

# PRODUCT MONOGRAPH

## <sup>N</sup>**BAR-morphine SR**

Morphine Sulfate Sustained Release Tablets

15 mg, 30 mg, 60 mg, 100 mg and 200 mg

Mfr. Std.

Opioid Analgesic

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## <sup>N</sup>BAR-morphine SR

(morphine sulfate sustained release tablets)

### PART I: HEALTH PROFESSIONAL INFORMATION

#### SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Sustained Release Tablets / 15, 30, 60, 100 and 200 mg	<p>Tablet core: Cetostearyl alcohol, hydroxyethyl cellulose, lactose (15, 30, and 60 mg only), magnesium stearate and talc.</p> <p>Tablet Coating: hydroxypropyl methylcellulose, polyethylene glycol and titanium dioxide.</p> <p>Additional coating ingredients specific to each strength:</p> <p>15 mg: D&amp;C Yellow No. 10 Aluminum Lake, FD&amp;C Blue No. 1 Aluminum Lake and FD&amp;C Blue No. 2 Aluminum Lake</p> <p>30 mg: D&amp;C Red No. 7 Calcium Lake, FD&amp;C Blue No. 2 Aluminum Lake, FD&amp;C Yellow No. 6 Aluminum Lake and Polysorbate 80</p> <p>60 mg: D&amp;C Yellow No. 10 Aluminum Lake, FD &amp; C Red No. 3 Aluminum Lake and FD&amp;C Yellow No. 6 Aluminum Lake</p> <p>100 mg: FD&amp;C Blue No. 2 Aluminum Lake, iron oxide yellow and iron oxide, black</p> <p>200 mg: FD&amp;C Red No. 3, FD&amp;C Yellow No. 6 Aluminum Lake and Polysorbate 80</p>

#### INDICATIONS AND CLINICAL USE

##### Adults

**BAR-morphine SR** (morphine sulfate sustained release tablets) is indicated for the management of pain severe enough to require daily, continuous, long-term opioid treatment, and:

- that is opioid-responsive; and,
- for which alternative treatment options are inadequate.

**BAR-morphine SR** is 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 (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics**).

**Pediatrics (<18 years of age):**

Individual dosing requirements vary considerably based on each patient's age, weight, severity of pain, medical and analgesic history (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Pediatrics**).

## **CONTRAINDICATIONS**

**BAR-morphine SR** (morphine sulfate sustained release tablets) is contraindicated in:

- Patients who are hypersensitive to the active substance (morphine) or other opioid analgesics, or to any ingredient in the formulation. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.
- Patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction, strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).
- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis).
- Patients with mild, intermittent or short duration pain that can be managed with other pain medications.
- The management of acute pain, including use in outpatient or day surgeries.
- Patients with acute asthma or other obstructive airway, and status asthmaticus.
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood, and cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, brain tumour and/or head injury.
- Patients with cardiac arrhythmias.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).

- Women who are breast-feeding, pregnant, or during labour and delivery.

## WARNINGS AND PRECAUTIONS

### Serious Warnings and Precautions

#### Limitations of Use

Because the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with sustained release opioid formulations, BAR-morphine SR (morphine sulfate sustained release tablets) should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide appropriate management of pain (see DOSAGE AND ADMINISTRATION).

#### Addiction, Abuse, and Misuse

BAR-morphine SR 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 BAR-morphine SR, and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS). BAR-morphine SR should be stored securely to avoid theft or misuse.

#### Life-threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of BAR-morphine SR. Patients should be monitored for respiratory depression, especially during initiation of BAR-morphine SR or following a dose increase. BAR-morphine SR 15, 30, 60 and 100 mg tablets must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving BAR-morphine SR can lead to rapid release and absorption of a potentially fatal dose of morphine (see WARNINGS AND PRECAUTIONS). Only the 200 mg tablet is scored and may be broken in half. The half tablet must also be swallowed intact.

#### Accidental Exposure

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

#### Neonatal Opioid Withdrawal Syndrome

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

#### General

BAR-morphine SR (morphine sulfate sustained release tablets) 15, 30, 60 and 100 mg tablets must be swallowed whole, and must not be cut, chewed, dissolved or crushed. Taking cut, broken, chewed, dissolved or crushed tablets could lead to the rapid release and absorption of a potentially fatal dose of morphine. Only the 200 mg tablet is scored and may be broken in half. The half tablet must also be swallowed intact.

**BAR-morphine SR 100 mg and 200 mg tablets are for use in opioid tolerant patients only (see also DOSAGE AND ADMINISTRATION). These tablet strengths may cause fatal respiratory depression if administered to patients not previously exposed to daily morphine equivalent dosages of 200 mg or more. Care should be taken in the prescribing of these tablet strengths.**

**Patients should be instructed not to give BAR-morphine SR to anyone other than for whom it was prescribed, as such, inappropriate use may have severe medical consequences, including death.**

Patients should be cautioned not to consume alcohol while taking **BAR-morphine SR**, as it may increase the chance of experiencing dangerous side effects.

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

#### **Addiction, Abuse and Misuse**

Like all opioids, **BAR-morphine SR** is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, **BAR-morphine SR** 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 **BAR-morphine SR**, 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.

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

#### **Carcinogenesis and Mutagenesis**

See **TOXICOLOGY** section.

#### **Cardiovascular**

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

### **Dependence/Tolerance**

As with other opioids, tolerance and physical dependence may develop upon repeated administration of **BAR-morphine SR** 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.

### **Use in Drug and Alcohol Addiction**

**BAR-morphine SR** is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission is for the management of pain requiring opioid analgesia.

### **Gastrointestinal Effects**

Morphine (and other morphine-like opioids) has been shown to decrease bowel motility. Morphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions (see **CONTRAINDICATIONS and ADVERSE REACTIONS, Nausea and Vomiting and Constipation**).

### **Neonatal Opioid Withdrawal Syndrome (NOWS)**

Prolonged maternal use of opioid during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

Use of **BAR-morphine SR** is contraindicated in pregnant women (see **CONTRAINDICATIONS**).

### **Neurologic**

**Interactions with Central Nervous System Depressants (including alcohol):** Morphine should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics, general anaesthetics, 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 or coma may result. When such combination therapy is contemplated, a

substantial reduction in the dose of one or both agents should be considered and patients should be carefully monitored. **BAR-morphine SR** should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects (see **DRUG INTERACTIONS**).

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

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

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

### **Peri-Operative Considerations**

**BAR-morphine SR** is not recommended for preoperative use or postoperatively within the first 24 hours.

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

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

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

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

### **Psychomotor Impairment**

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



## **Respiratory**

**Respiratory Depression:** Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO<sub>2</sub>) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

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

To reduce the risk of respiratory depression, proper dosing and titration of **BAR-morphine SR** are essential (see DOSAGE AND ADMINISTRATION). Overestimating the **BAR-morphine SR** dose when converting patients from another opioid product can result in a fatal overdose with the first dose.

**BAR-morphine SR** 100 mg and 200 mg tablets are for use in opioid tolerant patients only (see **DOSAGE AND ADMINISTRATION**). These tablet strengths may cause fatal respiratory depression if administered to patients not previously exposed to daily morphine equivalent dosages of 200 mg or more. Care should be taken in the prescribing of these tablet strengths.

## **Patient Counselling Information**

A patient information sheet should be provided when **BAR-morphine SR** tablets are dispensed to the patient.

Patients receiving **BAR-morphine SR** should be given the following instructions by the physician:

1. Patients should be informed that accidental ingestion or use by individuals (including children) other than the patient for whom it was originally prescribed, may lead to severe, even fatal, consequences.
2. Patients should be advised that **BAR-morphine SR** contains morphine, an opioid pain medicine.
3. Patients should be advised that **BAR-morphine SR** should only be taken as directed. The dose of **BAR-morphine SR** should not be adjusted without consulting with a physician.
4. **BAR-morphine SR** must be swallowed whole (not cut, broken, chewed, dissolved or crushed) due to the risk of fatal morphine overdose. Only the 200 mg tablet is scored and may be broken in half. The half tablet must also be swallowed intact.

5. Patients should be advised to report episodes of pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
6. Patients should not combine **BAR-morphine SR** with alcohol or other central nervous system depressants (sleep aids, tranquilizers) because dangerous additive effects may occur resulting in serious injury or death.
7. Patients should be advised to consult their physician or pharmacist if other medications are being used or will be used with **BAR-morphine SR**.
8. Patients should be advised that if they have been receiving treatment with **BAR-morphine SR** and cessation of therapy is indicated, it may be appropriate to taper the **BAR-morphine SR** dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms.
9. Patients should be advised of the most common adverse reactions that may occur while taking **BAR-morphine SR**: constipation, dizziness, hyperhidrosis, nausea, sedation and vomiting.
10. Patients should be advised that **BAR-morphine SR** may cause drowsiness, dizziness, or light-headedness and may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery). Patients started on **BAR-morphine SR** or patients whose dose has been adjusted should be advised not to drive a car or operate machinery unless they are tolerant to the effects of **BAR-morphine SR**.
11. Patients should be advised not to take **BAR-morphine SR** if they have seizure disorders.
12. Patients should be advised that **BAR-morphine SR** is a potential drug of abuse. They should protect it from theft or misuse.
13. Patients should be advised that **BAR-morphine SR** should never be given to anyone other than the individual for whom it was prescribed.
14. Women of childbearing potential who become or are planning to become pregnant should be advised to consult a physician prior to initiating or continuing therapy with **BAR-morphine SR**. Women who are breast-feeding or pregnant should not use **BAR-morphine SR**.

### **Special Populations**

**Special Risk Groups:** Morphine should be administered with caution to patients with a history of alcohol, seizures, and drug abuse and in a reduced dosage to elderly or debilitated patients, patients with reduced hepatic function or severe renal dysfunction, and to patients with adrenocortical insufficiency (e.g., Addison's disease), biliary tract disorders, hypotension with hypovolaemia, hypothyroidism, prostatic hypertrophy or urethral stricture.

**Pregnant Women:** Animal studies with morphine and other opioids have indicated the possibility of teratogenic effects. In humans, it is not known whether morphine can cause fetal harm when administered during pregnancy or can affect reproductive capacity. Since morphine crosses the placental barrier, **BAR-morphine SR** is contraindicated in patients who are pregnant (see **CONTRAINDICATIONS**).

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

**Labour/Delivery and Nursing Mothers:** In view of the potential for opioids to cross the placental barrier and to be excreted in breast milk, **BAR-morphine SR** is contraindicated during labour or in nursing mothers. Respiratory depression may occur in the infant if opioids are administered during labour.

**Pediatrics (< 18 years of age):** Individual dosing requirements vary considerably based on each patient's age, weight, severity of pain, medical and analgesic history.

An appropriate initial dose for children inadequately controlled on non-opioids or weak opioids is 0.5 - 1 mg/kg **BAR-morphine SR** orally every 12 hours.

**Geriatrics (> 65 years of age):** Dose selection for an elderly patient should be cautious, usually starting at one half the recommended adult dose, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

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

#### **In Vitro Dissolution Studies of Interaction with Alcohol**

Increasing concentrations of alcohol in the dissolution medium resulted in a decrease in the rate of release of morphine from **BAR-morphine SR** tablets. The clinical significance of these findings is unknown.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

Adverse effects of **BAR-morphine SR** (morphine sulfate sustained release tablets) 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 side effects of **BAR-morphine SR** are constipation, dizziness, hyperhidrosis, nausea, sedation and vomiting.

Sedation: Some degree of sedation is experienced by most patients upon initiation of therapy. This may be at least partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Drowsiness usually clears in three to five days and is usually not a reason for concern providing that it is not excessive, or associated with unsteadiness or confusion. If excessive sedation persists, the reason for it must be sought. Some of these are: concomitant sedative medications, hepatic or renal failure, exacerbated respiratory failure, higher doses than tolerated in an older patient, or the patient is actually more severely ill than realized. If it is necessary to reduce the dose, it can be carefully increased again after 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. It can be alleviated if the patient lies down. Because of the slower clearance in patients over 50 years of age, an appropriate dose in this age group may be as low as half or less the usual dose in the younger age group.

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

Constipation: Practically all patients become constipated while taking opioids on a persistent basis. In some patients, particularly the elderly or bedridden, fecal impaction may result. It is essential to caution the patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged opioid therapy. Stool softeners, stimulant laxatives and other appropriate measures should be used as required. As fecal impaction may present as overflow diarrhea, the presence of constipation should be excluded in patients on opioid therapy prior to initiating treatment for diarrhea.

The following adverse effects occur less frequently with **BAR-morphine SR** and opioid analgesics:

**General**: asthenic conditions, drug tolerance, drug withdrawal syndrome, peripheral oedema, weakness

**Cardiovascular**: faintness, palpitations, supraventricular tachycardia

**CNS**: agitation, confusion, convulsions, drug dependence, dysphoria, euphoria, hallucinations, headache, hyperalgesia, hypertonia, insomnia, involuntary muscle contractions, mood altered, paraesthesia, somnolence, syncope, thinking disturbances, vertigo

**Endocrine:** a syndrome of inappropriate antidiuretic hormone secretion characterized by hyponatraemia secondary to decreased free-water excretion may be prominent (monitoring of electrolytes may be necessary)

**Gastrointestinal:** abdominal pain, anorexia, dry mouth, dyspepsia, gastrointestinal disorders, ileus, taste perversion

**Genitourinary:** urinary retention or hesitance

**Hepatic/Biliary/Pancreatic:** biliary tract spasm, increased hepatic enzyme

**Immune:** allergic reaction, anaphylactic reaction, anaphylactoid reaction

**Ophthalmologic:** miosis, visual disturbance

**Respiratory:** bronchospasm, cough decreased, pulmonary oedema, respiratory depression

**Sexual Function/Reproduction:** amenorrhoea, decreased libido or potency, erectile dysfunction

**Skin:** edema, pruritus, other skin rashes, urticaria

**Vascular:** facial flushing, hypotension

**Withdrawal (Abstinence) Syndrome:** Physical dependence with or without psychological dependence tends to occur with 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, nausea, nervousness or restlessness, runny nose, sneezing, stomach cramps, tachycardia, tremors or shivering, trouble with sleeping, unexplained fever, hyperhidrosis, weakness and yawning. With appropriate medical use of opioids and gradual withdrawal from the drug, these symptoms are usually mild.

## DRUG INTERACTIONS

### Overview

**Interactions with Central Nervous System (CNS) Depressants:** **BAR-morphine SR** (morphine sulfate sustained release tablets) should be dosed with caution and started in a reduced dosage in patients who are currently taking other central nervous system depressants (e.g., other opioids, anaesthetics, sedatives, hypnotics, antidepressants, phenothiazines, neuroleptics, antihistamines and antiemetics) glutethimide or gabapentin, and beta-blockers, as they may enhance the CNS-depressant effect (e.g., respiratory depression) of **BAR-morphine SR**. **BAR-morphine SR** should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

### **Drug-Drug Interactions**

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

**Warfarin and Other Coumarin Anticoagulants:** Morphine may increase the anticoagulant activity of coumarin and other anticoagulants.

**Administration with Mixed Activity Agonist/Antagonist Opioids:** Mixed agonist/antagonist opioid analgesics (i.e., pentazocine, nalbuphine, butorphanol, and buprenorphine) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as morphine. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of morphine and/or may precipitate withdrawal symptoms in these patients.

**MAO Inhibitors:** Monoamine oxidase inhibitors intensify the effects of opioid drugs which can cause anxiety, confusion and decreased respiration. **BAR-morphine SR** is contraindicated in patients receiving MAO inhibitors or who have taken them within the previous 14 days (see **CONTRAINDICATIONS**).

### **Drug-Food Interactions**

Food has no significant effect on the extent of absorption of morphine from **BAR-morphine SR**.

### **Drug-Herb Interactions**

Interactions with herbal products have not been established.

### **Drug-Laboratory Interactions**

Interactions with laboratory tests have not been established.

### **Drug-Lifestyle Interaction**

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

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

**BAR-morphine SR (morphine sulfate sustained release tablets) should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, or not tolerated, or would be otherwise inadequate to provide appropriate management of pain.**

**BAR-morphine SR 15, 30, 60 and 100 mg tablets must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving BAR-morphine SR can lead to the rapid release and absorption of a potentially fatal dose of morphine. Only the 200 mg tablet is scored and may be broken in half. The half tablet must also be swallowed intact (see WARNINGS AND PRECAUTIONS).**

Administration and dosing of morphine should be individualized bearing in mind the properties of the drug. In addition, the nature and severity of the pain or pains experienced, and the total condition of the patient must be taken into account. Of special importance is other medication given previously or concurrently.

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

**BAR-morphine SR** should be used with caution within 24 hours pre-operatively and within the first 24 hours post-operatively (see **WARNINGS AND PRECAUTIONS, Peri-operative Considerations**).

**BAR-morphine SR** tablets are not indicated for rectal administration.

The sustained release tablets may be taken with or without food, with a glass of water.

#### **Recommended Dose and Dosage Adjustment**

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

The most frequent initial dose is 30 mg orally every 12 hours.

**Patients over the Age of 50:** Patients over 50 years of age tend to require much lower doses of morphine than in the younger age group.

**Elderly (>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):** Individual dosing requirements vary considerably based on each patient's age, weight, severity of pain, medical and analgesic history.

An appropriate initial dose for children inadequately controlled on non-opioids or weak opioids is 0.5 - 1 mg/kg **BAR-morphine SR** orally every 12 hours.

**Patients Not Receiving Opioids at the Time of Initiation of Morphine Treatment:** The usual initial adult dose of **BAR-morphine SR** for patients who have not previously received opioid analgesics is 30 mg orally, every 12 hours.

**Patients Currently Receiving Opioids:** Patients currently receiving other oral morphine formulations may be transferred to **BAR-morphine SR** at the same total daily morphine dosage, equally divided into two 12 hourly **BAR-morphine SR** doses.

For patients who are receiving an alternate opioid, the “oral morphine sulfate equivalent” of the analgesic presently being used should be determined. Having determined the total daily dosage of the present analgesic, **TABLE 1** can be used to calculate the approximate daily oral morphine sulfate dosage that should provide equivalent analgesia. This total daily oral morphine dosage should then be equally divided into two 12 hourly **BAR-morphine SR** doses. Further dose reductions should be considered due to incomplete cross-tolerance between opioids.

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

**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	10 <sup>3</sup>	60 <sup>3</sup>	3-4
Hydromorphone	1.5	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	-	10-15 <sup>6</sup>	2-4
Propoxyphene	50	100	2-4
<b>Mixed Agonist-Antagonists<sup>7</sup>:</b>			
Pentazocine <sup>4</sup>	60	180	3-4
Nalbuphine	10	-	3-6
Butorphanol	2	-	3-4

1. 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



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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 this data was 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 25-50% 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;335:1124-32.

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. These drugs are not recommended for the management of chronic pain.
5. Extremely variable equianalgesic dose. Patients should undergo individualized titration starting at an equivalent to 1/10 of the morphine dose.
6. In combination with acetaminophen or ASA. For acute pain, single entity oral oxycodone is twice as potent as oral morphine.
7. Mixed agonist-antagonists can precipitate withdrawal in patients on pure opioid agonists.

**Dose Titration:** Dose titration is the key to success with morphine therapy. **Proper optimization of doses scaled to the relief of the individual's pain should aim at regular administration of the lowest dose of sustained release morphine (BAR-morphine SR) which will achieve the overall treatment goal of satisfactory pain relief with acceptable side effects.**

Dose adjustments should be based on the patient's clinical response. Higher doses, at certain times, may be justified in some patients to cover periods of physical activity.

Because of the sustained release properties of **BAR-morphine SR**, dosage adjustments should generally be separated by 48 hours. If dose increments turn out to be required, they should be proportionately greater at the lower dose level (in terms of percentage of previous dose), than when adjusting a higher dose. The usual recommended dose (q12h) increments for **BAR-morphine SR** tablets are 15, 30, 45, 60, 90, 120, 150, 180 and 200 mg. Above the 200 mg/dose (400 mg/day) increments should be by 30-60 mg/dose.

**BAR-morphine SR** is designed to allow 12 hourly dosing. If pain repeatedly occurs at the end of a dose interval, it is generally an indication for a dosage increase, rather than more frequent administration of sustained release morphine (**BAR-morphine SR**). However, where judged necessary for optimization of drug effects, **BAR-morphine SR** tablets may be administered q8h. More frequent (than q8h) administration is not recommended.

**Adjustment or Reduction of Dosage:** Following successful relief of severe pain, periodic attempts to reduce the opioid dose should be made. Smaller doses or complete discontinuation may become feasible due to a change in the patient's condition or improved mental state. If treatment discontinuation is required, the dose of opioid may be decreased as follows: one-half of the previous daily dose given q12h for the first two days, followed thereafter by a 25% reduction every two days.

Opioid analgesics may only be partially effective in relieving dysesthetic pain, postherpetic neuralgia, stabbing pains, activity-related pain and some forms of headache. That is not to say that patients with advanced cancer suffering from some of these forms of pain should not be given an adequate trial of opioid analgesics, but it may be necessary to refer such patients at an early time to other forms of pain therapy.

### **Management of Patients Requiring Rescue Medication**

Some patients taking **BAR-morphine SR** according to a fixed time schedule may require immediate-release analgesics as "rescue" medication for pain. Selection of rescue medication should be based on individual patient conditions. **BAR-morphine SR** is a sustained release formulation and therefore is not intended for use as rescue medication.

### **Missed Dose**

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

### **Disposal**

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

Unused or expired **BAR-morphine SR** should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets. **BAR-morphine SR** should not be shared with others and steps should be taken to protect it from theft or misuse. The patient should speak to their pharmacist about temporary storage options, if required, until the medication can be returned to the pharmacy for safe disposal.

**BAR-morphine SR** should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended.

## **OVERDOSAGE**

For management of a suspected drug overdose, contact your regional Poison Control Centre.
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**Symptoms:** Serious overdose with morphine may be characterized by respiratory depression (respiratory rate and/or tidal volume; Cheyne-Stokes respiration; cyanosis), dizziness, confusion, extreme somnolence progressing to stupor or coma, miosis, rhabdomyolysis progressing to renal failure, hypotonia, cold and clammy skin, and sometimes bradycardia and hypotension. Pinpoint pupils are a sign of narcotic overdose, but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of morphine overdose. Severe overdose may result in apnea, circulatory collapse, cardiac arrest and death.

**Treatment:** Primary attention should be given to the establishment of adequate respiratory exchange through the provision of a patent airway and controlled or assisted ventilation. The

opioid antagonist naloxone hydrochloride is a specific antidote against respiratory depression due to overdosage or as a result of unusual sensitivity to morphine. An appropriate dose of one of the antagonists should therefore be administered, preferably by the intravenous route. The usual initial intravenous adult dose of naloxone is 0.4 mg or higher. Concomitant efforts at respiratory resuscitation should be carried out. Since the duration of action of morphine, particularly sustained release formulations, may exceed that of the antagonist, the patient should be under continued surveillance and doses of the antagonist should be repeated as needed to maintain adequate respiration.

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

In an individual physically dependent on opioids, the administration of the usual dose of opioid antagonist will precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of antagonist administered. The use of opioid antagonists in such individuals should be avoided if possible. If an opioid antagonist must be used to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care by using dosage titration, commencing with 10% to 20% of the usual recommended initial dose.

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

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

Morphine is an opioid analgesic which exerts an agonist effect at specific, saturable opioid receptors in the CNS and other tissues. In man, morphine produces a variety of effects including analgesia, constipation from decreased gastrointestinal motility, suppression of the cough reflex, respiratory depression from reduced responsiveness of the respiratory center to CO<sub>2</sub>, nausea and vomiting via stimulation of the CTZ, changes in mood including euphoria and dysphoria, sedation, mental clouding, and alterations of the endocrine and autonomic nervous systems.

### **Pharmacodynamics**

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

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

**Central Nervous System:** In man, the principal pharmacological actions of morphine are in the CNS; analgesia, drowsiness, mood changes, mental clouding, respiratory depression, nausea or emesis and miosis.

Morphine produces respiratory depression by direct action on brain stem respiratory centres. It depresses the cough reflex by direct effect on the cough centre in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

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

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

**Gastrointestinal Tract and Other Smooth Muscle:** Morphine causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm resulting in constipation.

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

#### **Concentration – Efficacy Relationships**

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

#### **Concentration – Adverse Reaction Relationship**

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

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

#### **Pharmacokinetics**

With repeated regular dosing, oral morphine is about 1/3 as potent as when given by intramuscular injection. The relationship between mean plasma concentration and dose has been shown to be linear over a dosage range of 60 - 600 mg/day in the case of the **BAR-morphine SR** tablets.

**Absorption:** Morphine is readily absorbed when given orally, rectally or by subcutaneous or intramuscular injection. Due to "first-pass" metabolism in the liver, the effect of an oral dose is less than after parenteral administration.

When administered every 12 hours, the sustained-release tablets provide equivalent analgesia to morphine oral solution given 4 hourly. In most cases, administration on a twelve hourly schedule produces equivalent pain control to eight hourly administration.

**Distribution:** Following absorption, approximately 30% to 35% of morphine is reversibly bound to plasma proteins. Free morphine readily leaves the circulation and is concentrated in the liver, kidney, lung, spleen and, to a lesser extent, skeletal muscle. In adults, only small quantities of morphine pass the blood brain barrier.

**Metabolism:** Conjugated morphine excreted in the bile may be hydrolyzed and reabsorbed from the large bowel. Conjugation with glucuronic acid is the major metabolic pathway for morphine. The major metabolites are morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). Minor metabolites include normorphine, morphine-3-6 diglucuronide and morphine-3-ethereal sulfate.

The mean elimination half-life of morphine is 2 to 3 hours with great inter-patient variability.

**Excretion:** The major route of elimination is via the kidney. Morphine is primarily excreted in the urine as morphine-3-glucuronide. About 7% to 10% of a dose of morphine is excreted in the feces via the bile.

### **Special Populations and Conditions**

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

**Geriatrics:** Dose selection for an elderly patient should be cautious, usually starting at one half the recommended adult dose, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

### **STORAGE AND STABILITY**

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

### **SPECIAL HANDLING INSTRUCTIONS**

Not applicable.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

### Dosage Forms

**BAR-morphine SR** (morphine sulfate sustained release tablets) 15 mg are round, green, film-coated, bi-convex tablets imprinted with 15 mg on one side and PF on the other.

**BAR-morphine SR** (morphine sulfate sustained release tablets) 30 mg are round, violet, film-coated, bi-convex tablets imprinted with 30 mg on one side and PF on the other.

**BAR-morphine SR** (morphine sulfate sustained release tablets) 60 mg are round, orange, film-coated, bi-convex tablets imprinted with 60 mg on one side and PF on the other.

**BAR-morphine SR** (morphine sulfate sustained release tablets) 100 mg are round, grey, film-coated, bi-convex tablets imprinted with 100 mg on one side and PF on the other.

**BAR-morphine SR** (morphine sulfate sustained release tablets) 200 mg are a capsule-shaped, red, film-coated, bi-convex tablets, imprinted with 200 mg on one side and PF on the other. The 200 mg tablet is scored and may be broken in half.

### Composition

**BAR-morphine SR** 15 mg, 30 mg, 60 mg, 100 mg and 200 mg contain the following non-medicinal ingredients:

**Tablet core:** cetostearyl alcohol, hydroxyethyl cellulose, lactose (15, 30, 60 mg only), magnesium stearate and talc.

**Tablet coating:** hydroxypropyl methylcellulose, polyethylene glycol and titanium dioxide. Additional coating ingredients specific to each strength are as follows:

15 mg: D&C Yellow No. 10 Aluminum Lake  
FD&C Blue No. 1 Aluminum Lake  
FD&C Blue No. 2 Aluminum Lake

30 mg: D&C Red No. 7 Calcium Lake  
FD&C Blue No. 2 Aluminum Lake  
FD&C Yellow No. 6 Aluminum Lake  
Polysorbate 80

60 mg: D&C Yellow No. 10 Aluminum Lake  
FD & C Red No. 3 Aluminum Lake  
FD&C Yellow No. 6 Aluminum Lake

100 mg: FD&C Blue No. 2 Aluminum Lake  
Iron oxide, yellow  
Iron oxide, black

200 mg: FD&C Red No. 3  
FD&C Yellow No. 6 Aluminum Lake  
Polysorbate 80

**Packaging**

**BAR-morphine SR** 15, 30, 60, 100 and 200 mg tablets are supplied in opaque, plastic bottles containing 60 tablets.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

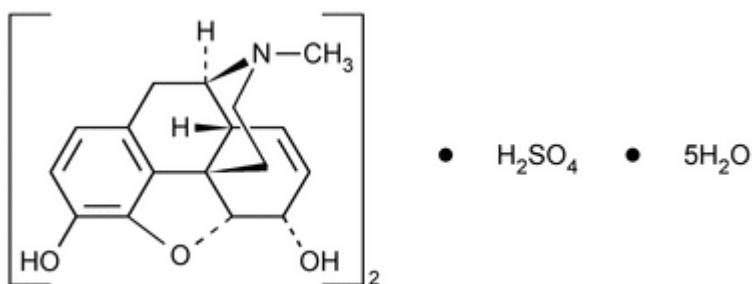
**Proper name:** morphine sulfate

**Chemical name:** 7,8-didehydro-4,5  $\alpha$ -epoxy-17-methyl-morphinan-3, 6 $\alpha$ -diol sulfate (2:1) (salt) pentahydrate

**Molecular formula:** (C<sub>17</sub>H<sub>19</sub>NO<sub>3</sub>) - H<sub>2</sub>SO<sub>4</sub>

**Molecular mass:** 758.8 (pentahydrate)  
668.8 (anhydrous)

**Figure 1: Structural Formula – morphine sulfate**



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

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

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

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

### DETAILED PHARMACOLOGY

Morphine is readily absorbed from the gastrointestinal tract, nasal mucosa, lung, and after subcutaneous or intramuscular injection. Due to first-pass metabolism the effect of an oral dose is less than that of the same dose given parenterally. The parenteral to oral morphine potency ratio has been reported to range from 1:6 to 1:2. In general, the greatest difference between parenteral and oral potency is seen in acute studies. With chronic dosing, oral morphine is about 1/3 as potent as when given by injection.



Absorption of the sustained-release tablets is equivalent to that of immediate-release tablet or liquid formulations and is not significantly affected by administration with food. At steady-state, the sustained-release tablets produce peak morphine levels approximately 4 to 5 hours post-dose and therapeutic levels persist for a 12 hour period.

In a steady-state crossover study utilizing **BAR-morphine SR** tablets every 12 hours versus morphine sulfate solution every 4 hours in cancer patients, there was no significant difference between formulations in respect to the extent of absorption of morphine. The mean maximum concentration following **BAR-morphine SR** was approximately 15% higher than with morphine oral solution and was achieved at a mean of 3.4 hours post-dose compared with 1.2 hours for the solution. There was a linear relationship between mean plasma morphine concentration and dose over the range of 60-600 mg/day.

## **TOXICOLOGY**

### **Animal**

<u>Acute:</u>	<u>Oral LD<sub>50</sub></u>
Mice	650 mg/kg
Rats	460 mg/kg
Guinea Pigs	1000 mg/kg

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

### **Human**

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

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

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**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE  
PATIENT MEDICATION INFORMATION**

**<sup>N</sup> BAR-morphine SR**

**Morphine Sulfate Sustained Release Tablets**

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

**Serious Warnings and Precautions**

- **Even if you take BAR-morphine SR as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to overdose and death. To understand your risk of opioid addiction, abuse, and misuse you should speak to your prescriber (e.g., doctor).**
- **Life-threatening breathing problems can happen while taking BAR-morphine SR, especially if not taken as directed.**
- **Never give anyone your BAR-morphine SR. They could die from taking it. If a person has not been prescribed BAR-morphine SR, taking even one dose can cause a fatal overdose. This is especially true for children.**
- **Babies born to mothers who have taken BAR-morphine SR (for short or long periods, in small or large doses) during their pregnancy can suffer life-threatening withdrawal symptoms. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has breathing changes (weak, difficult or fast), is unusually difficult to comfort, has tremors (shakiness), or has increased stools, sneezing, yawning, vomiting, or fever, seek immediate medical help for your baby.**

**What is BAR-morphine SR used for?**

**BAR-morphine SR** is used for the long-term management of pain, when:

- the pain is severe enough to require daily, around-the-clock pain medication
- the doctor determines that other treatment options are not able to effectively manage your pain

**BAR-morphine SR** is NOT used (“as needed”) to treat pain that you only have once in a while.

## How does BAR-morphine SR work?

**BAR-morphine SR** is an oral sustained release tablet that slowly releases morphine over a 12 hour period. Morphine is a pain medication belonging to the class of medicines known as opioids. It relieves pain by acting on specific nerve cells of the spinal cord and brain.

## What are the ingredients in BAR-morphine SR?

Medicinal ingredient: morphine sulfate

Non-medicinal ingredients: cetostearyl alcohol, hydroxyethyl cellulose, hydroxypropyl methylcellulose, lactose (15, 30, 60 mg only), magnesium stearate, polyethylene glycol, talc and dioxide. The tablet coatings contain the following additional ingredients:

15 mg - D&C Yellow No. 10 Aluminum Lake  
FD&C Blue No. 1 Aluminum Lake  
FD&C Blue No. 2 Aluminum Lake

30 mg - D&C Red No. 7 Calcium Lake  
FD&C Blue No. 2 Aluminum Lake  
FD&C Yellow No. 6 Aluminum Lake  
Polysorbate 80

60 mg - D&C Yellow No. 10 Aluminum Lake  
FD&C Red No. 3 Aluminum Lake  
FD&C Yellow No. 6 Aluminum Lake

100 mg - FD&C Blue No. 2 Aluminum Lake  
Iron oxide, yellow  
Iron oxide, black

200 mg - FD&C Red No. 3  
FD&C Yellow No. 6 Aluminum Lake  
Polysorbate 80

## BAR-morphine SR comes in the following dosage forms:

Sustained Release Tablets: 15 mg, 30 mg, 60 mg, 100 mg and 200 mg

## Do not use BAR-morphine SR if:

- you are allergic to morphine, other opioids, or any of the other ingredients of **BAR-morphine SR**
- your pain can be controlled by the occasional use of pain medications, including those available without a prescription
- you have severe asthma, trouble breathing, or any heart problems, including arrhythmias
- you have bowel blockage or narrowing of the stomach or intestines (e.g., paralytic ileus)
- you have severe pain in your abdomen
- you have a head injury or other risks for seizures

- you suffer from alcoholism
- you are pregnant or plan to become pregnant, breast-feeding, or in labour

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take **BAR-morphine SR**. 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 disease
- have low blood pressure
- are going to have, or recently had, a planned surgery
- have problems with your thyroid, adrenal or prostate gland
- have past or current depression
- suffer from chronic or severe constipation

**Other warnings you should know about:**

There are important differences between physical dependence and addiction, and each is a reason for close medical supervision and honest discussions with your doctor. If you have questions or concerns about abuse, addiction or physical dependence, please tell your doctor.

**Driving and using machines:** Before you perform tasks which may require special attention, wait until you know how you respond to **BAR-morphine SR**. Drowsiness, dizziness, or lightheadedness, can especially occur after the first dose and when the dose is increased.

**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 **BAR-morphine SR**:**

- alcohol, including prescription and non-prescription medications containing alcohol. Do not drink alcohol while taking **BAR-morphine SR**. This can lead to drowsiness, depressed breathing, serious side effects or a fatal overdose
- other sedative drugs which may enhance the drowsiness caused by **BAR-morphine SR**
- other opioid analgesics (for pain)
- general anesthetics (used during surgery)
- drugs used to help you sleep or to reduce anxiety
- antidepressants (for depression and mood disorders). Do not take **BAR-morphine SR** with monoamine oxidase (MAO) inhibitors or if you have taken MAO inhibitors in the last 14 days before treatment with **BAR-morphine SR**
- drugs used to treat serious mental or emotional disorders, such as schizophrenia
- antihistamines (for allergies)
- anti-emetics (for prevention of vomiting)
- drugs used to treat muscle spasms and back pain
- some heart medication (beta blockers)



- warfarin and other coumarin anticoagulants (for prevention/treatment of blood clots)

### **How to take BAR-morphine SR:**

**BAR-morphine SR** tablets are designed to work properly over 12 hours when swallowed whole.

**BAR-morphine SR 100 mg and 200 mg tablets are for use in “opioid tolerant” patients only. Your doctor will tell you when you are “opioid tolerant” to a certain dose of BAR-morphine SR.**

**Swallow whole. Do not cut, break, chew, dissolve or crush since this can cause the release of the entire 12-hour dose of morphine, which can seriously harm you. Only the 200 mg tablet is scored and may be broken in half. The half tablet must also be swallowed intact.**

**BAR-morphine SR** tablets must be taken regularly, every 12 hours (with or without food and with sufficient fluid, e.g., 4 to 6 oz. of water), to treat pain.

### **Usual Adult Starting Dose:**

Dosage is individualized. Be sure to follow your doctor’s dosing instructions exactly. Do not increase or decrease your dose without consulting your doctor.

Review your pain regularly with your doctor to determine if you still need **BAR-morphine SR**. Be sure to use **BAR-morphine SR** only for the condition for which it was prescribed.

Should your pain increase or any other complaint as a result of taking **BAR-morphine SR**, tell your doctor immediately.

### **Overdose:**

Signs of overdose may include abnormally slow or weak breathing, dizziness, confusion or extreme drowsiness.

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

### **Missed Dose:**

It is important that you do not miss any doses. If you miss a dose, take your next dose at your usual time. You should always try to get back on track with your regular dosing schedule (e.g., 8 o’clock in the morning and 8 o’clock in the evening). If you miss several doses in succession, talk to your doctor before restarting your medication.

### **Discontinuation:**

You should not stop taking **BAR-morphine SR** all at once if you have been taking it for more

than a few days.

Consult your doctor for instructions on how to stop this medicine slowly to avoid uncomfortable symptoms such as body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, unexplained fever, weakness and yawning.

### **Refilling Prescriptions for BAR-morphine SR:**

A new written prescription is required from your doctor each time you need more **BAR-morphine SR**. Therefore, it is important that you contact your doctor before your current supply runs out.

### **What are possible side effects from using BAR-morphine SR?**

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

Side effects may include:

- Constipation
- Dizziness
- Drowsiness
- Dry mouth
- Headache
- Itching
- Lack of muscle strength
- Nausea and/or vomiting
- Sweating

Talk with your doctor or pharmacist about ways to prevent constipation when you start using **BAR-morphine SR**.

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	
<b>Rare</b>	<b>Overdose:</b> hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone cold and clammy skin.			√
	<b>Respiratory Depression:</b> Slow, shallow or weak breathing.			√
	<b>Allergic Reaction:</b> rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
	<b>Bowel Blockage (impaction):</b> abdominal pain, severe constipation, nausea			√
	<b>Withdrawal:</b> nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating.		√	
	<b>Fast, Slow or Irregular Heartbeat:</b> heart palpitations.		√	
	<b>Low Blood Pressure:</b> dizziness, fainting, light-headedness.	√		

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

### **Reporting Side Effects**

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

#### **3 ways to report:**

- Online at [MedEffect](#);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program  
Health Canada, Postal Locator 0701E  
Ottawa, ON  
K1A 0K9Postage paid labels and the Consumer Side Effect Reporting Form are available at [MedEffect](#).

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

### **Storage:**

**Keep unused or expired BAR-morphine SR in a secure place to prevent theft, misuse or accidental exposure.**

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

**Keep BAR-morphine SR 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 BAR-morphine SR, get emergency help right away.**

### **Disposal:**

**BAR-morphine SR should never be thrown into household trash, where children and pets may find it.** It should be returned to a pharmacy for proper disposal.

### **If you want more information about BAR-morphine SR:**

- 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](#); or by calling the manufacturer at 1-800-387-4501

This leaflet was prepared by Bard Pharmaceuticals (1990) Inc.

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