PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[N] STATEX®

morphine sulfate

Oral Drops – 20 and 50 mg/mL
Suppositories – 5, 10, 20 and 30 mg
Oral Syrup – 1, 5 and 10 mg/mL
Tablets – 5, 10, 25 and 50 mg

Opioid Analgesic

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Oral drop 20 and 50 mg/mL	Citric acid anhydrous, dextrose monohydrate, glycerine, sodium benzoate, sodium cyclamate, propylene glycol, water
	Oral syrup 1, 5 and 10 mg/mL	Unflavoured: citric acid anhydrous, dextrose monohydrate, glycerine, sodium benzoate, sodium cyclamate, propylene glycol, water Orange flavour: citric acid anhydrous, glycerine, orange extract, propylene glycol, sodium benzoate, sucrose, water
	Tablet 5, 10, 25 and 50 mg	FD&C Blue No.1Lake, lactose monohydrate, lake blend yellow, magnesium stearate, microcrystalline cellulose
Rectal	Suppository 5, 10, 20 and 30 mg	Wecobee M (hydrogenated vegetable oil)

For a complete listing see Dosage Forms, Composition and Packaging section.

INDICATIONS AND CLINICAL USE

Adults
STATEX is indicated for the symptomatic relief of severe chronic pain.

STATEX 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)
The safety and efficacy of STATEX has not been studied in the pediatric population. Therefore the use of STATEX is not recommended in patients under 18 years of age.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

Limitations of Use
Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the risks of overdose and death with immediate release opioid formulations, STATEX (morphine sulfate drops, suppositories, syrup and 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
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 WARNINGS AND PRECAUTIONS). STATEX 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 STATEX. 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 WARNINGS AND PRECAUTIONS).

Accidental Exposure

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

Neonatal Opioid Withdrawal Syndrome

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

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 WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see WARNINGS AND PRECAUTIONS, Neurologic and DRUG INTERACTIONS).

- **Reserve concomitant prescribing of 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.**

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. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

STATEX drops, syrup and 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

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 **ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, <Adjustment or Reduction of Dosage>).**

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.

Endocrine

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

Gastrointestinal Effects

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

Neonatal Opioid Withdrawal Syndrome (NOWS)

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

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

Use of STATEX is contraindicated in pregnant women (see **CONTRAINDICATIONS**).

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, centrally-active anti-emetics and other CNS depressants. Respiratory depression, hypotension and profound sedation, coma or death may result.

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

Advise both patients and caregivers about the risks of respiratory depression and sedation when 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 **DRUG INTERACTIONS**).

STATEX should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see **CONTRAINDICATIONS** and **ADVERSE REACTIONS, Sedation,** and **DRUG INTERACTIONS**).

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

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 **CONTRAINDICATIONS).**

Serotonin Syndrome: The concomitant administration of STATEX and serotonergic drugs (e.g. anti-depressant, migraine medications) could cause a rare but potentially life-threatening condition. If such events (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma and/or gastrointestinal symptoms such as nausea, vomiting and diarrhea) occur, the healthcare professional should determine whether treatment with STATEX and/or the serotoninergic drug should be discontinued and supportive symptomatic treatment should be initiated. STATEX

should not be used in combination with MAO inhibitors or serotonin-precursors (such as L-tryptophan, oxitriptan) and should be used with caution in combination with other serotonergic drugs (triptans, certain tricyclic antidepressants, lithium, tramadol, St. John's Wort) due to the risk of serotonergic syndrome (see **DRUG INTERACTIONS**).

Peri-Operative Considerations

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.

Psychomotor Impairment

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.

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 **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 **DOSAGE AND ADMINISTRATION**).

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 **CONTRAINDICATIONS**).

Sexual Function/Reproduction

Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (see **ADVERSE REACTIONS**, **Post-Marketing Experience**).

Special Populations

Special Risk Groups: Morphine sulfate should be administered with caution to patients with 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.

Pregnant Women: Studies in humans have not been conducted. Morphine has been demonstrated to be teratogenic in animals at very high doses. STATEX crosses the placental barrier and should not 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 **WARNINGS AND PRECAUTIONS, *Neonatal Opioid Withdrawal Syndrome***).

Labour, Delivery and Nursing Women: Since opioids can cross the placental barrier and are excreted in breast milk, STATEX should not be used unless, in the judgement of the physician, the potential benefits outweigh the risks. Respiratory depression can occur in the infant if opioids are administered during labour. Naloxone, a drug that counters the effects of opiates, should be readily available.

Pediatrics (< 18 years of age): The safety and efficacy of STATEX have not been studied in the pediatric population. Therefore, use of STATEX is not recommended in patients under 18 years of age.

Geriatrics (> 65 years of age): In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range and titrate slowly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**, **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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse effects of STATEX (morphine sulfate) drops, suppositories, syrup and 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 edema.

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.

Post-marketing Experience

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

DRUG INTERACTIONS

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, antidepressants, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, phenothiazines, neuroleptics, antihistamines, antiemetics, and alcohol) and beta-blockers, increases the risk of respiratory depression, profound sedation, coma, and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see **WARNINGS AND PRECAUTIONS, Neurologic, Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol) and Psychomotor Impairment**). STATEX should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

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 overdosage 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 **WARNINGS AND PRECAUTIONS**).

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory 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.

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

DOSAGE AND ADMINISTRATION

STATEX 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 WARNINGS AND PRECAUTIONS).

Dosing Considerations
STATEX (morphine sulfate drops, suppositories, syrup and tablets) should be used with caution within 12 hours pre-operatively and within the first 12-24 hours post-operatively (see **WARNINGS AND PRECAUTIONS, Peri-operative Considerations**).

STATEX drops, syrup and tablets are not indicated for rectal administration

STATEX may be taken with or without food.

STATEX tablets may be taken with a glass of water.

STATEX oral unflavoured drops and syrup may be diluted in a glass of fruit juice just prior to ingestion if desired, to improve the taste.

STATEX suppositories should be placed against the rectal mucosa. The drug is not absorbed if pushed into a mass of stool or if it is placed in the anal canal.

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.

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: 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. It is usually appropriate to treat a patient with only one opioid at a time. Further dose reductions should be considered due to incomplete cross-tolerance between opioids.

TABLE 1. OPIOID ANALGESICS: APPROXIMATE ANALGESIC EQUIVALENCES[1]

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

Footnotes:

[1]References:

Expert Advisory Committee on the Management of Severe Chronic Pain in Cancer Patients, Health and Welfare Canada. Cancer pain: A monograph on the management of cancer pain. Ministry of Supplies and Services Canada, 1987. Cat. No. H42-2/5-1984E.

Foley KM. The treatment of cancer pain. N Engl J Med 1985;313(2):84-95.

Aronoff GM, Evans WO. Pharmacological management of chronic pain: A review. In: Aronoff GM, editor. Evaluation and treatment of chronic pain. 2nd ed. Baltimore (MD): Williams and Wilkins; 1992. p. 359-68.

Cherny NI, Portenoy RK. Practical issues in the management of cancer pain. In: Wall PD, Melzack R, editors. Textbook of pain. 3rd ed. New York: Churchill Livingstone; 1994. p. 1437-67.

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

[†]Levy MH. Pharmacologic treatment of cancer pain. N Engl J Med 1996;335:1124-1132.

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

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

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

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

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

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.

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 **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

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

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

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

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.

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.

Opioid agents do not relieve effectively disaffected 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.

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.

Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal for the drug, these symptoms are usually mild (see **WARNINGS AND PRECAUTIONS**).

Disposal

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.

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.

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.

OVERDOSAGE

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

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, hypotonia, dizziness, confusion, miosis, rhabdomyolysis progression to renal failure, cold or clammy skin, and sometimes hypotension and bradycardia. Pinpoint pupils are a sign of narcotic overdose, but are not pathognomonic (e.g. pontine lesions of hemorrhagic or ischemic origin may product 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 overdosage 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.

ACTION AND CLINICAL PHARMACOLOGY

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.

Pharmacodynamics

Central Nervous System: Morphine sulfate produces respiratory depression by direct action on brain stem respiratory centres. The respiratory depression involves both a reduction in the responsiveness of the brain stem centres to increases in CO_2 tension and to electrical stimulation.

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

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

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 **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

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

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

STORAGE AND STABILITY

Store all preparations between 15-30^{o}C in a well closed light resistant container.

SPECIAL HANDLING INSTRUCTIONS

Not applicable

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition:

Statex Oral Drops 20 mg/mL: Each 1mL of clear unflavored and colorless liquid contains 20 mg of morphine sulfate. The non-medicinal ingredients are citric acid anhydrous, dextrose monohydrate, glycerine, sodium benzoate, sodium cyclamate, propylene glycol, water. Calorie content: 160 KCal/100 mL.

Statex Oral Drop 50 mg/ mL: Each 1mL of clear unflavored and colorless liquid contains 50 mg of morphine sulfate. The non-medicinal ingredients are citric acid anhydrous, dextrose monohydrate, glycerine, sodium benzoate, sodium cyclamate, propylene glycol, water. Calorie content: 160 KCal/100 mL.

Statex Oral Syrup 1 mg/mL: Available as unflavored (clear) and orange flavored syrup. Each mL contains 1 mg of morphine sulfate. The non-medicinal ingredients of the unflavoured syrup are citric acid anhydrous, dextrose monohydrate, glycerine, propylene glycol, sodium benzoate, sodium cyclamate, water. The non-medicinal ingredients of the orange flavoured syrup are citric acid anhydrous, glycerine, orange extract, propylene glycol, sodium benzoate, sucrose, water.

Statex Oral Syrup 5 mg/mL: Available as unflavoured (clear) and orange flavoured syrup. Each mL contains 5 mg of morphine sulfate. The non-medicinal ingredients of the unflavoured syrup are citric acid anhydrous, dextrose monohydrate, glycerine, propylene glycol, sodium benzoate, sodium cyclamate, water. The non-medicinal ingredients of the orange flavoured syrup are citric acid anhydrous, glycerine, orange extract, propylene glycol, sodium benzoate, sucrose, water.

Statex Oral Syrup 10 mg/mL: Available as clear unflavoured syrup. Each mL contains 10 mg of morphine sulfate. The non-medicinal ingredients are citric acid anhydrous, dextrose monohydrate, glycerine, sodium benzoate, sodium cyclamate, propylene glycol, water.

Statex Suppositories: Each white cone-shape suppository contains: morphine sulfate 5, 10, 20, or 30 mg. The non-medicinal ingredient is wecobee M (hydrogenated vegetable oil).

Statex Oral Tablets: available as 5mg (green), 10 mg (blue), 25 mg (pink), 50 mg (orange) round, scored on one side, identified with Paladin logo on the other side tablets. The non-medicinal ingredients are FD&C Blue No.1 Lake, lactose monohydrate, lake blend yellow, magnesium stearate, microcrystalline cellulose.

Packaging:
Statex Oral Drops 20 mg/mL: Available in 25 mL graduated bottles and 100 mL non-graduated bottles with calibrated dropper, filled to deliver 1 mL (20 mg of Morphine Sulfate).

Statex Oral Drops 50 mg/ mL: Available in 50 mL non-graduated bottles with calibrated dropper, filled to deliver 1 mL (50 mg of Morphine Sulfate).

Statex Oral Syrup 1 mg/mL: Available in 250 and 500 mL graduated bottles in Pet or Pet G bottles, and in uni-dose of 5, 10 and 15 mL (unflavoured only) in amber glass bottles.

Statex Oral Syrup 5 mg/mL: Available in 250 and 500 mL graduated bottles in Pet G bottles, and in uni-dose of 5 and 10 mL (unflavoured only) in amber glass bottles.

Statex Oral Syrup 10 mg/mL: Available in 250 mL graduated bottles in Pet G bottles.

Statex Suppositories: Available in boxes of 10.

Statex Oral Tablets: Available in bottles of 100 or control packs of 100 (4 x 25 tablets in blister).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

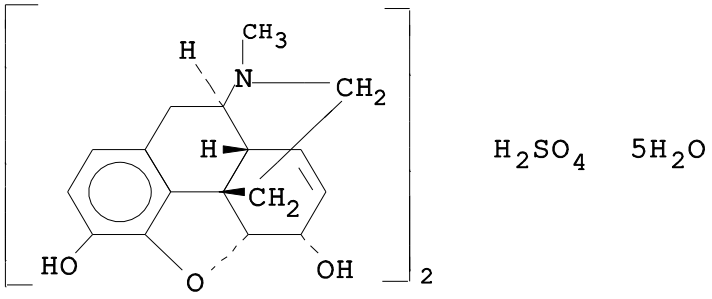
Proper name: morphine sulfate

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

Molecular formula: $(C_{17}H_{19}NO_3)\ H_2SO_4\ 5H_2O$

Molecular mass: 668.76

Structural formula:



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

DETAILED PHARMACOLOGY

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.

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.

Morphine sparingly crosses the blood brain barrier but appears in all tissues. Morphine is metabolized in the liver via biotransformation. 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.

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

[N] STATEX®

morphine sulfate oral drops, suppositories, oral syrup and tablets

Read this carefully before you start taking STATEX 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 STATEX.

Serious Warnings and Precautions

- **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.**
- **When you take STATEX tablets it must be swallowed whole. Do not cut, break, crush, chew, dissolve the tablet. This can be dangerous and can lead to death or seriously harm you.**
- **You may get life-threatening breathing problems while taking STATEX. This is less likely to happen if you take it as prescribed by your doctor.**
- **You should 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 fever**

  Seek immediate medical help for your baby.
- **You should not take STATEX with alcohol. This can be dangerous and can lead to death or seriously harm you.**
- **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 is STATEX used for?

STATEX is used to manage your pain.

How does STATEX work?

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

What are the ingredients in STATEX?

Medicinal ingredient: morphine sulfate
Non-medicinal ingredients:
Drops and unflavoured syrup: citric acid anhydrous, dextrose monohydrate, glycerine, sodium benzoate, sodium cyclamate, propylene glycol, water

Orange flavoured syrup: citric acid anhydrous, glycerine, orange extract, propylene glycol, sodium benzoate, sucrose, water.

Suppositories: hydrogenated vegetable oil

Tablets: FD&C Blue No.1 Lake, lactose monohydrate, lake blend yellow, magnesium stearate, microcrystalline cellulose

STATEX comes in the following dosage forms:

STATEX is available in oral drops (20 and 50 mg/mL), suppositories (5, 10, 20, 30 mg), syrup (1, 5 and 10 mg/mL) and tablets (5, 10, 25 and 50 mg).

Do not use STATEX if:

- you are allergic to morphine sulfate 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 a prescription.
- you have severe asthma, trouble breathing, or other breathing problems.
- you have any heart problems.
- you have bowel blockage or narrowing of the stomach or intestines.
- you have severe pain in your abdomen.
- you have a head injury.
- you are at risk for seizures.
- you suffer from alcoholism.
- you are taking or have taken within the past 2 weeks a Monoamine Oxidase inhibitor (MAOi) (such as phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline) .
- you are going to have a planned surgery.

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.
- have severe kidney disease.
- have severe liver disease.
- have low blood pressure.
- have or had depression.
- suffer from chronic or severe constipation.
- have problems with your thyroid, adrenal or prostate gland.
- have, or had in the past hallucinations or other severe mental problems.
- have a biliary tract disorder.
- are pregnant or planning to become pregnant.
- are breastfeeding.
- suffer from migraines.

Other warnings you should know about:

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.

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 STATEX:

- 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
    - unusually slow or weak breathing
    - serious side effects or
    - a fatal overdose
- other opioid analgesics (drugs used to treat pain);
- general anesthetics (drugs used during surgery);
- benzodiazepines (drugs used to help you sleep or that help reduce anxiety)
- antidepressants (for depression and mood disorders). **Do not** take STATEX with MAO inhibitors (MAOi) or if you have taken MAOi's in the last 14 days;
- drugs used to treat serious mental or emotional disorders (such as schizophrenia);
- antihistamines (drugs used to treat allergies);

- anti-emetics (drugs used for the prevention of vomiting);
- drugs used to treat muscle spasms and back pain;
- warfarin (such as coumadin) and other anticoagulants (used for prevention or treatment of blood clots);
- some heart medication (such as beta blockers);
- antimuscarinic medicine;
- drugs used to treat migraines (e.g. triptans).

How to take STATEX:

STATEX drops, syrup and tablets are **not** indicated for rectal administration

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

You can take your dose of STATEX with or without food. You can take you STATEX tablet with a glass of water.

To improve the taste, you can dilute STATEX oral unflavoured drops and syrup in a glass of fruit juice just before taking your dose.

You should place your STATEX suppository against the rectal mucosa. The medicine will not be absorbed if you push the suppository into a mass of stool or if you place it in the anal canal.

Usual Adult Starting Dose:

Your dose is tailored/personalized just for you. 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 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 doctor 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. You should check with your doctor for directions on how to slowly stop taking it. You should do it slowly to avoid uncomfortable symptoms such as having:

- body aches;
- diarrhea;
- gooseflesh;
- 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;
- palpitations;
- weakness;
- yawning.

Refilling your Prescription for STATEX:

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

Overdose:

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

Signs of overdose may include:

- unusually slow or weak breathing;
- dizziness;
- confusion;
- extreme drowsiness;
- cold or clammy skin;
- low muscle tone.

Missed Dose:

If you miss one dose, take your next dose at the scheduled time as usual. Do not take two doses at once. If you miss several doses in succession, talk to your doctor before restarting your medication.

What are possible side effects from using STATEX?

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

Side effects may include:

- Drowsiness;
- Insomnia;
- Dizziness;
- Fainting;
- Nausea, vomiting, or a poor appetite;
- Dry mouth;
- Headache;
- Problems with vision;
- Weakness, uncoordinated muscle movement;
- Itching ;
- Sweating;
- Constipation;
- Low sex drive, impotence (erectile dysfunction), infertility.

Talk with your doctor or pharmacist about ways to prevent constipation when you start using STATEX.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE			
Overdose: hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone cold and clammy skin			✓
Respiratory Depression: Slow, shallow or weak breathing			✓
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
Bowel Blockage (impaction): abdominal pain, severe constipation, nausea			✓
Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating		✓	

Fast, Slow or Irregular Heartbeat: heart palpitations		✓	
Low Blood Pressure: dizziness, fainting, light-headedness	✓		
Serotonin Syndrome: agitation or restlessness, loss of muscle control or muscle twitching, tremor, diarrhea			✓

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

Reporting Side Effects

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 0K9

Postage 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:

Store all preparations between 15-30^{o}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 out of sight and reach of children and pets.

Disposal:

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 this consumer medication information by visiting the Health Canada website; the manufacturer's website www.paladinlabs.com, or by calling 1-888-867-7426.

This leaflet was prepared by Paladin Labs Inc.

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