

# **PRODUCT MONOGRAPH**

**STATEX**

**(morphine sulfate)**

**OPIOID ANALGESIC**

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## **ACTION AND CLINICAL PHARMACOLOGY**

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

## **INDICATIONS**

Statex (Morphine Sulfate) is indicated for the symptomatic relief of severe chronic pain.

## **CONTRAINDICATIONS**

Statex (Morphine Sulfate) should not be employed when the following medical problems exist: Hypersensitivity to opioid analgesics, diarrhea caused by poisoning, acute respiratory disease or depression or impairment, concomitantly with MAO inhibitors or within 14 days of such treatment. The risk-benefit of morphine use should be evaluated when the following medical problems are present; abdominal conditions, asthma, cardiac arrhythmias, history of convulsions, drug abuse, emotional instability, suicidal ideation, gallbladder disease or gallstones, gastrointestinal tract surgery, head injury, increased intracranial pressure of preexisting intracranial lesions, hepatic function impairment, hypothyroidism, inflammatory bowel disease, prostatic hypertrophy of obstruction, urethral stricture, urinary tract surgery, renal function impairment and hypotension.

## **WARNINGS**

### **DRUG DEPENDENCE:**

Statex (Morphine Sulfate) can produce psychological and physical dependence and tolerance may develop with repeated administration. The chance of drug dependence in intractable pain of the terminally ill is substantially reduced when the patient is placed on a scheduled opioid program instead of a "pain to relief of pain" cycle of a PRN regimen.

Tolerance to the analgesic, respiratory depressant, sedative, and euphoric effects of morphine usually develops on long-term use. However, tolerance to all side effects does not develop at an equal rate; therefore, muscle twitching, tremor, mental confusion, hallucinations, and convulsions can occur. Cross-tolerance exists with all opioids. Continued use may lead to physical and psychological dependence. Withdrawal symptoms will occur if the opioid is abruptly discontinued or an opioid

antagonist given. Therefore, patients on prolonged therapy with morphine should be withdrawn gradually from the drug if it is no longer required for pain control.

## **PRECAUTIONS**

Administer with great caution in CNS depression, anoxia, hypercapnia, respiratory insufficiency (patients may become comatose because of carbon dioxide retention) patients with substantially decreased respiratory reserve (emphysema, kyphoscoliosis, pulmonary disorders), fulminant ulcerative colitis, biliary colic, untreated myxedema, chronic pulmonary disease, prostatic hypertrophy or urethral stricture, and in shock.

Morphine may cause a decrease in systemic vascular resistance in patients with myocardial infarction. A transient fall in systemic arterial pressure may result in severe hypotension. Administered in large doses, morphine may cause severe hypotension even in the supine patient.

Exercise caution in administering morphine to patients with hypothyroidism, Addison's disease, renal insufficiency, hypopituitarism, anemia, reduced blood volume, severe malnutrition, and patients receiving anti psychotic agents, barbiturates, or other drugs that depress respiration.

In the long-term use tolerance may develop. Increase dosage according to the patient's requirements.

Abrupt withdrawal of morphine administration or administration of an opioid antagonist will result in withdrawal symptoms since continued use may lead to physical and psychological dependence.

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.

### **Pregnancy**

Risk-benefit must be considered since opioid analgesics cross the placenta, and fetal levels may possibly be higher than in the maternal circulation. Use only if potential benefits outweigh possible risk to the fetus and the mother. Regular use during pregnancy may cause physical dependence in the fetus, leading to withdrawal symptoms (convulsions, irritability, excessive crying, tremors, hyperactive reflexes, fever, vomiting, diarrhea, sneezing, yawning and sleeplessness) in the neonate.

Use of opioid analgesics during labor may cause respiratory depression in the neonate, especially the premature neonate. These agents should be used with caution, if at all, during delivery of a premature infant.

Although teratogenic effects in humans have not been documented, morphine has been demonstrated to be teratogenic in animals at very high doses.

### **Breast-Feeding:**

Morphine has been shown to be excreted in breast milk. Caution should be exercised if morphine must be administered to a nursing mother.

### **Pediatrics:**

Pediatric patients may be more susceptible to the effects, especially the respiratory depressant effects, of morphine.

### **Geriatrics:**

Geriatric patients are more susceptible to the effects, especially the respiratory depressant effects, of morphine. Lower doses than those usually recommended for adults may be required for these patients.

### **Drug Interactions:**

Morphine should be used with caution concomitantly with: alcohol, general anesthetics, and CNS depressants; additive effects may be seen. Death may occur; concurrent use may result in

potentiation of CNS depression. If used concurrently with CNS depressants, dosage adjustment may be required.

**Oral Anticoagulants:**

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

**Phenothiazines:**

May augment respiratory depression of morphine and also may increase risk of hypotension as additive hypotensive effects may occur.

Concurrent use of phenothiazines may enhance sedative effects; but, at the same time, some phenothiazines (promethazine) have an anti analgesic 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.

**Tricyclic Antidepressant:**

May enhance morphine-induced respiratory depression, possibly due to additive anticholinergic effects. Exert caution if morphine is given to patients taking tricyclic depressants with lung disease, or in whom respiratory depression could be dangerous. This applies to all opioid analgesics but to a lesser degree with morphine.

**Antimuscarinics:**

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

**Hydroxyzine:**

May result in increased analgesia and sedation.

**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.

**Methadone or Opioid Agonist Analgesics:**

Additive CNS depressant, respiratory depressant and hypotensive effects may occur if two or more opioid agonist analgesics are used concurrently.

**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.

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.

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

## **ADVERSE REACTIONS**

The major hazards associated with morphine, as with other opioid analgesics, are respiratory depression and, to a lesser degree, circulatory depression. Respiratory arrest, shock and cardiac arrest have occurred following oral or parenteral use of morphine.

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

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

#### **Sedation:**

Most patients experience initial drowsiness partly for pharmacokinetic reasons and partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Drowsiness usually clears in three to five days and is usually not a reason for concern providing that it is not excessive, or associated with unsteadiness or confusional symptoms. If excessive sedation persists, the reason for it must be sought. Some of these are: concomitant sedative medications, hepatic or renal failure, exacerbated respiratory failure, higher doses than tolerated in an older patient, or the patient is actually more severely ill than realized. If it is necessary to reduce the dose, it can be carefully increased again after three or four days if it is obvious that the pain is not being well controlled. Dizziness and unsteadiness may be caused by postural hypotension particularly in elderly or debilitated patients. It can be alleviated if the patient lies down. Because of the slower clearance in patients over 50 years of age, an appropriate dose in this age group may be as low as half or less than the usual dose in the younger age group.

#### **Nausea and Vomiting:**

Nausea and vomiting occur frequently after single doses of opioids or as unwanted effect of regular opioid therapy. When instituting prolonged therapy for chronic pain the routine prescription of antiemetics should be considered. Patients taking doses of 20 mg or more of morphine q4h usually require an antiemetic during early therapy. Small doses of prochlorperazine or haloperidol are the most frequently prescribed antiemetics. Nausea and vomiting tend to lessen in a week or so but may persist due to opioid-induced gastric stasis. In such patients, metoclopramide is often useful.

**Constipation:**

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

**Other adverse reactions include:****Cardiovascular:**

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

**Central Nervous System:**

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

**Gastrointestinal:**

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

**Genitourinary:**

Urinary retention or hesitance, reduced libido or potency.

**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).

**Allergic:**

Pruritus, urticaria, other skin rashes and edema. Psychological dependence tend to occur on chronic administration.

### **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.

**SYMPTOMS AND TREATMENT OF OVERDOSAGE:** Symptomatology: 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, flaccidity of skeletal muscle, cold or clammy skin, and sometimes hypotension and bradycardia. Severe overdosage 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.

### **DOSAGE AND ADMINISTRATION**

See PRECAUTIONS, CONTRAINDICATIONS, and OVERDOSAGE for detailed information. Individual dosing requirements vary considerably based on each patient's age, weight, severity of pain, and medical and analgesic history.

Initial Adult Dose: The most frequent initial dose is 10-30 mg q4h around the clock. The oral unflavoured liquid may be diluted in a glass of fruit juice just prior to ingestion if desired, to improve the taste.

The suppository 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.

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

Dose titration: Dose titration is the key to success with morphine therapy. PROPER OPTIMIZATION OF DOSES SCALED TO THE RELIEF OF THE INDIVIDUAL'S PAIN SHOULD AIM AT THE REGULAR ADMINISTRATION OF THE LOWEST DOSE OF MORPHINE WHICH WILL MAINTAIN THE PATIENT FREE OF PAIN AT ALL TIMES. Dose adjustments should be based on the patient's clinical response. Higher doses may be justified in some patients to cover periods of physical activity.

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.

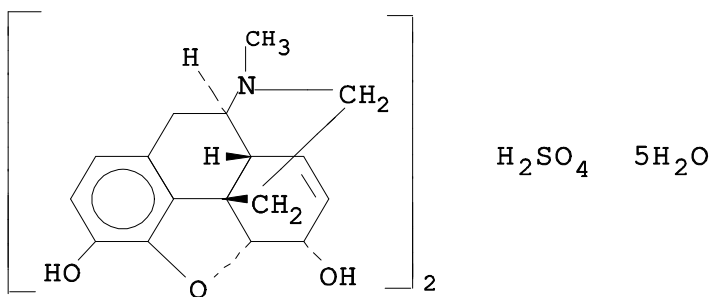
Opioid agents do not relieve effectively disaffected pain, post-herpetic neuralgia, stabbing pains, activity-related pain, and some forms of headache. This is not to say that patients with advanced cancer suffering from some of these forms of pain should not be given an adequate trial of opiate analgesics, 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.

#### **PHARMACEUTICAL INFORMATION:**

Proper Name: 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.

Structural Formula:



Molecular Weight: 668.76

Description: 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.

#### **AVAILABILITY OF DOSAGE FORMS:**

Stalex Oral Drops: 20mg/mL: Each 1mL of clear unflavored and colorless liquid contains 20mg of Morphine Sulfate. Available in 25mL and 100mL graduated bottles with calibrated dropper, filled to deliver 1mL (20mg of Morphine Sulfate). Calorie content: 160 KCal/100mL.

Stalex Oral Drops: 50mg/ mL: Each 1mL of clear unflavored and colorless liquid contains 50mg of Morphine Sulfate. Available in 50mL graduated bottles with calibrated dropper, filled to deliver 1mL (50mg of Morphine Sulfate). Calorie content: 160 KCal/100mL.

Stalex Oral Syrup: 1mg/mL: Available as unflavored (Clear) and orange flavored syrup. Each mL contains 1mg of Morphine Sulfate. Available in 250 mL and 500mL graduated bottles in Pet G bottles, and in uni-dose of 5, 10 and 15 mL (unflavoured) in amber glass bottles.

Stalex Oral Syrup: 5mg/mL: Available as unflavoured (clear), and orange flavoured syrup. Each mL contains 5 mg of Morphine Sulfate. Available in 250 and 500 mL graduated bottles in Pet G bottles, and in uni-dose of 5 and 10 mL (unflavoured) in amber glass bottles.

Stalex Oral Syrup 10mg/mL: Available as unflavoured syrup. Each mL contains 10 mg of Morphine Sulfate. Available in 250 mL graduated bottles in Pet G bottles.

Statex Suppositories: Each white cone-shape suppository contains: morphine sulfate 5, 20, or 30 mg. Available in boxes of 10. The suppository 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.

Statex Oral Tablets: Strengths Available: 5mg (green), 10 mg (blue), 25 mg (pink), 50 mg (orange) round, scored on one side, identified "pms" on the other side. In bottles of 100 or control packs of 100. (4 x 25 tablets in blister).

100mg (white) round, flat-faced bevelled edge, plain on one side and pms imprinted above the bisect and 100 below on the other side. In bottles of 100 and control packs of 100 (4 x 25 tablets in blister).

Packaging and Storage: Store all preparations between 15-30°C (59-86°F) in a well closed light resistant container.

### **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.

**TABLE 1**  
**OPIOID ANALGESICS: APPROXIMATE ANALGESIC EQUIVALENCES <sup>(1)</sup>**

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

<sup>(1)</sup> References:

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- (2) Most of these data were derived from single-dose, acute pain studies and should be considered an approximation for selection of doses when treating chronic pain.
- (3) For acute pain, the oral dose of morphine is six times the injectable dose. However, for chronic dosing, this ratio becomes 2 or 3:1, possibly due to the accumulation of active metabolites.
- (4) These drugs are not recommended for the management of chronic pain.
- (5) Extremely variable equianalgesic dose. Patients should undergo personalized titration starting at an equivalent to 1/10 of the morphine dose.
- (6) Mixed agonist-antagonists can precipitate withdrawal in patients on pure opioid agonists.

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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