

PRESCRIBING INFORMATION

<sup>N</sup> **MORPHINE SULFATE INJECTIONBP**

10 mg/mL and 15 mg/mL

Opioid Analgesic

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Date of Preparation: April 20, 2018

Control no.: 207332

## <sup>N</sup> **MORPHINE SULFATE INJECTION BP**

10 mg/mL and 15 mg/mL Opioid Analgesic

### **PHARMACOLOGY**

Morphine exerts its main actions by acting as an opioid agonist at specific opioid receptor sites in the CNS and other tissues.

Morphine produces many effects including analgesia, decreased gastrointestinal motility, respiratory depression, nausea, vomiting, drowsiness, changes in mood and alterations of the endocrine and autonomic nervous system.

Maximum analgesia occurs within 50 to 90 minutes after subcutaneous (SC) administration, 30 to 60 minutes after intramuscular (IM) administration and 20 minutes after intravenous (IV) administration. Analgesia persists for 2.5 to 7 hours.

Morphine is rapidly metabolized by the liver and excreted in the urine primarily as the active metabolite, morphine-6-glucuronide. The half-life of morphine in young adults is about 2 hours; the half-life of morphine-6-glucuronide is somewhat longer. In older patients, the volume of distribution is considerably smaller and initial concentrations of morphine are correspondingly higher.

### **INDICATIONS AND CLINICAL USE**

Morphine Sulfate Injection BP, used **with or without dilution**, is indicated exclusively for the symptomatic relief of moderate to severe pain.

### **CONTRAINDICATIONS**

Hypersensitivity to morphine; respiratory insufficiency or depression; severe CNS depression; attack of bronchial asthma; heart failure secondary to chronic lung disease; cardiac arrhythmias; increased intracranial or cerebrospinal pressure; head injuries, brain tumour; acute alcoholism; delirium tremens; convulsive disorders; after biliary tract surgery; suspected surgical abdomen; surgical anastomosis; concomitantly with MAO inhibitors or within 14 days of such treatment.

## WARNINGS

**Drug Dependence:** As with other opioids, tolerance and physical dependence tend to develop upon repeated administration of morphine and there is potential for abuse of the drug and for development of strong psychological dependence. Morphine should therefore be prescribed and handled with the high degree of caution appropriate to the use of a drug with strong abuse potential. Drug abuse is not, however, a problem in patients with severe pain in which morphine is appropriately indicated.

On the other hand, in the absence of a clear indication for a strong opioid analgesic, drug-seeking behaviour must be suspected and resisted, particularly in individuals with a history of, or propensity for drug abuse. Withdrawal symptoms may occur following abrupt discontinuation of morphine therapy or upon administration of an opioid antagonist. Therefore, patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control.

Morphine should be used with caution and in reduced dosage in patients who are concurrently receiving other opioid analgesics, general anaesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, tricyclic antidepressants and other CNS depressants (including alcohol). Respiratory depression, hypotension and profound sedation or coma may result.

## PRECAUTIONS

### General

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

Morphine should also be used with extreme caution in patients having an acute asthmatic attack, patients with chronic obstructive pulmonary disease or cor pulmonale, patients having a substantially decreased respiratory reserve and patients with preexisting respiratory depression, hypoxia or hypercapnia. In such patients, even usual therapeutic doses of opioids may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.

### Acute Abdominal Condition

The administration of morphine or other opioids may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

### Special Risk Groups

Morphine should be administered with caution, and in reduced dosages, to elderly or debilitated patients, and to patients with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. Morphine should be used with

extreme caution in patients with disorders characterized by hypoxia, since even usual therapeutic doses of opioids may decrease respiratory drive to the point of apnea while simultaneously increasing airway resistance.

### **Hypotensive Effect**

Morphine, like other opioids, may produce orthostatic hypotension in ambulatory patients. The administration of morphine may result in severe hypotension in the postoperative patient, or any individual whose ability to maintain blood pressure has been compromised by a depleted blood volume or the administration of drugs such as the phenothiazines or certain anaesthetics.

### **Supraventricular Tachycardias**

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.

### **Convulsions**

Morphine may exacerbate preexisting 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.

### **Kidney or Liver Dysfunction**

Morphine may have a prolonged duration and cumulative effect in patients with kidney or liver dysfunction. In these patients, analgesia may last for 6, 8 or even up to 24 hours following a standard dose. Continuous infusions should be avoided.

### **In Patients with Shock**

Impaired perfusion may prevent complete absorption following SC or IM injection of morphine. Repeated administration may result in overdosage due to an excessive amount of morphine suddenly being absorbed when circulation is restored.

### **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. CNS depressants, such as other opioids, anaesthetics, sedatives, hypnotics, barbiturates, phenothiazines, chloral hydrate and glutethimide may enhance the depressant effects of morphine. MAO inhibitors (including procarbazine), pyrazolidone antihistamines, beta-blockers and alcohol may also enhance the depressant effect of morphine.

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

### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

Morphine has no known carcinogenic or mutagenic potential. However, no long-term animal study is available to support this observation.

### **Pregnancy**

Animal reproduction studies have not been conducted with morphine. It is not known whether morphine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. On the basis of the historical use of morphine during all stages of pregnancy, there is no known risk of fetal abnormality. Morphine should not be given to a pregnant woman unless it is clearly necessary and when the anticipated benefits outweigh the potential risks to the fetus.

### **Labour and Delivery**

Morphine should not be used in pregnant women prior to labour unless the potential benefits outweigh the possible hazards. The use of morphine in obstetrics may prolong labour. Morphine crosses the placental barrier and may produce respiratory depression in the newborn. For resuscitation and in severe depression, the administration of an opiate antagonist such as naloxone or nalorphine may be required.

### **Nursing Women**

Morphine sulfate appears in the milk of nursing mothers. Breast feeding should be discontinued if morphine is required.

### **Children**

Safety and efficacy of morphine in neonates and children has not been established.

### **Information for the patient**

#### **Occupational Hazards**

Morphine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. Morphine, in combination with other opioid analgesics, general anaesthetics, phenothiazines, tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) has additive depressant effects. The patient should be cautioned accordingly.

### **ADVERSE REACTIONS**

The major hazards of morphine, as with other opioid analgesics, are respiratory depression and, to a lesser degree, circulatory depression; respiratory arrest, shock and cardiac arrest have occurred. The most frequently observed adverse reactions include: lightheadedness, dizziness, sedation, nausea, vomiting, constipation and sweating. These effects seem to be more prominent in ambulatory patients and in those who are not experiencing severe pain. In such individuals, lower doses are advisable. Some adverse reactions in ambulatory patients may be alleviated if the patient lies down.

Rapid IV injection of the drug may result in an increased frequency of opiate-induced adverse effects: severe respiratory depression, apnea, hypotension, peripheral circulatory collapse, chest wall rigidity, cardiac arrest and possible anaphylactoid reactions.

### **Most Common Adverse Effects Requiring Medical Attention**

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

#### **Sedation**

Most patients experience initial drowsiness partly for pharmacokinetic reasons and partly because patients with chronic pain often recuperate from prolonged fatigue after the relief of persistent pain. Drowsiness usually clears in 3 to 5 days and is usually not a reason for concern providing that it is not excessive, or associated with unsteadiness or confusional symptoms.

#### **Nausea and Vomiting**

Nausea and vomiting occur frequently after single doses of opioids or as an early unwanted effect of regular opioid therapy. When instituting prolonged therapy for chronic pain, the routine prescription of an antiemetic should be considered. Patients taking a single dose of 20 mg or more of morphine usually require an antiemetic during early therapy. Small doses of prochlorperazine or haloperidol are the most frequently prescribed antiemetics. Nausea and vomiting tend to lessen in a week or so but may persist due to opioid-induced gastric stasis. In such patients, metoclopramide is often useful.

#### **Constipation**

Practically all patients become constipated while taking opioids on a persistent basis. In some instances, particularly the elderly or bedridden, patients may become impacted. It is essential to caution the patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged opioid therapy. In addition to ample intake of fluid, softeners, laxatives and other appropriate measures should be used as required.

### **Other Adverse Reactions Include the Following**

#### **Central Nervous System**

Euphoria, dysphoria, weakness, headache, insomnia, agitation, tremor, uncoordinated muscle movements, transient hallucinations, disorientation and visual disturbances.

#### **Gastro-intestinal**

Dry mouth, anorexia, constipation, cramps, taste alterations and biliary tract spasm.

#### **Cardiovascular**

Flushing of the face, tachycardia, bradycardia, palpitation, faintness and syncope.

#### **Genitourinary**

Urinary retention or hesitance, antidiuretic effect and reduced libido or potency.

**Allergic**

Pruritus, urticaria, other skin rashes, edema and rarely hemorrhagic urticaria, wheal and flare over the vein with IV injection.

**Endocrine**

A syndrome of inappropriate antidiuretic hormone secretion characterized by hyponatremia secondary to decreased free-water excretion may be prominent (monitoring of electrolytes may be necessary).

**Withdrawal (Abstinence) Syndrome**

Physical dependence with or without psychological dependence tends to occur on chronic administration. An abstinence syndrome may be precipitated when opioid administration is discontinued or opioid antagonists administered. The following withdrawal symptoms may be observed after opioids are discontinued: body aches, diarrhea, gooseflesh, loss of appetite, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, nausea, trouble with sleeping, unusual increase in sweating and yawning, weakness, tachycardia and unexplained fever. With appropriate medical use of opioids and gradual withdrawal from the drug, these symptoms are usually mild.

**Other**

Pain at injection site; local tissue irritation and induration following SC injection, particularly when repeated.

**OVERDOSAGE**

**Symptoms:** Serious morphine overdose is characterized by respiratory depression (reduced respiratory rate and/or tidal volume; Cheyne-Stokes respiration; cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold or clammy skin, and sometimes bradycardia and hypotension. 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, is a specific antidote against respiratory depression due to overdose or resulting from an unusual sensitivity to morphine. Therefore, an appropriate dose of this antagonist should be administered, preferably by the IV route. The usual initial IV 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, IV fluids, vasopressors and other supportive measures should be employed as indicated.

**Note:** In an individual physically dependent on opioids, the administration of the usual dose of opioid antagonist will precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of antagonist administered. The use of an opioid antagonist 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.

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

## **DOSAGE AND ADMINISTRATION**

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 medications given previously or concurrently.

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

Individual dosing requirements vary considerably based on each patient's age, weight, severity of pain, and medical and analgesic history.

Orally administered morphine should be used in preference to parenteral morphine whenever adequate pain control can be achieved by this route. However oral morphine is often inadequate or impractical in the terminally ill patient.

Morphine Sulfate Injection BP should be given regularly around the clock, in most instances every 4 hours. The basis of pain control with morphine sulfate injection should be regular scheduling rather than on an «as required» or PRN opioid order. Patients requiring high doses of morphine usually need to be awakened for medication during the night to prevent morning pain.

Patients over the age of 50 tend to require much lower doses of morphine than in the younger age group. In elderly and debilitated patients and those with impaired respiratory function or significantly decreased renal function, the initial dose should be one half the usual recommended

dose.

For patients who are receiving an alternate opioid, the «oral morphine sulfate equivalent» of the analgesic presently being used should be determined. Having determined the total daily dosage of the present analgesic, Table 1 can be used to calculate the approximate daily morphine sulfate dosage that should provide equivalent analgesia.

**Table 1 - Opioid Analgesics: Approximate Analgesic Equivalences <sup>(1)</sup>**

DRUG	Equivalent Dose (mg) <sup>(2)</sup> (compared to morphine 10 mg IM)		Duration of Action (Hours)
	Parenteral	Oral	
<b>Strong Opioid Agonists:</b>			
Morphine (single dose)	10	60	3 - 4
Morphine (chronic dose)	10	20 - 30 <sup>(3)</sup>	3 - 4
Hydromorphone	1.5 - 2	6 - 7.5	2 - 4
Anileridine	25	75	2 - 3
Levorphanol	2	4	4 - 8
Meperidine <sup>(4)</sup>	75	300	1 - 3
Oxymorphone	1.5	5 (rectal)	3 - 4
Methadone <sup>(5)</sup>			
Heroin	5 - 8	10 - 15	3 - 4
<b>Weak Opioid Agonists:</b>			
Codeine	120	200	3 - 4
Oxycodone	5 - 10	10 - 15	2 - 4
Propoxyphene	50	100	2 - 4
<b>Mixed Agonist-Antagonists <sup>(6)</sup>:</b>			
Pentazocine <sup>(4)</sup>	60	180	3 - 4
Nalbuphine	10		3 - 6
Butorphanol	2		3 - 4

(1) References:

- Cancer Pain: A Monograph on the Management of Cancer Pain, Health and Welfare Canada, 1984.
- Foley, KM, New Engl. J. Med. 313: 84-95, 1985.
- Aronoff, GM and Evans, WO, In: Evaluation and Treatment of Chronic Pain, 2nd Ed., GM Aronoff (Ed.), Williams and Wilkins, Baltimore, pp. 359-368, 1992.
- Cherny, NI and Portenoy, R.K., In: Textbook of Pain, 3rd Ed., PD Wall and R Melzack (Eds.), Churchill Livingstone, London, pp. 1437-1467, 1994.

(2) Most of these data were derived from single dose, acute pain studies and should be considered an approximation for selection of doses when treating chronic pain.

(3) For acute pain, the oral dose of morphine is six times the injectable dose. However, for chronic dosing, this ratio becomes 2 or 3:1, possibly due to the accumulation of active metabolites.

(4) These drugs are not recommended for the management of chronic pain.

(5) Extremely variable equianalgesic dose. Patients should undergo personalized titration starting at an equivalent to 1/10 of the morphine dose.

(6) Mixed agonist-antagonists can precipitate withdrawal in patients on pure opioid agonists.

### Dose Titration

In patients with chronic pain, dose titration is the key to success with morphine therapy. Proper optimization of doses scaled to the relief of the individual's pain should aim at the **regular** administration of the lowest dose of morphine which will maintain the patient free of pain at all times. Dose adjustments should be based on the patient's clinical response. Higher doses may be

justified in some patients to cover periods of physical activity.

### **Morphine Dosage Reduction**

During the first two to three 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 opioid dose should be made. Lower doses or complete discontinuation of the opioid analgesic may become feasible due to a physiological change or the improved mental state of the patient.

### **Morphine Dosage Increase**

Dosage increases should not be made more frequently than every 24 hours, since it will take approximately 4 to 5 morphine half-lives to attain a new steady-state concentration in a patient with normal liver and kidney function.

Following all dosage increases, the patient must be monitored closely for side effects, the most common being sedation, nausea, vomiting, constipation and hypotension.

Opioid agents do not relieve effectively dysesthetic pain, postherpetic neuralgia, stabbing pains, activity-related pain, and some forms of headache. This is not to say that patients with advanced cancer suffering from some of these forms of pain should not be given an adequate trial of opiate analgesics, but it may be necessary to refer such patients at an early time for other forms of pain therapy. Pain without nociception is usually not opioid-responsive.

### **IM, SC or IV Injection**

Morphine Sulfate Injection BP may be administered by IM, SC or IV injection. The usual adult dose should be individualized according to the patient needs.

### **IV and SC Infusion**

Morphine Sulfate Injection BP may be diluted in a parenteral solution: dextrose injection 5% in water or sodium chloride injection 0.9% to the desired concentration (usually 0.1 to 0.5 mg/mL) or used without dilution and administered by IV infusion as required.

Continuous IV or SC infusion is useful in patients who are not able to tolerate oral or rectal routes and require frequent SC, IM or IV injections; have poor pain control with intermittent injections; require high doses of intermittent injections; and in cachectic or thrombocytopenic patients and those with coagulation disorders.

If a patient is presently in pain and was previously poorly controlled on analgesics, start loading dose of 1 to 2 mg/min until pain is relieved. Administer loading dose in 4 to 5 mL of IV fluid slowly over 1 minute. Check vital signs. If diastolic blood pressure decreases more than 10% or if respiration rate is less than 10/min, postpone further dosing until vital signs are acceptable.

If the patient's pain is presently controlled, calculate previous day's 24-hour opioid requirement

(keeping route and analgesic equivalents in mind) and calculate hourly dose.

When morphine is administered by continuous IV or SC infusion for relief of severe chronic pain associated with cancer, the dosage of the drug must be individualized according to the response and tolerance of the patient. Continuous IV infusions of the drug have been initiated at 0.8 to 10 mg/hour in adults and then increased to an effective dosage as necessary; an IV loading dose of 15 mg or more can be administered for initial relief of pain prior to initiating continuous IV infusion of the drug. In adults with severe chronic pain, maintenance dosages usually have ranged from 0.8 to 80 mg/hour infused IV, although higher (e.g. 150 mg/hour) maintenance dosages occasionally have been required. In addition, relatively high dosages (e.g. 275 to 440 mg/hour) occasionally have been infused IV for several hours or days to provide relief of exacerbations of chronic pain in adults previously stabilized on lower dosages or whose dosage had been gradually titrated to relatively high levels; subsequent dosage reductions according to patient response generally were possible.

When morphine is administered by multiple, slow IV injections for patient-controlled analgesia (PCA), dosage is adjusted according to the severity of the pain and response of the patient; the operator's manual for the patient-controlled infusion device should be consulted for directions on administering the drug at the desired rate of infusion. Care must be exercised to avoid overdosage, which could result in respiratory depression, or abrupt cessation of therapy with the drug, which could precipitate opiate withdrawal.

If a patient has low muscle mass, is cachectic or has no accessible peripheral veins, morphine sulfate injection may be given by SC infusion using a portable pump. When switching from IV to SC infusion, use the same dose and monitor the 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 administered. The infusion rate tolerated by patients is variable. Most patients can tolerate 10 mL/hour subcutaneously, and some may tolerate higher infusion rates. When an infusion rate is excessive there may be leakage at the infusion site. This is most likely to occur at lower infusion rates in severely cachectic patients who have minimal SC tissue. In such cases, higher strength solutions or potent narcotics will permit lower infusion rates and minimize the chance of leakage.

Erythema, bruising, induration or tenderness around the injection site may occur. The injection site must be inspected daily for these effects, and for injection or leakage of medication. The needle site should be changed periodically (every 7 to 10 days, although some clinicians prefer every 48 hours).

Morphine Sulfate Injection BP and dilutions of Morphine Sulfate Injection BP in dextrose injection 5 % or sodium chloride injection 0.9% can be stored in portable infusion pump cassettes, syringes, and PVC minibags. Protected from light, they will stay stable for 24 hours at room temperature (between 15 and 30°C) or for 72 hours if kept refrigerated (between 2 and 8°C). Appropriate aseptic techniques must be used in order to minimize contamination of the solution.

**Warning** : As with all parenteral drug products, IV admixtures should be inspected visually for clarity, particulate matter, precipitation and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate or leakage should not be used. Development of a yellow colour in morphine solutions does not indicate toxicity nor loss of potency or efficacy.

**Not for intrathecal or epidural use.**

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

**Morphine Sulfate Injection BP, 10 mg/mL** is available in 1 mL ampoules, boxes of 10.

Each mL of clear, colourless or pale yellow, sterile solution contains: morphine sulfate  $\cdot 5\text{H}_2\text{O}$  10 mg, sodium metabisulfite 0.1%, sodium hydroxide and/or sulfuric acid to adjust pH and water for injection.

**Morphine Sulfate Injection BP, 15 mg/mL** is available in 1 mL ampoules, boxes of 10.

Each mL of clear, colourless or pale yellow, sterile solution contains: morphine sulfate  $\cdot 5\text{H}_2\text{O}$  15 mg, sodium metabisulfite 0.1%, sodium hydroxide and/or sulfuric acid to adjust pH and water for injection.

**Do not use if the solution is darker than pale yellow, is discoloured in any other way or contains a precipitate.**

## **STORAGE AND STABILITY**

Store between 15 and 30°C. Protect from light.