

**Product Monograph**  
**Including Patient Medication Information**

**<sup>N</sup>STATEX<sup>®</sup>**

Morphine sulfate tablets

For Oral use

5 mg and 10 mg of Morphine sulfate

British Pharmacopoeia (BP)

Opioid Analgesic

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Quebec, Canada

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## Recent Major Label Changes

7 Warnings and Precautions, Hepatic/biliary/pancreatic	2025-08
7 Warnings and Precautions, Respiratory	2025-08
7 Warnings and Precautions, Skin	2025-08

## Table of Contents

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

<b>Recent Major Label Changes</b> .....	<b>2</b>
<b>Table of Contents</b> .....	<b>2</b>
<b>Part 1: Health Professional Information</b> .....	<b>4</b>
<b>1. Indications</b> .....	<b>4</b>
1.1. Pediatrics.....	4
1.2. Geriatrics.....	4
<b>2. Contraindications</b> .....	<b>4</b>
<b>3. Serious Warnings and Precautions Box</b> .....	<b>4</b>
<b>4. Dosage and Administration</b> .....	<b>6</b>
4.1. Dosing Considerations .....	6
4.2. Recommended Dose and Dosage Adjustment .....	6
4.4. Administration .....	8
4.5. Missed Dose.....	8
<b>5. Overdose</b> .....	<b>8</b>
<b>6. Dosage Forms, Strengths, Composition, and Packaging</b> .....	<b>9</b>
<b>7. Warnings and Precautions</b> .....	<b>9</b>
General.....	10
Cardiovascular.....	10
Dependence, Tolerance and/or Abuse Liability.....	10
Driving and Operating Machinery.....	11
Endocrine and Metabolism.....	11
Gastrointestinal.....	11
Hepatic/biliary/pancreatic.....	12
Neurologic.....	12
Perioperative considerations.....	13

Renal .....	14
Reproductive health.....	14
Respiratory.....	14
Skin.....	15
7.1. Special Populations .....	15
7.1.1. Pregnant Women .....	15
7.1.2. Breastfeeding .....	16
7.1.3. Pediatrics .....	16
7.1.4. Geriatrics .....	16
<b>8. Adverse Reactions .....</b>	<b>16</b>
8.1. Adverse Reaction Overview .....	16
8.5. Post-Market Adverse Reactions.....	17
<b>9. Drug Interactions .....</b>	<b>18</b>
9.1. Serious Drug Interactions .....	18
9.2. Drug Interactions Overview .....	18
9.3. Drug-Behaviour Interactions.....	18
9.4. Drug-Drug Interactions .....	18
9.5. Drug-Food Interactions .....	19
9.6. Drug-Herb Interactions .....	19
9.7. Drug-Laboratory Test Interactions.....	19
<b>10. Clinical Pharmacology .....</b>	<b>19</b>
10.1. Mechanism of Action.....	19
10.2. Pharmacodynamics .....	20
10.3. Pharmacokinetics .....	20
<b>11. Storage, Stability, and Disposal .....</b>	<b>21</b>
<b>Part 2: Scientific Information .....</b>	<b>22</b>
<b>13. Pharmaceutical Information .....</b>	<b>22</b>
<b>14. Clinical Trials.....</b>	<b>22</b>
<b>15. Microbiology .....</b>	<b>22</b>
<b>16. Non-Clinical Toxicology .....</b>	<b>22</b>
<b>Patient Medication Information .....</b>	<b>23</b>

## Part 1: Health Professional Information

### 1. Indications

STATEX (morphine sulfate tablets) is indicated in adult patients for:

- the symptomatic relief of severe chronic pain.

STATEX is not indicated as an as-needed (prn) analgesic.

#### 1.1. Pediatrics

**Pediatrics (< 18 years of age):** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

#### 1.2. Geriatrics

**Geriatrics (> 65 years of age):** In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or other drug therapy (see [4.2 Recommended Dose and Dosage Adjustment, Geriatrics](#)).

### 2. Contraindications

STATEX is contraindicated in patients:

- who are hypersensitive to the active substance morphine sulfate or other opioid analgesics, to any ingredient in the formulation, including any non-medicinal ingredient, or to a component of the container. For a complete listing, see [6 Dosage Forms, Strengths, Composition, and Packaging](#).
- with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction or strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).
- with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis).
- with mild pain that can be managed with other pain medications.
- with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus.
- with acute respiratory depression, elevated carbon dioxide levels in the blood and cor pulmonale.
- with acute alcoholism, delirium tremens, and convulsive disorders.
- with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.
- taking monoamine oxidase inhibitors (MAOIs) (or within 14 days of such therapy).
- with cardiac arrhythmias.
- with emotional instability and/or suicidal ideation.

### 3. Serious Warnings and Precautions Box

#### Limitations of use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the risks of overdose and death with immediate release opioid formulations, STATEX (morphine sulfate tablets) should only be used in patients for whom alternative treatment options

(e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide appropriate management of pain (see [4.1 Dosing Considerations](#)).

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

STATEX 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 STATEX, and all patients should be monitored regularly for the development of these behaviours or conditions (see [7 Warnings and Precautions, General, Abuse and Misuse](#)). STATEX should be stored securely to avoid theft or misuse.

### **Life-threatening Respiratory Depression: OVERDOSE**

Serious, life-threatening, or fatal respiratory depression may occur with use of STATEX. Infants exposed *in-utero* or through breast milk are at risk of life-threatening respiratory depression upon delivery or when nursed. Patients should be monitored for respiratory depression, especially during initiation of STATEX or following a dose increase.

STATEX tablets must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving STATEX can lead to dangerous adverse events including death (see [7 Warnings and Precautions, General, Abuse and Misuse](#)). Further, instruct patients of the hazards related to taking opioids including fatal overdose.

### **Accidental Exposure**

Accidental ingestion of even one dose of STATEX, especially by children, can result in a fatal overdose of morphine sulfate (see [11 Storage, Stability, and Disposal](#) for instructions on proper disposal).

### **Neonatal Opioid Withdrawal Syndrome**

Prolonged maternal use of STATEX during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see [7 Warnings and Precautions, Dependence, Tolerance and/or Abuse Liability, Neonatal Opioid Withdrawal Syndrome](#)).

### **Interaction with Alcohol**

The co-ingestion of alcohol with STATEX should be avoided as it may result in dangerous additive effects, causing serious injury or death (see [7 Warnings and Precautions, Neurologic, Interactions with Central Nervous System Depressants \(Including Benzodiazepines and Alcohol\)](#); [9.4 Drug-Drug Interactions](#)).

### **Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants**

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see [7 Warnings and Precautions, Neurologic, Interactions with Central Nervous System Depressants \(Including Benzodiazepines and Alcohol\)](#); [9.4 Drug-Drug Interaction](#)).

- Reserve concomitant prescribing of STATEX and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

## 4. Dosage and Administration

### 4.1. Dosing Considerations

- STATEX (morphine sulfate tablets) should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics).
- STATEX tablets must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving STATEX can lead to dangerous adverse events including death (see [7 Warnings and Precautions](#)).
- For opioid products used in acute pain, a maximum of 7 days treatment is recommended at the lowest dose that provides adequate relief.
- All doses of opioids carry an inherent risk of fatal or non-fatal adverse events. This risk is increased with higher doses. For the management of chronic non-cancer, non-palliative pain, it is recommended that the daily dose of STATEX not exceed 90 mg (90 morphine milligram equivalent). Each patient should be assessed for their risk prior to prescribing STATEX, as the likelihood of experiencing serious adverse events can depend upon the type of opioid, duration of treatment, level of pain as well as the patient's own level of tolerance. In addition, the level of pain should be assessed routinely to confirm the most appropriate dose and the need for further use of STATEX (see [4.2 Dosage and Administration, Recommended Dose and Dosage Adjustment, Adjustment or Reduction of Dosage](#)).
- STATEX should be used with caution within 12 hours pre-operatively and within the first 12-24 hours post-operatively (see [7 Warnings and Precautions, Perioperative considerations](#)).
- STATEX tablets are not indicated for rectal administration.

### 4.2. Recommended Dose and Dosage Adjustment

#### Recommended Dose

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

**Patients Not Receiving Opioids at the Time of Initiation of Morphine Sulfate Treatment:** The usual initial adult dose is 10-30 mg q4h around the clock.

Because of the slower clearance in patients over 50 years of age, in elderly and debilitated patients, and in those with impaired respiratory function or significantly decrease renal function, an appropriate dose in those patient groups may be as low as half or less than the usual dose in the younger age group.

**Patients Currently Receiving Opioids:** 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. Conversion ratios for opioids are subject to variations in kinetics governed by genetics and other factors. When switching from one opioid to another, consider reducing the calculated dose by 25-50% to minimize the risk of overdose. Subsequently, up-titrate the dose, as required, to reach the appropriate maintenance dose. It is usually appropriate to treat a patient with only one opioid at a time.

**Table 1 – Opioid Conversion Table<sup>a</sup>**

Opioids	To convert to oral morphine equivalent	To convert from oral morphine multiply by	Daily 90 mg MED <sup>b</sup>
Morphine	1	1	90 mg/d
Codeine	0.15	6.67	600 mg/d
Hydromorphone	5	0.2	18 mg/d
Oxycodone	1.5	0.667	60 mg/d
Tapentadol	0.3-0.4	2.5-3.33	300 mg/d
Tramadol	0.1-0.2	6	***
Methadone	Morphine dose equivalence is not reliably established		

\*\*\* The maximum recommended daily dose of tramadol is 300 mg - 400 mg depending on the formulation.

a. Adapted from the 2017 Canadian guideline for opioids for chronic non-cancer pain. McMaster University; 2017

b. MED: Morphine Equivalent Dose

**Pediatrics (<18 years old of age):** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

**Geriatrics (>65 years of age):** Respiratory depression has occurred in the elderly following administration of large initial doses of opioids to patients who were not opioid-tolerant or when opioids were co-administered with other agents that can depress respiration. STATEX should be initiated at a low dose and slowly titrated to effect (see [7.1.4 Geriatrics](#); [10.3 Pharmacokinetics, Special populations and conditions, Geriatrics](#)).

**Patients with Hepatic Impairment:** Morphine should be administered with caution and in a reduced dosage in patient with hepatic impairment.

**Patients with Renal Impairment:** Morphine should be administered with caution and in a reduced dosage in patient with renal impairment.

**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. STATEX can be safely used concomitantly with usual doses of other non-opioid analgesics.

### Dosage Adjustment

**Dose Titration:** Dose titration is the key to success with opioid analgesic therapy. Proper optimization of doses scaled to the relief of the individual's pain should aim at administration of the lowest dose which will achieve the overall treatment goal of satisfactory pain relief with acceptable side effects.

Dosage adjustments should be based on the patient's clinical response.

Higher doses may be justified in some patients to cover periods of physical activity.

**Adjustment or Reduction of Dosage:** During the first two or three days of effective pain relief, the patient may exhibit drowsiness or sleep for prolonged periods. 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 at least three days before reduction, provided the sedation is not excessive or associated with unsteadiness and confusional symptoms, and respiratory activity and other vital signs are adequate. If excessive sedation persists, the reason(s) for such an effect must be

sought. Some of these are: concomitant sedative medications, hepatic or renal failure, exacerbated respiratory failure, higher doses than tolerated by 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.

Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including STATEX. Withdrawal (abstinence) symptoms may occur following abrupt discontinuation of therapy. These symptoms may include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning.

Following successful relief of severe pain, periodic attempts to reduce the opioid dose should be made. Smaller doses or complete discontinuation of the opioid analgesic may be feasible due to changes in the patient's condition or improved mental state.

Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal for the drug, these symptoms are usually mild (see [7 Warnings and Precautions](#)). Tapering should be individualized and carried out under medical supervision.

Patient should be informed that reducing and/or discontinuing opioids decreases their tolerance to these drugs. If treatment needs to be re-initiated, the patient must start at the lowest dose and titrate up to avoid overdose.

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

#### **4.4. Administration**

STATEX may be taken with or without food.

STATEX tablets may be taken with a glass of water.

#### **4.5. Missed Dose**

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

### **5. Overdose**

**Symptoms:** Serious morphine overdosage is characterized by respiratory depression (reduced respiratory rate and /or tidal volume: Cheyne-Stokes respiration; cyanosis), extreme somnolence progressing to stupor or coma, aspiration pneumonia, hypotonia, dizziness, confusion, miosis, rhabdomyolysis progression to renal failure, cold or clammy skin, toxic leukoencephalopathy, delayed post-hypoxic leukoencephalopathy, and sometimes hypotension, bradycardia and hypoglycemia. 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 over-dosage 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 overdose or as a result of unusual sensitivity to morphine. An appropriate dose of the antagonist should therefore be administered, preferably by the intravenous route. The usual initial i.v. adult dose of naloxone is 0.4 mg or higher. Concomitant efforts at respiratory resuscitation should be carried out. Since the duration of action of morphine may exceed that of the antagonist, the patient should be under continued surveillance and doses of the antagonist should be repeated as needed to maintain adequate respiration.

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

In an individual physically dependent on opioids, the administration of the usual dose of opioid antagonists 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.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

## 6. Dosage Forms, Strengths, Composition, and Packaging

Table 2 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form/ Strength/Composition	Non-Medicinal Ingredients
Oral	Tablet 5 mg and 10 mg Morphine sulfate	FD&C Blue No.1 Lake 13%, lactose monohydrate, lake blend yellow 17% LB-111 (5 mg), magnesium stearate, microcrystalline cellulose

Statex Oral Tablets: available as 5 mg (green) and 10 mg (blue), scored on one side, identified with a shield logo on the other side tablets. The non-medicinal ingredients are FD&C Blue No.1 Lake 13%, lactose monohydrate, lake blend yellow 17% (5 mg), magnesium stearate, microcrystalline cellulose.

### Packaging:

Statex oral tablets are available in bottles of 100.

## 7. Warnings and Precautions

See [3 Serious Warnings and Precautions Box](#).

## General

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

STATEX should only be prescribed by persons knowledgeable in the continuous administration of potent opioids, in the management of patients receiving potent opioids for the treatment of pain, and in the detection and management of respiratory depression, including the use of opioid antagonists.

Patients should be cautioned not to consume alcohol while taking STATEX as it may increase the chance of experiencing serious adverse events, including death.

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

**Abuse and Misuse:** Like all opioids, STATEX is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, STATEX 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 STATEX, should be used with particular care in patients with a history of alcohol and illicit/prescription drug abuse and other mental health disorders including, but not limited to, major depression and anxiety. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

STATEX tablets are intended for oral use only. The tablets should be swallowed whole, and not chewed or crushed. Abuse of oral dosage forms can be expected to result in serious adverse events, including death.

## Cardiovascular

Morphine sulfate administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of drugs such as phenothiazines and other tranquilizers, sedative/hypnotics, tricyclic antidepressants or general anesthetics. These patients should be monitored for signs of hypotension after initiating or titrating the dose of STATEX.

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

## Dependence, Tolerance and/or Abuse Liability

As with other opioids, tolerance and physical dependence may develop upon repeated administration of STATEX 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.

However, tolerance does not develop at an equal rate for all side effects. Cross-tolerance exists with all opioids. In the wake of tolerance, the patient's dosage might be increased if needed.

Patients on prolonged therapy should be tapered gradually from the drug if it is no longer required for pain control. Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist. Some of the symptoms that may be associated with abrupt withdrawal of an opioid analgesic include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, anxiety, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning (see [4.2 Recommended Dose and Dosage Adjustment](#)).

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

**Neonatal Opioid Withdrawal Syndrome (NOWS):** STATEX is not recommended to be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the risks. If STATEX was used during pregnancy, special attention to NOWS is warranted.

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

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

### **Driving and Operating Machinery**

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

### **Endocrine and Metabolism**

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

### **Gastrointestinal**

Morphine sulfate and other morphine-like opioids have been shown to decrease bowel motility. Morphine sulfate may obscure the diagnosis or clinical course of patients with acute abdominal conditions (see [2 Contraindications](#)).

## Hepatic/biliary/pancreatic

**Patients with Hepatic Impairment:** Morphine should be administered with caution and in a reduced dosage in patient with hepatic impairment.

Morphine is contraindicated in patients with suspected surgical abdomen (see [2 Contraindications](#)). In addition, morphine is known to cause spasm of the Sphincter of Oddi, thus increasing intrabiliary pressure, which exacerbates the biliary tract symptoms and increases the risk of pancreatitis. Other opioid related effects may include a blockage of biliary and pancreatic secretions or elevations in serum amylase.

## Neurologic

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

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (see [9 Drug Interactions](#)). If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when STATEX is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use with the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk of overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see [9 Drug Interactions](#)).

STATEX should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see [2 Contraindications](#); [8 Adverse Reactions, Sedation](#); [9 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 sulfate, and the capacity to elevate cerebrospinal fluid pressure, may be greatly increased in the presence of an already elevated intracranial pressure produced by trauma. Also, morphine sulfate may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, morphine sulfate must be used with extreme caution and only if it is judged essential (see [2 Contraindications](#)).

**Use in Patients with Convulsive or Seizure Disorders:** The morphine sulfate in STATEX may aggravate convulsions in patients with convulsive disorders, and may induce or aggravate seizures in some clinical settings. Therefore, STATEX should not be used in these patients (see [2 Contraindications](#)). Morphine may lower the seizure threshold in patients with a history of epilepsy.

**Opioid Induced Hyperalgesia:** Opioid induced hyperalgesia (OIH) is a paradoxical response to an opioid in which there is an increase in pain perception despite stable or increased opioid exposure. It differs from tolerance, in which higher opioid doses are required to achieve the same analgesic effect or treat recurring pain. Clinically, OIH may be associated with high opioid doses, long term opioid treatment, and intra-operative opioid use. OIH may manifest as an unexplained increase in pain, more diffuse pain than pre-existing, or as pain from ordinary (i.e. non-painful stimuli (allodynia)), in the absence of disease progression. When OIH is suspected, the dose of opioid should be reduced or tapered off, if possible. It is reasonable to consider opioid rotation, or the use of a non-opioid strategy for pain control. There is currently no well-established treatment for OIH.

**Serotonin Toxicity / Serotonin Syndrome:**

Serotonin toxicity, also known as serotonin syndrome, is a potentially life-threatening condition and has been reported with morphine, including STATEX, particularly during combined use with other serotonergic drugs (see [9 Drug Interactions](#)). Serotonin toxicity is characterised by neuromuscular excitation, autonomic stimulation (e.g., tachycardia, flushing) and altered mental state (e.g., anxiety, agitation, hypomania). In accordance with the Hunter Criteria, serotonin toxicity diagnosis is likely when, in the presence of at least one serotonergic agent, one of the following is observed:

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

If concomitant treatment with STATEX and other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see [9 Drug Interactions](#)). If serotonin toxicity is suspected, discontinuation of the serotonergic agents should be considered.

**Perioperative considerations**

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

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

Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. Thereafter, if STATEX 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 sulfate and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common post-operative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in post-operative patients receiving

opioids. Standard supportive therapy should be implemented.

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

## Renal

Morphine should be administered with caution and in a reduced dosage in patient with renal impairment.

## Reproductive health

- **Function**

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

## Respiratory

**Respiratory Depression:** Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Morphine sulfate should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia (see [2 Contraindications](#)).

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

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

To reduce the risk of respiratory depression, proper dosing and titration of STATEX are essential. Overestimating the STATEX dose when converting patients from another opioid product can result in a fatal overdose with the first dose. In these patients, the use of non-opioid analgesics should be considered, if feasible (see [4.2 Recommended Dose and Dosage Adjustment](#)).

**Use in Patients with Chronic Pulmonary Disease:** Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression for respiratory depression, particularly when initiating therapy and titrating with STATEX, as in these patients, even usual therapeutic doses of STATEX may decrease respiratory drive to the point of apnea. In these patients, use of alternative non-opioid analgesics should be considered, if possible. The use of STATEX is contraindicated in patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see [2 Contraindications](#)).

**Sleep Apnea:** Opioids can cause sleep-related breathing disorders such as sleep apnea syndromes (including central sleep apnea [CSA]) and hypoxia (including sleep-related hypoxia). Opioid use increases the risk of CSA in a dose-dependent fashion. Evaluate patients on an ongoing basis for the onset of a new sleep apnea, or a worsening of an existing sleep apnea. In these patients, consider

reducing or stopping the opioid treatment if appropriate, using best practices for tapering of opioids (see [7 Warnings and Precautions, Dependence, Tolerance and/or Abuse Liability](#) and [4.2 Recommended Dose and Dosage Adjustment, Adjustment or Reduction of Dosage](#)).

**Acute Chest Syndrome (ACS) in Patients with Sickle Cell Disease (SCD):** Due to a possible association between ACS and morphine use in SCD patients treated with morphine during a vaso-occlusive crisis, close monitoring for ACS symptoms is warranted.

## Skin

**Severe Cutaneous Adverse Reactions (SCARs):** Acute Generalized Exanthematous Pustulosis (AGEP), which can be life-threatening or fatal, has been reported in association with morphine treatment. Most of these reactions occurred within the first 10 days of treatment. Patients should be informed about the signs and symptoms of AGEP and be advised to seek immediate medical care if they experience such symptoms.

If signs and symptoms suggestive of these skin reactions appear, morphine should be withdrawn, and an alternative treatment considered.

### 7.1. Special Populations

**Special Risk Groups:** Morphine sulfate should be administered with caution to patients with a history of alcohol and drug abuse and in a reduced dosage to debilitated patients, and in patients with severely impaired pulmonary function, Addison's disease, hypothyroidism, myxedema, toxic psychosis, prostatic hypertrophy or urethral stricture, hypopituitarism, reduced renal and/or hepatic function, hypotension, biliary tract disorder, anemia, reduced blood volume and severe malnutrition.

**Cancer Patients:** Nausea and vomiting are symptoms frequently observed in terminal cancer patients. If a phenothiazine drug is to be employed as an antiemetic agent, it should be administered 30 minutes before morphine and not in the same preparation because of its potentiating activity on morphine. The dose and choice of a phenothiazine drug will depend on the individual patient, the disease, therapy/ies, and degree of sedation required.

#### 7.1.1. Pregnant Women

Studies in humans have not been conducted. Morphine sulfate crosses the placental barrier and is not recommended to be administered to pregnant women unless, in the judgment of the physician, potential benefits outweigh the risks.

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal Opioid Withdrawal Syndrome (NOWS), unlike opioid withdrawal syndrome in adults, may be life-threatening (see [7 Warnings and Precautions, Dependence, Tolerance and/or Abuse Liability, Neonatal Opioid Withdrawal Syndrome \(NOWS\)](#)).

Pregnant women using opioids should not discontinue their medication abruptly as this can cause pregnancy complication such as miscarriage or still-birth. Tapering should be slow and under medical supervision to avoid serious adverse events to the fetus.

- **Teratogenic Risk**

Morphine has been demonstrated to be teratogenic in animals at very high doses.

### 7.1.2. Breastfeeding

Since opioids can cross the placental barrier and are excreted in breast milk, STATEX is not recommended to be used in nursing women and during labour and delivery unless, in the judgment of the physician, the potential benefits outweigh the risks. Life-threatening respiratory depression can occur in the infant if opioids are administered to the mother. Naloxone, a drug that counters the effects of opioids, should be readily available if STATEX is used in this population.

### 7.1.3. Pediatrics

**Pediatrics (< 18 years of age):** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

### 7.1.4. Geriatrics

**Geriatrics (> 65 years of age):** In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range and titrate slowly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see [4.2 Recommended Dose and Dosage Adjustment](#); [10.3 Pharmacokinetics, Special Populations and Conditions, Geriatrics](#)).

## 8. Adverse Reactions

### 8.1. Adverse Reaction Overview

Adverse effects of STATEX (morphine sulfate) 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 adverse effects of STATEX are sedation, nausea and vomiting, constipation and sweating.

**Sedation:** Sedation is a common side effect of opioid analgesics, especially in opioid naïve individuals. Sedation may also occur partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Most patients develop tolerance to the sedative effects of opioids within three to five days and, if the sedation is not severe, will not require any treatment except reassurance. If excessive sedation persists beyond a few days, the dose of the opioid should be reduced and alternate causes investigated. Some of these are: concurrent CNS depressant medication, hepatic or renal dysfunction, brain metastases, hypercalcemia and respiratory failure. If it is necessary to reduce the dose, it can be carefully increased again after three or four days if it is obvious that the pain is not being well controlled. Dizziness and unsteadiness may be caused by postural hypotension, particularly in elderly or debilitated patients, and may be alleviated if the patient lies down.

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

accompanied by other symptoms including anorexia, early satiety, vomiting and abdominal fullness. These symptoms respond to chronic treatment with gastrointestinal prokinetic agents.

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

The following adverse effects occur less frequently with opioid analgesics.

#### **Less Common Adverse Drug Reactions**

**Cardiovascular:** Supra-ventricular tachycardia, postural hypotension, palpitations, faintness and syncope.

**Dermatologic:** Pruritus, urticaria, other skin rashes and oedema.

**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).

**Gastrointestinal:** Dry mouth, anorexia, constipation, cramps, taste alterations and biliary tract cramps.

**CNS:** Euphoria, dysphoria, weakness, insomnia, dizziness, confusional symptoms and occasionally hallucinations.

**Genitourinary:** Urinary retention or hesitance, reduced libido or potency.

**Withdrawal (Abstinence) Syndrome:** Physical dependence with or without psychological dependence tend 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.

#### **8.5. Post-Market Adverse Reactions**

**Androgen deficiency:** Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

**Metabolic and Nutritional Disorders:** Cases of hypoglycemia have been reported in patients taking opioids. Most reports were in patients with at least one predisposing risk factor (e.g., diabetes).

**Immune System Disorders:** Anaphylactic reaction, anaphylactoid reaction

## 9. Drug Interactions

### 9.1. Serious Drug Interactions

- Concomitant use of STATEX with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma and death (see [3 Serious Warnings and Precautions Box](#); [7 Warnings and Precautions, Neurologic](#); [9.2 Drug Interaction Overview](#)).
- Do not use STATEX in patients currently using or within 14 days of using a monoamine oxidase inhibitor (MAOI) (see [2 Contraindications](#); [9.4 Drug-Drug Interactions](#)).
- The co-ingestion of alcohol with STATEX may result in increased plasma levels and a potentially fatal overdose of morphine (see [2 Contraindications](#); [3 Serious Warnings and Precautions Box](#); [7 Warnings and Precautions, General](#) and [Neurologic](#); [9.3 Drug-Behavioural Interactions](#)).

### 9.2. Drug Interactions Overview

**Interaction with Benzodiazepines and Other Central Nervous System (CNS) Depressants:** Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants (e.g. other opioids, sedatives/hypnotics, gabapentinoids such as gabapentin and pregabalin, baclofen,, antidepressants, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, phenothiazines, neuroleptics, antihistamines, antiemetics, and alcohol) and beta-blockers, increases the risk of respiratory depression, profound sedation, coma, and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see [7 Warnings and Precautions, Neurologic, Interactions with Central Nervous System Depressants \(including benzodiazepines and alcohol\)](#); [7 Warnings and Precautions, Driving and Operating Machinery](#)). STATEX should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

### 9.3. Drug-Behaviour Interactions

The concomitant use of alcohol should be avoided (see [3 Serious Warnings and Precautions Box](#)).

### 9.4. Drug-Drug Interactions

**Oral Anticoagulants:** Morphine may enhance response to anticoagulants; however, short term use does not likely have a significant effect.

**Skeletal Muscle Relaxants:** CNS depressant effect of morphine adds to the neuromuscular blockade of muscle relaxants and atelectasis and increased respiratory depression may occur. Exert great caution if used concurrently.

**Antimuscarinics:** May result in increased risk of severe constipation and/or urinary retention.

**Levallorphan/Naloxone:** Antagonize the analgesic, CNS and respiratory depressant effects of opioid agonist analgesics and may precipitate withdrawal symptoms in physically dependent patients: dosage of levallorphan or naloxone should be carefully titrated when used to treat opioid overdose in dependent patients.

**Neuromuscular Blocking Agents:** Respiratory depressant effects of neuromuscular blocking agents may be additive to central respiratory depressant effects of opioid analgesics; caution is recommended

when an opioid drug is administered during surgery or in the immediate post-operative period to a patient who has received a neuromuscular blocking agent.

Serotonergic agents: Co-administration of morphine sulfate with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor or a Serotonin Norepinephrine Re-uptake Inhibitor, may increase the risk of serotonin syndrome, a potentially life-threatening condition (see [7 Warnings and Precautions, Serotonin Syndrome](#)).

Diuretics: Morphine reduces the efficacy of diuretics by inducing the release of antidiuretic hormone. Morphine may also lead to urinary retention by causing spasm of the sphincter of the bladder, particularly in men with prostatism.

P2Y12 inhibitors: The co-administration of oral P2Y12 inhibitors with morphine can decrease the absorption and peak concentration of oral P2Y12 inhibitors and delay the onset of the antiplatelet effect, due to morphine's effect on gastric emptying. Examples of P2Y12 inhibitors include but are not limited to: clopidogrel, prasugrel, ticagrelor.

Rifampin: Plasma concentrations of morphine may be reduced by rifampin. The analgesic effect of morphine should be monitored and doses of morphine adjusted during and after treatment with rifampin.

Ritonavir: Ritonavir is a potent inhibitor of CYP3A and to a lesser extent CYP2D6. Ritonavir also appears to induce CYP3A, CYP1A2, CYP2C9, CYP2C19, and CYP2B6. Ritonavir exhibits a biphasic, time-dependent effect on P-glycoprotein of inhibition followed by induction, as well as induction of glucuronyl transferases. Inhibition of P-glycoprotein facilitates morphine absorption whereas induction of P-glycoprotein impedes its absorption. The combined effects of ritonavir on P-glycoprotein and glucuronyl transferases may make the exposure to morphine unpredictable, since morphine is absorbed through the P-glycoprotein and metabolized by glucuronyl transferases.

## **9.5. Drug-Food Interactions**

Interactions with food have not been established.

## **9.6. Drug-Herb Interactions**

Interactions with herbal products have not been established.

## **9.7. Drug-Laboratory Test Interactions**

Morphine interferes with the diagnostic determination of cerebrospinal fluid pressure, the concentrations of; plasma amylase, plasma lipase, serum alanine aminotransferase (SGPT), serum aspartate aminotransferase (SGOT), serum bilirubin and serum alkaline phosphatase.

# **10. Clinical Pharmacology**

## **10.1. Mechanism of Action**

Morphine sulfate is an opioid analgesic that acts as an agonist, interacting with stereo specific receptor sites in the brain and other tissues.

Morphine alters both the perception of pain and the emotional response to pain. The spectrum of actions of morphine due to its receptor affinity also include decreased gastrointestinal motility, respiratory depression, nausea, vomiting, drowsiness, changes in mood, alterations of the endocrine and autonomic nervous systems, and suppression of the cough reflex.

It has been proposed that there are multiple subtypes of opioid receptors, each mediating various therapeutic and/or side effects of opioid drugs. The actions of an opioid analgesic may therefore depend upon its binding affinity for each type of receptor and whether it acts as a full agonist or a partial agonist or is inactive at each type of receptor. At least two of these types of receptors ( $\mu$  and  $\kappa$ ) mediate analgesia. A third type of receptor ( $\sigma$ ) may not mediate analgesia; action at this receptor may produce the subjective and psychotomimetic effects characteristic of opioids having mixed agonist/antagonist activity.

## 10.2. Pharmacodynamics

**Central Nervous System:** Morphine sulfate produces respiratory depression by direct action on brain stem respiratory centres. The respiratory depression involves both a reduction in the responsiveness of the brain stem centres to increases in  $\text{CO}_2$  tension and to electrical stimulation.

Morphine sulfate depresses the cough reflex by direct effect on the cough centre in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

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

**Gastrointestinal Tract and Other Smooth Muscle:** Morphine sulfate causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

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

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

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

## 10.3. Pharmacokinetics

### Absorption

Morphine sulfate is absorbed from the gastrointestinal tract. Two thirds of an oral dose is absorbed with maximum analgesic effect occurring after 60 minutes, however, the effect of a given dose is variable. The time curve is often long by the oral route and peak plasma levels of morphine occur 15 minutes post ingestion. The plasma half-life of morphine occurs at 2 to 3 hours post ingestion with large inter-subject variability.

### Distribution

Morphine sparingly crosses the blood brain barrier but appears in all tissues.

## Metabolism

Morphine is metabolized in the liver via biotransformation.

## Elimination

About 10% of a dose of morphine is excreted through the bile into the faeces. The remainder is excreted via glomerular filtration in the urine as conjugates or free morphine. Small quantities are excreted in breast milk and sweat. About 90% of a single dose of morphine is excreted in 24 hours with traces up to 48 hours.

## Special populations and conditions

- **Pediatrics:** Individuals under 18 years of age should not take STATEX.
- **Geriatrics:** Respiratory depression has occurred in the elderly following administration of large initial doses of opioids to patients who were not opioid-tolerant or when opioids were co-administered with other agents that can depress respiration. STATEX should be initiated at a low dose and slowly titrated to effect (see [7.1.4 Geriatrics](#)).
- **Hepatic Insufficiency:** Morphine should be administered with caution and in a reduced dosage in patient with hepatic impairment.
- **Renal Insufficiency:** Morphine should be administered with caution and in a reduced dosage in patient with renal impairment.

## 11. Storage, Stability, and Disposal

Store STATEX between 15-30°C in a well closed light resistant container.

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

### Disposal

STATEX should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired STATEX should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets. If temporary storage is required before disposal, a sealed child-proof container, such as a biohazard waste container or a lockable medication box could be obtained from a pharmacy.

## Part 2: Scientific Information

### 13. Pharmaceutical Information

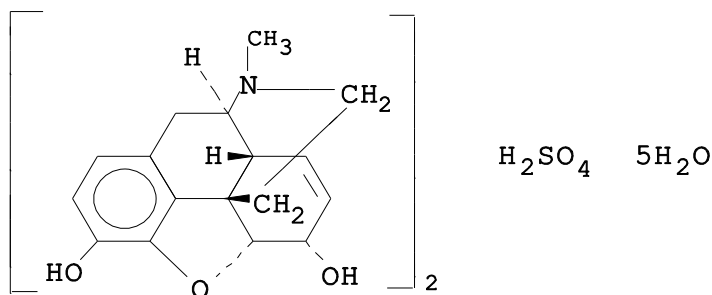
#### Drug Substance

Non-proprietary name of the drug substance: morphine sulfate

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

Molecular formula and molecular mass: (C<sub>17</sub>H<sub>19</sub>NO<sub>3</sub>) H<sub>2</sub>SO<sub>4</sub> 5H<sub>2</sub>O and 668.76

Structural formula:



Physicochemical properties: Pentahydrate, white fine odorless, crystals or powder or cubical masses (with a bitter taste). Loses some water at ordinary temperature, discolors on exposure to light. Soluble in water, sparingly soluble in alcohol, insoluble in chloroform or ether.

#### 14. Clinical Trials

The clinical trial data on which the original indication was authorized is not available.

#### 15. Microbiology

No microbiological information is required for this drug product.

#### 16. Non-Clinical Toxicology

No long-term animal studies have been performed to evaluate the carcinogenic potential of morphine sulfate tablets.

No studies have been performed to evaluate the mutagenic potential of morphine sulfate tablets.

No dedicated animal fertility studies have been performed for morphine sulfate tablets.

## Patient Medication Information

### READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

<sup>N</sup>STATEX<sup>®</sup>

#### morphine sulfate tablets

This Patient Medication Information is written for the person who will be taking **STATEX**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **STATEX**, talk to a healthcare professional.

#### Serious warnings and precautions box

- Even if you take STATEX as prescribed you are at a risk for opioid addiction, abuse and misuse. This can lead to overdose and death. To understand your risk of opioid addiction, abuse, and misuse you should speak to your healthcare professional.
- When you take STATEX tablets it must be swallowed whole. Do not cut, break, crush, chew, or dissolve the tablet. This can be dangerous and can lead to death or seriously harm you.
- Life-threatening breathing problems can happen while taking STATEX, especially if not taken as directed. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.
- Never give anyone your STATEX. They could die from taking it. If a person has not been prescribed STATEX, taking even one dose can cause a fatal overdose. This is especially true for children.
- If you took STATEX while you were pregnant, whether for short or long periods of time or in small or large doses, your baby can suffer life-threatening withdrawal symptoms after birth. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has any of the following symptoms:
  - has changes in their breathing (such as weak, difficult or fast breathing)
  - is unusually difficult to comfort
  - has tremors (shakiness)
  - has increased stools, sneezing, yawning, vomiting, or feverSeek immediate medical help for your baby.
- Taking STATEX with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.

#### What STATEX is used for:

STATEX is used in adults to manage severe pain. It is used when continuous treatment is required for several days or more. STATEX is not used "as needed" to treat pain that you only have once in a while.

#### How STATEX works:

STATEX is a painkiller belonging to the class of medicines known as opioids. It relieves pain by acting on specific nerve cells of the spinal cord and brain.

**The ingredients in STATEX are:**

Medicinal ingredient: morphine sulfate

Non-medicinal ingredients: FD&C Blue No.1 Lake 13%, lactose monohydrate, lake blend yellow 17% LB-111 (5 mg), magnesium stearate, and microcrystalline cellulose.

**STATEX comes in the following dosage form:**

Tablets: 5 and 10 mg.

**Do not use STATEX if:**

- your healthcare professional did not prescribe it for you.
- you are allergic to morphine sulfate, other opioids or any of the other ingredients in STATEX.
- you can control your pain by the occasional use of other pain medications. This includes those available without prescription.
- you have severe asthma, trouble breathing, or cor pulmonale (a heart problem related to lung issues).
- you have any heart problems.
- you have bowel blockage or narrowing of the stomach or intestines.
- you have a condition where the bowel does not work properly (ileus) or have severe pain in your abdomen.
- you have a head injury.
- you are at risk for seizure.
- you suffer from alcoholism or alcohol withdrawal.
- you are taking, or have taken within the past 14 days, a certain type of antidepressant called Monoamine Oxidase inhibitors (MAOIs).
- you are going to have a surgery or operation, or have had a surgery within the last 24 hours.
- are emotionally unstable or have suicidal thoughts.

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

- have a history of illicit or prescription drug or alcohol abuse.
- are taking any other medications.
- are drinking or planning to drink alcohol, or take medications that contain alcohol.
- have kidney or liver problems.
- have low blood pressure.
- have circulatory shock (i.e., your body does not get enough oxygen and nutrients to function properly due to lack of blood flow).
- suffer from chronic or severe constipation.
- have problems with your thyroid, adrenal or prostate gland.
- have, or have a history of, problems with your mood (such as depression or anxiety), or other mental problems.
- have difficulty urinating.
- are severely malnourished.
- have been told by a healthcare professional that you have low levels of red blood cells.
- are breastfeeding or planning to breast-feed.
- have diabetes or high blood sugar levels.
- are pregnant or planning to become pregnant or are in labour or delivery.

- have sickle cell disease.
- have a history of pancreas or gall bladder problems.
- have a condition that causes weakness or frailty.
- have a sleep disorder which causes pauses in breathing or shallow breathing while sleeping (sleep apnea).

**Other warnings you should know about:**

**Opioid dependence and addiction:** Like any opioid, STATEX may cause mental and physical dependence; it also has the potential to cause addiction even at regular doses. There are important differences between physical dependence and addiction. If you use opioids for a long time, you may develop tolerance. This means that you may need higher doses of STATEX to feel the same level of pain relief. It is important that you talk to your healthcare professional if you have questions or concerns about addiction, physical dependence, or tolerance. Your healthcare professional should prescribe and administer STATEX with the same degree of caution appropriate to the use of other oral opioid medications. It is not recommended to use these products for a long period of time.

**Pregnancy, nursing, labour and delivery:** Opioids can be transferred to your baby through breast milk, or while still in the womb. STATEX can then cause life-threatening breathing problems in your unborn baby or nursing infant. Your healthcare professional will determine if the benefits of using STATEX outweigh the risks to your unborn baby or nursing infant.

If you are pregnant and are taking STATEX, it is important that you don't stop taking your medication all of a sudden. If you do, it can cause a miscarriage or a still-birth. Your healthcare professional will monitor and guide you on how to slowly stop taking STATEX. This may help avoid serious harm to your unborn baby.

**Driving and using machines:** Before you do tasks which may require special attention, you should wait until you know how you react to STATEX. STATEX can cause:

- drowsiness,
- dizziness or
- lightheadedness.

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

**Sexual Function/Reproduction:** Long term use of opioids may lead to a decrease in sex hormone levels. It may also lead to low libido (desire to have sex), erectile dysfunction or being infertile.

**Disorder of the adrenal gland:** You may develop a disorder of the adrenal gland called adrenal insufficiency. This means that your adrenal gland is not making enough of certain hormones. You may experience symptoms such as:

- nausea, vomiting
- feeling tired, weak or dizzy
- decreased appetite

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

**Serotonin Toxicity (also known as serotonin syndrome):** STATEX can cause serotonin toxicity, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and

digestive system work. You may develop serotonin toxicity if you take STATEX with certain anti-depressants or migraine medications.

Serotonin Syndrome symptoms include:

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

**Sleep Apnea:** Opioids can cause a problem called sleep apnea (stopping breathing from time to time while sleeping). Tell your healthcare professional if you have a history of sleep apnea or if anyone notices that you stop breathing from time to time while sleeping.

**Worsening Pain:** Taking opioids for pain can sometimes have the unintended effect of making your pain feel worse (opioid-induced hyperalgesia) even though your opioid dose has been unchanged or increased. This can also include feeling pain in new places in your body, or feeling pain from something that would not normally hurt, for example, feeling pain from clothing touching your skin. Tell your healthcare professional if you notice a change like this in your pain while you are taking STATEX.

**Testing and check-ups:** Your healthcare professional will regularly monitor your health. This includes monitoring for signs of:

- misuse and abuse
- sleep apnea (a sleep disorder which causes pauses in breathing or shallow breathing while sleeping)
- respiratory depression and sedation (e.g., slow, shallow, or weak breathing)
- low blood pressure

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

**Serious drug interactions:**

Serious drug interactions with STATEX include:

- benzodiazepines (drugs used to help you sleep or that help reduce anxiety);
- central nervous system (CNS) depressants used to slow down the nervous system. These can include:
  - other opioids and mixed opioid agonists/antagonists used to relieve pain (e.g., methadone, pentazocine, nalbuphine, butorphanol, buprenorphine);
  - hypnotics used to help with sleeping;
  - antidepressants used for depression and mood disorders (e.g., fluoxetine, citalopram, venlafaxine; tricyclic antidepressants such as amitriptyline, imipramine, maprotiline, paroxetine; serotonin norepinephrine re-uptake inhibitors [SNRIs]; and selective serotonin re-uptake inhibitors [SSRIs] such as St. John's Wort);
  - anxiolytics, tranquilizers, and phenothiazines used to treat mental or emotional disorders;
  - muscle relaxants used to treat muscle spasms and back pain (e.g., baclofen);
  - general anesthetics used during surgery;
  - antipsychotics and neuroleptics used to treat mental health disorders (e.g., chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone, and risperidone);
  - antihistamines used to treat allergies;

- antiemetics used to prevent nausea or vomiting (e.g., domperidone, granisetron, dolasetron, and ondansetron);
- sedatives which may enhance the drowsiness;
- pregabalin, used to treat nerve pain;
- gabapentin, used to prevent and control seizures in the treatment of epilepsy;
- beta blockers used to lower blood pressure;
- alcohol. This includes prescription and non-prescription medications that contain alcohol. Do not drink alcohol while you are taking STATEX. It can lead to drowsiness, usually slow or weak breathing, serious side effects, or a fatal overdose.
- monoamine oxidase inhibitors (MAOIs) used to treat depression. Do not take STATEX with MAOIs or if you have taken MAOIs in the last 14 days.

**The following may also interact with STATEX:**

- anticoagulants, used to thin the blood and prevent blood clots (e.g., warfarin and other coumarins, clopidogrel, prasugrel, ticagrelor)
- medicines called “antimuscarinic”
- drugs used to treat migraines (e.g. triptans)
- medicines used to help reduce fluid build-up in the body, also known as diuretics (e.g., furosemide, indapamide, spironolactone)
- rifampin, used to treat bacterial infections including tuberculosis
- ritonavir, used to treat HIV infection

**How to take STATEX:**

- STATEX must be taken orally, by mouth. Do **NOT** administer the STATEX tablets via any other route as this can cause serious harm, including death.
- **Swallow the tablet whole. Do not cut, break, crush, chew or dissolve STATEX tablets. This can be dangerous and can lead to death or seriously harm you.**
- Take STATEX with or without food, with a glass of water.

**Usual dose:**

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

Your healthcare professional will prescribe the lowest dose that works to control your pain and will determine the best dose for you to lower the risk of side effects and overdose. Higher doses can lead to more side effects and a greater chance of overdose.

Review your pain regularly with your healthcare professional to determine if you still need STATEX. Be sure to use STATEX only for the condition for which it was prescribed.

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

Stopping your Medication:

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

You should do it slowly to avoid uncomfortable symptoms such as having:

- body aches

- diarrhea
- goosebumps
- loss of appetite
- nausea
- feeling nervous or restless
- runny nose
- sneezing
- tremors or shivering
- stomach cramps
- rapid heart rate (tachycardia)
- having trouble sleeping
- an unusual increase in sweating
- an unexplained fever
- heart palpitations
- weakness
- yawning

By reducing or stopping your opioid treatment, your body will become less used to opioids. If you start treatment again, you will need to start at the lowest dose. You may overdose if you restart at the last dose you took before you slowly stopped taking STATEX.

Refilling your Prescription for STATEX:

A new written prescription is required from your healthcare professional each time you need more STATEX. Therefore, it is important that you contact your healthcare professional before your current supply runs out.

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

**Overdose:**

Signs of overdose with STATEX may include:

- unusually slow or weak breathing
- dizziness
- confusion
- extreme drowsiness
- cold or clammy skin
- floppy muscles/low muscle tone
- shrinking or widening of the pupils
- slow heart rate
- low blood pressure
- low blood sugar
- muscle weakness, cramping, or aching
- toxic leukoencephalopathy (a brain disorder affecting the brain's white matter)
- sleep apnea (a sleep disorder which causes pauses in breathing or shallow breathing while sleeping)
- cardiac arrest (heart stops beating suddenly)
- aspiration pneumonia (lung infection caused by inhaling food, liquid or other substances into the

lungs)

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

**Missed dose:**

It is important that you do not miss any doses. If you miss:

- **One dose:** Skip the missed dose and take your next dose as scheduled. Do not take two doses at once to make-up for a missed dose.
- **Several doses in a row:** Talk to your healthcare professional before restarting your medication.

**Possible side effects from using STATEX:**

These are not all the possible side effects you may have when taking STATEX. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- drowsiness
- insomnia
- dizziness
- fainting
- nausea, vomiting, or a poor appetite
- dry mouth
- headache
- problems with vision
- weakness, uncoordinated muscle movement
- itching
- sweating
- constipation. Talk with your healthcare professional about ways to prevent constipation when you start taking STATEX.
- low sex drive, impotence (erectile dysfunction), infertility
- worsening abdominal pain of biliary or pancreatic origin

**Serious side effects and what to do about them**

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this 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.			✓

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
<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>Hypotension (low blood pressure):</b> dizziness, fainting, light-headedness.	✓		
<b>Serotonin toxicity (also known as serotonin syndrome):</b> a reaction which may cause feelings of agitation or restlessness, flushing, muscle twitching, involuntary eye movements, heavy sweating, high body temperature (>38°C), or rigid muscles.			✓
<b>Unknown</b>			
<b>Disorder of the adrenal gland:</b> nausea, vomiting, anorexia, fatigue, weakness, dizziness, or low blood pressure.			✓
<b>Hypoglycemia (low blood sugar):</b> thirst, frequent urination, hunger, nausea and dizziness, fast heartbeat, tingling, trembling, nervousness, sweating, low energy.		✓	
<b>Sleep apnea:</b> stop breathing for short periods during your normal nightly sleep.		✓	
<b>Severe Cutaneous Adverse Reactions (SCAR)</b> (severe skin			✓

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
reactions that may also affect other organs): skin peeling, scaling, or blistering (with or without pus) which may also affect your eyes, mouth, nose or genitals, itching, severe rash, bumps under the skin, skin pain, skin color changes (redness, yellowing, purplish). Swelling and redness of eyes or face. Flu-like feeling, fever, chills, body aches, swollen glands, cough. Shortness of breath, chest pain or discomfort.			
<b>Seizures (fits):</b> uncontrollable shaking with or without loss of consciousness.			✓
<b>Hallucinations:</b> seeing or hearing things that are not there.			✓

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

#### Reporting side effects

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

- Visiting the Web page on Adverse Reaction Reporting ([canada.ca/drug-device-reporting](http://canada.ca/drug-device-reporting)) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

#### Storage:

- Store STATEX between 15-30°C in a well closed light resistant container.
- Keep unused or expired STATEX in a secure place to prevent theft, misuse or accidental exposure.
- Keep STATEX 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 STATEX, get emergency help right away.
- STATEX 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 STATEX:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); manufacturer's website (<https://knighttx.com>), by emailing [medinfo@knighttx.com](mailto:medinfo@knighttx.com), or by calling 1-844-483-5636.

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