiac arrhythmias.
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood and cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury or brain tumor.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

Morphine HP 25 and Morphine HP 50 are highly concentrated solutions of morphine. They should be used without dilution only in narcotic-tolerant patient requiring high doses of opiate agonists. Do not confuse Morphine HP 25 and Morphine HP 50 with the standard dosage strengths of parenteral morphine, since overdose and death could result.

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, Morphine HP 25 and Morphine HP 50 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

Morphine HP 25 and Morphine HP 50 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 Morphine HP 25 and Morphine HP 50 and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS, Abuse and Misuse). Morphine HP 25 and Morphine HP 50 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 Morphine HP 25 and Morphine HP 50. 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 Morphine HP 25 and Morphine HP 50 or following a dose increase. Further, instruct patients of the hazards related to taking opioids including fatal overdose.

Accidental Exposure
Accidental exposure of even one dose of Morphine HP 25 and Morphine HP 50 especially by children, can result in a fatal overdose of morphine sulfate (see DOSAGE AND ADMINISTRATION, Disposal, for instructions on proper disposal).

Neonatal Opioid Withdrawal Syndrome
Prolonged maternal use of Morphine HP 25 and Morphine HP 50 during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome (NOWS)).

Interaction with Alcohol
Caution should be observed when administering Morphine HP 25 and Morphine HP 50 to patients who have been or are taking alcohol. Morphine HP 25 and Morphine HP 50 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 central nervous system (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 Morphine HP 25/Morphine HP 50 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
Morphine HP 25 and Morphine HP 50 should be stored securely to avoid theft or misuse.

Morphine HP 25 and Morphine HP 50 should only be prescribed by persons 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 Morphine HP 25 and Morphine HP 50 as they may increase the chance of experiencing serious adverse events, including death.

Hyperalgesia that will not respond to a further dose increase of morphine sulfate can occur at

particularly high doses. A morphine sulfate dose reduction or change in opioid may be required.

Do not use unless solution is clear and package is undamaged (see DOSAGE AND ADMINISTRATION). Morphine products may discolor over a period of time. No loss of analgesic potency and no increase in toxicity has ever been demonstrated for such discolored solutions.

Abuse and Misuse
Like all opioids, Morphine HP 25 and Morphine HP 50 are a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, Morphine HP 25 and Morphine HP 50 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 Morphine HP 25 and Morphine HP 50 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.

Carcinogenesis and Mutagenesis
Long-term studies in animals have not been performed to evaluate the carcinogenic or the mutagenic potential of morphine. No long-term follow-up studies of patients receiving morphine epidurally have been conducted

Cardiovascular
Morphine sulfate 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 drugs such as phenothiazines and other tranquilizers, sedative/hypnotics, tricyclic antidepressants or general anesthetics. Morphine sulfate may produce orthostatic hypotension in ambulatory patients. These patients should be monitored for signs of hypotension after initiating or titrating the dose of Morphine HP 25 and Morphine HP 50.

The use of Morphine HP 25 and Morphine HP 50 in patients with circulatory shock should be avoided as it may cause vasodilation that can further reduce cardiac output and blood pressure.

Rapid intravenous injection of opioid analgesics increases the possibility of hypotension and respiratory depression and should be avoided (see DOSAGE AND ADMINISTRATION).

Because of possible vagolytic action that may produce a significant increase in the ventricular response rate, morphine should be used with caution in patients with atrial flutter and other supraventricular tachycardias.

Dependence/Tolerance

As with other opioids, tolerance and physical dependence may develop upon repeated administration of Morphine HP 25 and Morphine HP 50 and there is a potential 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.
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, goosebumps, 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
Morphine HP 25 and Morphine HP 50 are opioids 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 Morphine HP 25 and Morphine HP 50; extreme caution and awareness are 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 sulfate and other morphine-like opioids have been shown to decrease bowel motility. Morphine sulfate 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.

Morphine HP 25 and Morphine HP 50 are not recommended to be used in pregnant women, unless, in the judgement of the physician, the potential benefits outweigh the risks. If Morphine HP 25 and Morphine HP 50 were used during pregnancy, special attention to NOWS is warranted.

Neurologic

Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol): Morphine HP 25 and Morphine HP 50 should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics, general anesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, benzodiazepines, centrally-active anti-emetics and other CNS depressants. Respiratory depression, hypotension and profound sedation, coma or death may result.

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 Morphine HP 25 and Morphine HP 50 are 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).
Morphine HP 25 and Morphine HP 50 should not be administered to patients who have been or are consuming alcohol as it may increase the chance of experiencing dangerous side effects, including death (see CONTRAINDICATIONS; 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.

Morphine may aggravate pre-existing convulsions in patients with convulsive disorders. If dosage is escalated substantially above recommended levels because of tolerance development, convulsions may occur in individuals without a history of convulsive disorders.

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

Serotonin Syndrome: Morphine HP 25 and Morphine HP 50 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 serotoninergic 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. Morphine HP 25 and Morphine HP 50 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).
Peri-Operative Considerations

Morphine HP 25 and Morphine HP 50 are 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 Morphine HP 25 and Morphine HP 50 for at least 24 hours before the operation and Morphine HP 25 and Morphine HP 50 should not be used in the immediate post-operative period.

Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. Thereafter, if Morphine HP 25 and Morphine HP 50 are 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 sulfate 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. Morphine HP 25 and Morphine HP 50 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
Morphine HP 25 and Morphine HP 50 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 sulfate with other CNS depressants, including other opioids, phenothiazine, sedative/hypnotics and alcohol.

Respiratory
Respiratory Depression: Dose related respiratory depression is produced by morphine acting directly on brain stem respiratory centers (see WARNINGS AND PRECAUTIONS). Morphine also affects centers controlling respiratory rhythm and may produce irregular or periodic breathing. 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 HP 25 and Morphine HP 50 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 Morphine HP 25 and Morphine HP 50 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 Morphine HP 25 and Morphine HP 50 and following dose increases. If significant respiratory depression occurs, it may be reversed by the use of naloxone hydrochloride (see OVERDOSAGE).

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 Morphine HP 25 and Morphine HP 50 are essential. Overestimating the Morphine HP 25 and Morphine HP 50 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).

Indiscriminate use of morphine in patients with asthma or pulmonary emphysema may, due to its drying action upon the respiratory tract mucosa, precipitate severe respiratory insufficiency

resulting from increased viscosity of bronchial secretions and suppression of the cough reflex. Morphine HP 25 and Morphine HP 50 should be used with great caution in patients having an acute asthmatic attack.

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, particularly when initiating therapy and titrating with Morphine HP 25 and Morphine HP 50 as in these patients, even at usual therapeutic doses of Morphine HP 25 and Morphine HP 50 may decrease respiratory drive to the point of apnea while simultaneously increasing airway resistance. In these patients, use of alternative non-opioid analgesics should be considered, if possible. The use of Morphine HP 25 and Morphine HP 50 are contraindicated in patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see CONTRAINDICATIONS).

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 sulfate should be administered with caution to patients with impaired hepatic or renal function, a history of alcohol and drug abuse and in a reduced dosage to elderly or debilitated patients, and in patients with severely impaired pulmonary function, Addison's disease, hypothyroidism, myxedema, toxic psychosis, prostatic hypertrophy or urethral stricture.

Pregnant Women: Studies in human have not been conducted. Morphine sulfate crosses the placental barrier and are not recommended to be administered to pregnant women unless in the judgement of the physician, potential benefits outweigh the risks.

Morphine sulfate administered a short time (i.e., up to 4 hours) prior to delivery to women with no history of chronic abuse or dependence has been associated with a delay in initial respiration and transient respiratory depression in the neonate. Respiratory depression may be produced in the neonate.

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, may be life-threatening (see WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome (NOWS)).

Pregnant women using opioids should not discontinue their medication abruptly as this can cause pregnancy complication 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, Morphine HP 25 and Morphine HP 50 are not recommended to be used in nursing women and during labour and delivery unless, in the judgement of the physician, the potential benefits outweigh the risks. Life-threatening respiratory depression may occur in the infant if opioids are administered to the mother. Naloxone, a drug that counters the effects of opioids, should be readily available if Morphine HP 25 and Morphine HP 50 are used in this population.

Occasionally, morphine sulfate may prolong labour through actions which temporarily reduce the strength, duration and frequency of uterine contraction. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labour.

Morphine HP 25 and Morphine HP 50 should be used with caution in women delivering premature infants since respiratory depression in the neonate may occur. Neonates whose mothers received morphine sulfate during labor should be observed closely for signs of respiratory depression. A specific opioid antagonist, naloxone, is available for reversal of morphine-induced respiratory depression in the neonate.

Pediatrics (< 18 years of age): The safety and efficacy of morphine sulfate have not been studied in the pediatric population. Therefore, use of Morphine HP 25 and Morphine HP 50 are 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 titrate slowly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see DOSAGE AND ADMINISTRATION).

Patients with Hepatic or Renal Impairment:
Elimination half-life may be prolonged in patients with reduced metabolic rates and with hepatic or renal dysfunction. Therefore, care should be exercised in administering Morphine HP 25 and Morphine HP 50 in these conditions, particularly with repeated dosing.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
Adverse effects of morphine sulfate are similar to those of other opioid analgesics, and represent an extension of pharmacological effects of the drug class. The major hazards of 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 adverse effects of morphine sulfate are lightheadedness, dizziness, sedation, nausea, vomiting, constipation and sweating. These effects seem to be more prominent in ambulatory patients and in those who are not suffering severe pain. In such individuals, lower doses may be advisable. Some adverse effects may be alleviated in the ambulatory patient if he lies down. Other adverse effects include the following:

Central Nervous System:
Sedation, drowsiness, mental clouding, dizziness, lethargy, impairment of mental and physical performance, anxiety, convulsion, fear, miosis, dysphoria, psychic dependence, and mood changes.

Gastrointestinal System:
Nausea, vomiting, increased pressure in the biliary tract, constipation.

Cardiovascular System:
Orthostatic hypotension, fainting, tachycardia, peripheral circulatory collapse, and cardiac arrest have occurred after rapid intravenous injection.

Genitourinary System:
Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported.

Other:
Flushing, sweating, pruritus, allergic reactions, suppressed cough reflex.

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.

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.

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

Interaction with Benzodiazepines and Other Central Nervous System (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 Central Nervous System Depressants (including benzodiazepines and alcohol) and Psychomotor Impairment). Morphine HP 25 and Morphine HP 50 should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

Incompatibility:
Morphine sulfate are incompatible with admixtures of soluble barbiturates, chlorothiazide, aminophylline, heparin, meperidine, methicillin, phenytoin, sodium bicarbonate, iodide, sulfadiazine and sulfisoxazole.

Drug-Drug Interactions
Morphine analgesia may be decreased when given concomitantly with phenothiazines. When such combined therapy is contemplated, the dose of one or both agents should be appropriately adjusted. Coadministration of morphine 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).

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

DOSAGE AND ADMINISTRATION

Morphine HP 25 and Morphine HP 50 should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics).

For acute pain, it is recommended that Morphine HP 25 and Morphine HP 50 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 (90 morphine milligram equivalent) of Morphine HP 25 or Morphine HP 50 not be exceeded. Each patient should be assessed for their risk prior to prescribing Morphine HP 25 or Morphine HP 50, 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 Morphine HP 25 or Morphine HP 50 (see DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage).

Dosing Considerations

Morphine HP 25 and Morphine HP 50 (morphine sulfate injection USP) 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).

Morphine HP 25 and Morphine HP 50 are not indicated for rectal administration

Rapid intravenous injection of opioid analgesics increases the possibility of hypotension and respiratory depression.

Because Morphine HP 25 and Morphine HP 50 contain 25 mg/mL and 50 mg/mL of morphine respectively, a smaller injection volume can be used to avoid the discomfort associated with subcutaneous intramuscular injection of larger volumes of solution.

Recommended Dose and Dosage Adjustment

Morphine HP 25 and Morphine HP 50, used without dilution are indicated for the relief of severe pain in narcotic-tolerant patients and therefore are not to be given to patients who are not already receiving large doses of narcotics.

The initial dosage should be based on the preceding (or previous) morphine or other narcotic regimen used by the patient. If the patient is being changed from a less concentrated morphine injection, similar doses should be used depending on the patient's clinical response to the drug. If the patient is being changed from one narcotic analgesic to the other, the dose should be adjusted according to the severity of pain and the patient's clinical response. There can be considerable variability in both the dosage requirement and the patient's response.

If Morphine HP 25 or Morphine HP 50 are substituted for a different narcotic analgesic, the appropriate starting dose must be determined.

Following are the equivalence of commonly used narcotic analgesics (Table 1), and comparison of effects of strong analgesics used in the treatment of cancer pain (Table 2).

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 ANALGESICS: APPROXIMATE ANALGESIC EQUIVALENCES[1]

DRUG	Equivalent Dose (mg)[2] (compared to morphine 10 mg IM)		Duration of Action (Hours)
	Parenteral	Oral	
Strong Opioid Agonists:			
Morphine	10	60[3]	3 - 4
Oxycodone	15	30[4]	2 - 4
Hydromorphone	1.5	7.5	2 - 4
Anileridine	25	75	2 - 3
Levorphanol	2	4	4 - 8
Meperidine[6]	75	300	1 - 3
Oxymorphone	1.5	5 (rectal)	3 - 4
Methadone[5]	-	-	-
Heroin	5 - 8	10 - 15	3 - 4
Weak Opioid Agonists:			
Codeine	120	200	3 - 4
Propoxyphene	50	100	2 - 4
Mixed Agonist-Antagonists[7]:			
Pentazocine[6]	60	180	3 - 4
Nalbuphine	10	-	3 - 6
Butorphanol	2	-	3 - 4

Footnotes:

[1] References:
Expert Advisory Committee on the Management of Severe Chronic Pain in Cancer Patients, Health and Welfare Canada. Cancer pain: A monograph on the management of cancer pain. Ministry of Supplies and Services Canada, 1987. Cat. No. H42-2/5-1984E.
Foley KM. The treatment of cancer pain. N Engl J. Med 1985; 313(2): 84-95.
Aronoff GM, Evans WO. Pharmacological management of chronic pain: A review. In: Aronoff GM, editor. Evaluation and treatment of chronic pain. 2nd ed. Baltimore (MD); Williams and Wilkins; 1992. p. 359-68.
Cherny NI Portenoy RK. Practical issues in the management of cancer pain. In: Wall PD, Melzack R, editors. Textbook of pain. 3rd ed. New York: Churchill Livingstone; 1994. p. 1437-67.

[2] **Most of the data were derived from single-dose, acute pain studies and should be considered an approximation for selection of doses when treating chronic pain. As analgesic conversion factors are approximate and patient response may vary, dosing should be individualized according to relief of pain and side effects. Because of incomplete cross-tolerance, dose reductions of 25% to 50% of the equianalgesic dose may be appropriate in some patients when converting from one opioid to another, particularly at high doses.† Upward titration may be required to reach appropriate maintenance doses.**
†Levy MH. Pharmacologic treatment of cancer pain. N Engl J Med 1996;335:1124-1132.

[3] **For acute pain, the oral or rectal dose of morphine is six times the injectable dose. However, for chronic dosing, clinical experience indicates that this ratio is 2-3:1 (i.e., 20-30 mg of oral or rectal morphine is equivalent to 10 mg of parenteral morphine).**

[4] Based on single entity oral oxycodone in acute pain.

[5] Extremely variable equianalgesic dose. Patients should undergo individualized titration starting at an equivalent to 1/10 of the morphine dose.

[6] Not recommended for the management of chronic pain.

[7] Mixed agonist-antagonists can precipitate withdrawal in patients on pure opioid agonists.

Table 2: COMPARISON OF STRONG ANALGESICS AND STRUCTURALLY RELATED DRUGS USED IN THE TREATMENT OF CANCER PAIN* – I.M. OR S.C. ADMINISTRATION

Non Proprietary (Trade) Names	Dose, mg Equianalgesic to 10 mg of I.M. Morphine**	Duration Compared with Morphine
Morphine Sulfate	10	Same
Papaveretum (Pantopon)	20	Same
Hydromorphone hydrochloride (Dilaudid)	1.3	Slightly shorter
Oxymorphone hydrochloride (Numorphan)	1.1	Slightly shorter
Nalbuphine hydrochloride (Nubain)	12	Same
Diamorphine hydrochloride (Heroine)	4-5	Slightly shorter
Levorphanol tartrate (Levo-Dromoran)	2.3	Same
Butorphanol tartrate (Stadol)	1.5 - 2.5	Same
Pentazocine (Talwin) lactate or hydrochloride	60	Shorter
Meperidine pethidine (Demerol) hydrochloride	80	Shorter
Methadone hydrochloride (Dolophine)	10	Same

* Beaver WT. Management of cancer pain with parenteral medication. JAMA 1980: 244; 2653-2657.

** In terms of the area under the analgesic time effect curve.

Morphine HP 25 and Morphine HP 50, administered subcutaneously or intramuscularly, when required, should usually be given regularly around the clock, in most instances every 4 hours.

Directions for use: Morphine HP 25 and Morphine HP 50 must be diluted in a sterile area by a pharmacist.

For I.V. Infusion with dilution: Morphine HP 25 and Morphine HP 50 may be diluted in Dextrose 5%, in Water or Sodium Chloride Injection to the desired concentration (usually 0.1 to 0.5 mg/mL) and administered by I.V. infusion as required.

S.C. Infusion: If a patient has low muscle mass or is cachectic or has no accessible peripheral veins, S.C. infusion using a portable pump can be tried. When switching from I.V. to S.C. infusion, use same dose and monitor same parameters. The maximum dose that can be safely given has not been defined but doses as high as 480 mg/24 hours have been given. Erythema

around the injection site may occur. Change needle site periodically (every 5 days, although some clinicians prefer every 48 hours).
Morphine HP 25 and Morphine HP 50, as well as dilutions of Morphine HP 25 and Morphine HP 50 in Dextrose 5% in Water or Sodium Chloride Injection, can be stored in portable infusion pump cassettes and PVC minibags. Protected from light and at room temperature, they will stay stable for more than 15 days.

Morphine Dosage Reduction:
During the first 2 to 3 days of effective pain relief, the patient may sleep for many hours. This can be misinterpreted as the effect of excessive analgesic dosing rather than the first sign of relief in a pain exhausted patient. The dose, therefore, should be maintained for about 3 days before reduction, if respiratory activity and other vital signs are adequate. Following successful relief of severe pain, periodic attempts to reduce the narcotic dose should be made. Lower doses or complete discontinuation of the narcotic analgesic may become feasible due to a physiological change or the improved mental state of the patient.

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. Morphine HP 25 and Morphine HP 50 should be initiated at a low dose and slowly titrated to effect (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY).

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. Morphine HP 25 and Morphine HP 50 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 administration of the lowest dose which will achieve the overall treatment goal of satisfactory pain relief with acceptable side effects.**

Dosage 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 Morphine HP 25 and Morphine HP 50. Withdrawal (abstinence) symptoms may occur following abrupt discontinuation of therapy. These symptoms may include body aches, diarrhea, goosebumps, 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.

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.

Disposal
Morphine HP 25 and Morphine HP 50 should be kept in a safe place, out of the sight and reach of children before, during and after use. Morphine HP 25 and Morphine HP 50 should not be used in front of children, since they may copy these actions.

OVERDOSAGE

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

Symptoms: Overdosage with morphine is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), pinpoint pupils, extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, particularly by the intravenous route, apnea, circulatory collapse, cardiac arrest and death may occur.

Treatment: Primary attention should be given to the re-establishment of adequate respiratory exchange through the provision of a patent airway and institution of assisted or controlled ventilation. Naloxone hydrochloride is a specific and effective antagonist for respiratory depression which may result from overdosage or sensitivity to narcotics. The usual initial adult dose is 0.4 mg to 2 mg naloxone administered I.V. If the desired degree of counteraction and improvement in respiratory function is not obtained immediately following I.V. administration, it may be repeated intravenously at 2 to 3 minute intervals. Failure to obtain significant improvement after 2 or 3 doses suggests that the condition may be due partly or completely to other disease processes or nonopioid drugs. The usual initial dose in narcotic-induced respiratory depression in neonates is 0.01 mg/kg body weight given I.V., I.M. or S.C. This dose may be repeated in accordance with the adult administration guideline. If necessary, naloxone can be diluted with Sterile Water for Injection, USP. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated. An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Morphine is not dialyzable.

Toxic dose of morphine in humans by parenteral routes; a dose in excess of 30 mg rapidly administered is likely to induce significant toxic effects in the nonaddicted adult who is not in pain.

Note: If an individual is physically dependent on narcotics, the administration of the usual dose of a narcotic antagonist will precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of antagonist administered. The use of narcotic antagonists in such individuals should be avoided if possible. If a narcotic antagonist must be used to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care and only one-tenth (10%) to one-fifth (20%) the usual dose administered.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Morphine, an opium alkaloid, is a narcotic analgesic and provides analgesia at a dose that does not produce severe alterations in consciousness. Its principal therapeutic effect is relief of pain. Its exact mechanism and focus of action are not known, but are believed to relate to the existence of opiate receptors in the central nervous system. The drug affects both the initial perception of pain and the emotional response to it and although pain relief is not usually complete, the level of distress or suffering is markedly decreased. In addition to analgesia, narcotics produce drowsiness, changes in mood, and mental clouding; however, neither sensory modalities nor motor activity are blocked at therapeutic doses. There is no intrinsic limit to the analgesic effect, but high dosages can produce adverse effects, such as respiratory depression, nausea and vomiting, cough reflex depression, miosis, mild vasodilation and an increase in tone of the gastrointestinal and genitourinary tracts.

Pharmacodynamics

Central Nervous System:
Morphine sulfate 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 sulfate 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 sulfate causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid 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 sulfate overdose.

Gastrointestinal Tract and Other Smooth Muscle: Morphine sulfate 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 may be 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.

Cardiovascular System:
Morphine sulfate may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, flushing, red eyes, hyperhidrosis and/or orthostatic hypotension.

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.

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
Pain relief generally begins within several minutes after I.V administration. Higher doses provide greater analgesic effect and longer duration of action but adverse effects limit the maximum tolerated dose.

Pharmacokinetics
Morphine is detoxified in the liver by conjugation with glucuronic acid. Small amounts of the free drug and larger amounts of conjugated morphine are found in the urine. These account for most of the administered drug and 90% of the total excretion occurs within the first 24 hours.

Special Populations and Conditions
Pediatrics: Individuals under 18 years of age should not take Morphine HP 25 nor Morphine HP 50.

STORAGE AND STABILITY

Store between 15 and 30°C. Protect from light. Discard unused portion. Do not autoclave.

LATEX-FREE STOPPER – Stoppers contains no dry natural rubber.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Morphine HP 25/Morphine HP 50 are clear, colourless or yellow isotonic, sterile, and preservative free solution of morphine sulfate. **No loss of analgesic potency and no increase in toxicity have ever been demonstrated for discoloured solutions.**

Morphine HP 25 (25 mg/mL)
Each mL contains: morphine sulfate 25 mg, sodium chloride for tonicity, sulfuric acid and/or sodium hydroxide to adjust pH and water for injection. Available in single use amber vials of 1 mL, boxes of 10; and of 4 mL, boxes of 5.

Morphine HP 50 (50 mg/mL)
Each mL contains: morphine sulfate 50 mg, sodium chloride for tonicity, sulfuric acid and/or sodium hydroxide to adjust pH and water for injection. Available in single use amber vials of 1 mL, boxes of 10; of 5 mL, boxes of 5; of 10 mL, boxes of 5; and 50 mL, boxes of 1.

PART II: SCIENTIFIC INFORMATION

REFERENCES

Morphine Forte, and Morphine Extra-Forte. Pfizer Canada ULC. Product Monograph. Control Number: 220077. Date of Revision: August 6, 2018.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

ⓃMORPHINE HP 25
ⓃMORPHINE HP 50
(Morphine sulfate injection USP)

Read this carefully before you start taking Morphine HP 25 and Morphine HP 50. 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 Morphine HP 25 and Morphine HP 50.

Serious Warnings and Precautions

- **Even if you take Morphine HP 25 and Morphine HP 50 as prescribed you are at a risk for opioid addiction, abuse and misuse. This can lead to overdose and death.**

- **You may get life-threatening breathing problems while taking Morphine HP 25 and Morphine HP 50. 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.**

- **If a person has not been prescribed Morphine HP 25 and Morphine HP 50 taking even one dose can cause a fatal overdose. This is especially true for children.**

- **If you took Morphine HP 25 and Morphine HP 50 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 Morphine HP 25 and Morphine HP 50 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 are Morphine HP 25 and Morphine HP 50 used for?
Morphine HP 25 and Morphine HP 50 are injections containing morphine sulfate (an opioid

analgesic) used to control severe pain in patients who need an opioid administered by injection.

How does Morphine HP 25 and Morphine HP 50 work?
Morphine HP 25 and Morphine HP 50 are painkillers belonging to the class of drugs known as opioids. It relieves pain by acting on specific nerve cells of the spinal cord and brain.

What are the ingredients in Morphine HP 25 and Morphine HP 50?
Medicinal ingredient: Morphine sulfate
Non-medicinal ingredients: Sodium chloride, sulfuric acid and/or sodium hydroxide and water for injection

Morphine HP 25 and Morphine HP 50 comes in the following dosage forms:
Solution for injection of 25 mg/mL and 50 mg/mL

Do not use Morphine HP 25 and Morphine HP 50 if:
- your doctor did not prescribe them for you
- you are allergic to morphine sulfate or any of the other ingredients in Morphine HP 25 and Morphine HP 50
- 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 suffer from alcoholism
- you are taking or have taken within the past 2 weeks a Monoamine Oxidase inhibitor (MAOi) (such as phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline)
- you are going to have, or recently had, a planned surgery

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Morphine HP 25 and Morphine HP 50. 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: Opioids can be transferred to your baby through breast milk, or while still in the womb. Morphine HP 25 and Morphine HP 50 can then cause life-threatening breathing problems in your unborn baby or nursing infant. Your doctor will determine if the benefits of using Morphine HP 25 or Morphine HP 50 outweigh the risks to your unborn baby or nursing infant.

If you are pregnant and are taking Morphine HP 25 or Morphine HP 50, 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 Morphine HP 25 or Morphine HP 50. 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 Morphine HP 25 and Morphine HP 50. Morphine HP 25 and Morphine HP 50 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 Morphine HP 25 and Morphine HP 50.

Serotonin Syndrome: Morphine HP 25 and Morphine HP 50 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 Morphine HP 25 and Morphine HP 50 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.

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 Morphine HP 25 and Morphine HP 50:

- Alcohol. This includes prescription and non-prescription medications that contain alcohol. **Do not** drink alcohol while you are taking Morphine HP 25 and Morphine HP 50. 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 Morphine HP 25 and Morphine HP 50
- 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 **Morphine HP 25 and Morphine HP 50** 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)
- antihistamines (drugs used to treat allergies)
- anti-emetics (drugs used for the prevention of vomiting)
- drugs used to treat muscle spasms and back pain
- drugs used to treat migraines (e.g. triptans)
- St. John's Wort

How to take Morphine HP 25 and Morphine HP 50:

Morphine HP 25 and Morphine HP 50, used without dilution are indicated for the relief of severe pain in narcotic-tolerant patients and therefore are not to be given to patients who are not already receiving large doses of narcotics.

Morphine HP 25 and Morphine HP 50 are given under the skin, into the muscle or vein in doses or concentrations that are higher than those usually needed.

The initial dosage should be based on the preceding (or previous) morphine or other narcotic regimen used by the patient.

Usual Adult Starting Dose:
Your dose is tailored/personalized just for you.

Your doctor will prescribe the lowest dose that works to control your pain. It is recommended that you only take Morphine HP 25 and Morphine HP 50 for up to 7 days. If you need to take Morphine HP 25 and Morphine HP 50 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 Morphine HP 25 and Morphine HP 50. Be sure to use Morphine HP 25 and Morphine HP 50 only for the condition for which it was prescribed.

If your pain increases or you develop any side effect as a result of taking Morphine HP 25 and Morphine HP 50 tell your doctor immediately.

Stopping your Medication
If you have been taking Morphine HP 25 and Morphine HP 50 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 Morphine HP 25 and Morphine HP 50. 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 Morphine HP 25 or Morphine HP 50.

Refilling your Prescription for Morphine HP 25 and Morphine HP 50:
A new written prescription is required from your doctor each time you need more Morphine HP 25 and Morphine HP 50.

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 Morphine HP 25 and Morphine HP 50, 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

What are possible side effects from using Morphine HP 25 and Morphine HP 50?
These are not all the possible side effects you may feel when taking Morphine HP 25 and Morphine HP 50. 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 Morphine HP 25 and Morphine HP 50.

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

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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) 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 Morphine HP 25 and Morphine HP 50 in a secure place to prevent theft, misuse or accidental exposure.**
- Store between 15°C to 30°C. Protect from light. Discard unused portion. Do not autoclave.
- **Keep Morphine HP 25 and Morphine HP 50 under lock, out of sight and reach of children and pets.**
- **Never take medicine in front of small children as they will want to copy you. Accidental ingestion by a child is dangerous and may result in death. If a child accidentally takes Morphine HP 25 or Morphine HP 50, get emergency help right away.**

If you want more information about Morphine HP 25 and Morphine HP 50:

- 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://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); or by calling 1-800-361-3062.

This leaflet was prepared by Sandoz Canada Inc.
110 rue de Lauzon
Boucherville, Quebec
J4B 1E6

Last Revised: May 17, 2019