



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

NDC#	WHOLESALE ITEM NUMBERS			
	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.

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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 overdose 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.