
# NEOSTIGMINE METHYLSULFATE Injection, USP

| PRODUCT | DELIVERY SYSTEM | UNIT SIZE | UNITS / BOX | NDC# |
|---|---|---|---|---|
| Neostigmine Methylsulfate Injection, USP (0.5 mg/mL) | Multi-Dose Vial | 10 mL | 10 | 0548-9601-00 |
| Neostigmine Methylsulfate Injection, USP (1 mg/mL) | Multi-Dose Vial | 10 mL | 10 | 0548-9602-00 |

| | WHOLESALER ITEM NUMBERS | | | |
|---|---|---|---|---|
| NDC# | AMERISOURCE BERGEN | CARDINAL | MCKESSON | MORRIS & DICKSON |
| 0548-9601-00 | 10182474 | 5400643 | 3731940 | 176784 |
| 0548-9602-00 | 10182473 | 5400650 | 3731973 | 176818 |

**TO PLACE AN ORDER, PLEASE CALL 1-800-423-4136**

**AMPHASTAR PHARMACEUTICALS INC.**
**11570 Sixth Street, Rancho Cucamonga, CA 91730**
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Please see reverse for important safety information, including Warnings and Precautions and Indications and Usage, for Neostigmine Methylsulfate Injection, USP.

**Rx Only**
**11/17**
**01-507-01**

# NEOSTIGMINE METHYLSULFATE
Injection, USP

## DESCRIPTION
Neostigmine Methylsulfate Injection, USP, is a sterile, nonpyrogenic solution intended for intravenous use. Each mL of the 0.5 mg/mL strength contains neostigmine methylsulfate 0.5 mg, phenol 4.5 mg (used as preservative) and sodium acetate trihydrate 0.2 mg, in water for injection. The pH is adjusted, when necessary, with acetic acid/sodium hydroxide to a value of 5.5.

## INDICATIONS AND USAGE
Neostigmine Methylsulfate Injection, USP, is a cholinesterase inhibitor indicated for the reversal of the effects of nondepolarizing neuromuscular blocking agents after surgery.

## CONTRAINDICATIONS
Neostigmine Methylsulfate Injection, USP, is contraindicated in patients with:
- known hypersensitivity to neostigmine methylsulfate (known hypersensitivity reactions have included urticaria, angioedema, erythema multiforme, generalized rash, facial swelling, peripheral edema, pyrexia, flushing, hypotension, bronchospasm, bradycardia and anaphylaxis).
- with peritonitis or mechanical obstruction of the intestinal or urinary tract.

## WARNINGS AND PRECAUTIONS
### Bradycardia
Neostigmine has been associated with bradycardia. Atropine sulfate or glycopyrrolate should be administered prior to Neostigmine Methylsulfate Injection, USP, to lessen the risk of bradycardia [*see Dosage and Administration*].

### Serious Adverse Reactions in Patients with Certain Coexisting Conditions
Neostigmine Methylsulfate Injection, USP, should be used with caution in patients with coronary artery disease, cardiac arrhythmias, recent acute coronary syndrome or myasthenia gravis. Because of the known pharmacology of neostigmine methylsulfate as an acetylcholinesterase inhibitor, cardiovascular effects such as bradycardia, hypotension or dysrhythmia would be anticipated. In patients with certain cardiovascular conditions such as coronary artery disease, cardiac arrhythmias or recent acute coronary syndrome, the risk of blood pressure and heart rate complications may be increased. Risk of these complications may also be increased in patients with myasthenia gravis. Standard antagonism with anticholinergics (e.g., atropine) is generally successful to mitigate the risk of cardiovascular complications.

### Hypersensitivity
Because of the possibility of hypersensitivity, atropine and medications to treat anaphylaxis should be readily available.

### Neuromuscular Dysfunction
Large doses of Neostigmine Methylsulfate Injection, USP, administered when neuromuscular blockade is minimal can produce neuromuscular dysfunction. The dose of Neostigmine Methylsulfate Injection, USP, should be reduced if recovery from neuromuscular blockade is nearly complete.

### Cholinergic Crisis
It is important to differentiate between myasthenic crisis and cholinergic crisis caused by overdosage of Neostigmine Methylsulfate Injection, USP. Both conditions result in extreme muscle weakness but require radically different treatment. [*see Overdosage*]

## DRUG INTERACTIONS
The pharmacokinetic interaction between neostigmine methylsulfate and other drugs has not been studied. Neostigmine methylsulfate is metabolized by microsomal enzymes in the liver. Use with caution when using Neostigmine Methylsulfate Injection, USP, with other drugs which may alter the activity of metabolizing enzymes or transporters.

## ADVERSE REACTIONS
### Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse reactions to neostigmine methylsulfate are most often attributable to exaggerated pharmacological effects, in particular, at muscarinic receptor sites. The use of an anticholinergic agent, e.g., atropine sulfate or glycopyrrolate, may prevent or mitigate these reactions.

Quantitative adverse event data are available from trials of neostigmine methylsulfate in which 200 adult patients were exposed to the product. The following table lists the adverse reactions that occurred with an overall frequency of 1% or greater.

| System Organ Class | Adverse Reaction |
|---|---|
| **Cardiovascular Disorders** | bradycardia, hypotension, tachycardia/heart rate increase |
| **Gastrointestinal Disorders** | dry mouth, nausea, post-procedural nausea, vomiting |
| **General Disorders and Administration Site Conditions** | incision site complication, pharyngolaryngeal pain, procedural complication, procedural pain |
| **Nervous System Disorders** | dizziness, headache, postoperative shivering, prolonged neuromuscular blockade |
| **Psychiatric Disorders** | insomnia |
| **Respiratory, Thoracic and Mediastinal Disorders** | dyspnea, oxygen desaturation <90% |
| **Skin and Subcutaneous Tissue Disorders** | pruritus |

### Post Marketing Experience
The following adverse reactions have been identified during parenteral use of neostigmine methylsulfate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

| System Organ Class | Adverse Reaction |
|---|---|
| **Allergic Disorders** | allergic reactions, anaphylaxis |
| **Nervous System Disorders** | convulsions, drowsiness, dysarthria, fasciculation, loss of consciousness, miosis, visual changes |
| **Cardiovascular Disorders** | cardiac arrest, cardiac arrhythmias (A-V block, nodal rhythm), hypotension, nonspecific EKG changes, syncope |
| **Respiratory, Thoracic and Mediastinal Disorders** | bronchospasm; increased oral, pharyngeal and bronchial secretions; respiratory arrest; respiratory depression |
| **Skin and Sub-cutaneous Tissue Disorders** | rash, urticaria |
| **Gastrointestinal Disorders** | bowel cramps, diarrhea, flatulence, increased peristalsis |
| **Renal and Urinary Disorders** | urinary frequency |
| **Musculoskeletal and Connective Tissue Disorders** | arthralgia, muscle cramps, spasms, weakness |
| **Miscellaneous** | diaphoresis, flushing |

## OVERDOSAGE
Muscarinic symptoms (nausea, vomiting, diarrhea, sweating, increased bronchial and salivary secretions, and bradycardia) may appear with overdosage of Neostigmine Methylsulfate Injection, USP (cholinergic crisis), but may be managed by the use of additional atropine or glycopyrrolate. The possibility of iatrogenic overdose can be lessened by carefully monitoring the muscle twitch response to peripheral nerve stimulation. Should overdosage occur, ventilation should be supported by artificial means until the adequacy of spontaneous respiration is assured, and cardiac function should be monitored.

Overdosage of Neostigmine Methylsulfate Injection, USP, can cause cholinergic crisis, which is characterized by increasing muscle weakness, and through involvement of the muscles of respiration, may result in death. Myasthenic crisis, due to an increase in the severity of the disease, is also accompanied by extreme muscle weakness and may be difficult to distinguish from cholinergic crisis on a symptomatic basis. However, such differentiation is extremely important because increases in the dose of Neostigmine Methylsulfate Injection, USP, or other drugs in this class, in the presence of cholinergic crisis or of a refractory or "insensitive" state, could have grave consequences. The two types of crises may be differentiated by the use of edrophonium chloride as well as by clinical judgment.

Treatment of the two conditions differs radically. Whereas the presence of myasthenic crisis requires more intensive anticholinesterase therapy, cholinergic crisis calls for the prompt withdrawal of all drugs of this type. The immediate use of atropine in cholinergic crisis is also recommended. Atropine may also be used to lessen gastrointestinal side effects or other muscarinic reactions; but such use, by masking signs of overdosage, can lead to inadvertent induction of cholinergic crisis.

## CLINICAL STUDIES
The evidence for the efficacy of neostigmine methylsulfate for the reversal of the effects of non-depolarizing neuromuscular blocking agents after surgery is derived from the published literature. Randomized, spontaneous-recovery or placebo-controlled studies using similar efficacy endpoints evaluated a total of 404 adult and 80 pediatric patients undergoing various surgical procedures. Patients had reductions in their recovery time from neuromuscular blockade with neostigmine methylsulfate treatment compared to spontaneous recovery.