

## Hikma launches Neostigmine Methylsulfate Injection, USP in prefilled syringe

**London, 15 June 2023** – Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, has launched Neostigmine Methylsulfate Injection, USP, in prefilled syringe (PFS) form. The 3mg/3mL PFS has been launched in the US and is a cholinesterase inhibitor, indicated for reversal of the effects of nondepolarizing neuromuscular blocking agents (NMBAs) after surgery.

Hikma is a top three supplier of generic injectable medicines by volume in the US<sup>1</sup>, with a growing portfolio of more than 150 products. We are continuously expanding our portfolio of essential medicines and introducing new dosage forms that enhance patient care.

- ENDS -

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### About Hikma

(LSE: HIK) (NASDAQ Dubai: HIK) (OTC: HKMPY) (rated BBB-/stable S&P and BBB-/stable Fitch)

Hikma helps put better health within reach every day for millions of people around the world. For more than 40 years, we've been creating high-quality medicines and making them accessible to the people who need them. Headquartered in the UK, we are a global company with a local presence across the North America, the Middle East and North Africa (MENA) and Europe, and we use our unique insight and expertise to transform cutting-edge science into innovative solutions that transform people's lives. We're committed to our customers, and the people they care for, and by thinking creatively and acting practically, we provide them with a broad range of branded and non-branded generic medicines. Together, our 8,800 colleagues are helping to shape a healthier world that enriches all our communities. We are a leading licensing partner, and through our venture capital arm, are helping bring innovative health technologies to people around the world. For more information, please visit: [www.hikma.com](http://www.hikma.com)

<sup>1</sup> Source: IQVIA MAT April 2023, generic injectable volumes by eachees, excluding branded generics and Becton Dickinson

***This product has been approved for marketing in the United States by the US FDA. This product approval does not confer the right on Hikma, or any other party, to market this product outside the United States.***

## **Important Safety Information for Neostigmine Methylsulfate Injection, USP, 3mg/3mL:**

### **CONTRAINDICATIONS**

Neostigmine 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).
- peritonitis or mechanical obstruction of the urinary or intestinal tracts.

### **WARNINGS & PRECAUTIONS**

- **Bradycardia** – Neostigmine has been associated with bradycardia. An anticholinergic agent, (e.g., atropine sulfate or glycopyrrolate) should be administered prior to neostigmine methylsulfate injection administration to lessen the risk of bradycardia.
- **Cardiovascular Complications** – Cardiac arrhythmias, nonspecific electrocardiogram changes, cardiac arrest, syncope and hypotension have been reported with neostigmine methylsulfate. 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 (Anaphylaxis)** – Hypersensitivity reactions including anaphylaxis have been reported with neostigmine. Ensure that appropriate medical support measures, including atropine, cardiopulmonary resuscitation equipment, and medications to treat anaphylaxis are readily available.
- **Neuromuscular Dysfunction** – Neuromuscular dysfunction has been associated with administration of large doses of neostigmine when neuromuscular blockade is minimal. To mitigate the risk of neuromuscular dysfunction, consider reducing the dose of neostigmine if recovery from neuromuscular blockade is nearly complete.
- **Cholinergic Crisis** – Overdosage of neostigmine may cause cholinesterase inhibitor toxicity or cholinergic crisis which may be difficult to differentiate from myasthenia crisis since both conditions present with similar symptoms. Both conditions result in extreme muscle weakness but require radically different treatments. Cholinergic crisis requires immediate withdrawal of all anticholinergic medication and immediate use of atropine.

### **ADVERSE REACTIONS**

#### **Clinical Trial 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.

The following serious adverse reactions are described below and elsewhere in the labeling:

- Bradycardia [see *Warnings and Precautions (5.1)*]
- Cardiovascular Complications [see *Warnings and Precautions (5.2)*]
- Hypersensitivity (Anaphylaxis) [see *Warnings and Precautions (5.3)*]

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.

Adverse reactions that occurred with an overall frequency of 1% or greater included the following:

**Allergic:** Allergic reactions and anaphylaxis.

**Neurological:** Dizziness, syncope, weakness, convulsions, loss of consciousness, drowsiness, headache, dysarthria, miosis and visual changes.

**Cardiovascular:** Cardiac arrhythmias including bradycardia, tachycardia, atrioventricular block and nodal rhythm, as well as cardiac arrest, and hypotension.

**Respiratory:** Increased oral, pharyngeal and bronchial secretions, dyspnea, respiratory depression, oxygen desaturation, respiratory arrest and bronchospasm.

**Dermatologic:** Diaphoresis, flushing, rash, pruritus, and urticaria.

**Gastrointestinal:** Dry mouth, nausea, emesis, flatulence and increased peristalsis.

**Genitourinary:** Increased urinary frequency.

**Musculoskeletal:** Muscle cramps and spasm, arthralgia.

**Psychiatric:** Insomnia.

**General:** Incision site complication, pharyngolaryngeal pain, procedural complication, procedural pain.

## 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.

**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 Subcutaneous Tissue Disorders:** Rash, urticaria diaphoresis, flushing

**Gastrointestinal Disorders:** Bowel cramps, diarrhea, flatulence, increased peristalsis

**Renal and Urinary Disorders:** Urinary frequency

**Musculoskeletal and Connective Tissue Disorders:** Arthralgia, muscle cramps, spasms, weakness

## 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. Closely monitor patients for a longer period of time when using Neostigmine Methylsulfate Injection with other drugs which may alter the activity of metabolizing enzymes or transporters.

## Depolarizing Muscle Relaxants

Use of neostigmine to reverse the effects of depolarizing muscle relaxants such as succinylcholine is not recommended, because it may prolong the phase-1 block.

## Antibiotics

Certain antibiotics, particularly neomycin, streptomycin and kanamycin have nondepolarizing neuromuscular blocking action, and therefore, neostigmine dose adjustments may be required to reverse neuromuscular block in patients who have been taking these drugs. There was no effect on neostigmine action on rocuronium reversal by cefuroxime, metronidazole, cefuroxime or metronidazole.

## USE IN SPECIFIC POPULATIONS

### Pregnancy

#### Risk Summary

There are no adequate or well-controlled studies of neostigmine methylsulfate injection in pregnant women. It is not known whether neostigmine methylsulfate injection can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. The incidence of malformations in human pregnancies has not been established for neostigmine as the data are limited. All pregnancies, regardless of drug exposure, have a background risk of 2 to 4% for major birth defects, and 15 to 20% for pregnancy loss.

Anticholinesterase drugs, including neostigmine may cause uterine irritability and induce premature labor when administered to pregnant women near term. Neostigmine methylsulfate injection should be given to a pregnant woman only if clearly needed.

## Lactation

It is not known whether neostigmine methylsulfate injection is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions from neostigmine methylsulfate injection in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

## Pediatric Use

Data from published literature support the intravenous use of neostigmine methylsulfate for reversal of nondepolarizing neuromuscular blocking agents in all pediatric age groups.

Recovery of neuromuscular activity occurs more rapidly with smaller doses of cholinesterase inhibitors in infants and children than in adults. However, infants and small children may be at greater risk of complications from incomplete reversal of neuromuscular blockade due to decreased respiratory reserve. The risks associated with incomplete reversal outweigh any risk from giving higher doses of neostigmine methylsulfate (up to 0.07 mg/kg or up to a total of 5 mg, whichever is lower).

The dose of neostigmine methylsulfate injection required to reverse neuromuscular blockade in children varies between 0.03 mg to 0.07 mg/kg, the same dose range shown to be effective in adults, and should be selected using the same criteria as used for adult patients [see *Clinical Pharmacology* (12.3)].

Since the blood pressure in pediatric patients, particularly infants and neonates is sensitive to changes in heart rate, the effects of an anticholinergic agent (e.g., atropine) should be observed prior to administration of neostigmine to lessen the probability of bradycardia and hypotension.

## Geriatric Use

Elderly patients are likely to have decreased renal function, which may prolong the duration of action of neostigmine methylsulfate. However, elderly patients also experience slower spontaneous recovery from neuromuscular blocking agents. Therefore, dosage adjustments are generally not needed in geriatric patients; however, they should be monitored for longer periods than younger adults to assure additional doses of neostigmine methylsulfate injection are not required. The duration of monitoring should be predicated on the anticipated duration of action for the neuromuscular blocking agents used on the patient.

## Renal Impairment

Elimination half-life of neostigmine was prolonged in anephric patients compared to normal subjects, so neostigmine concentration may increase in patients with impaired renal functions. Although no adjustments to neostigmine methylsulfate injection dosing appear to be warranted in patients with impaired renal function, they should be closely monitored for a longer period of time.

To assure the effects of the neuromuscular blocking agent, particularly one cleared by the kidneys, do not persist beyond those of neostigmine methylsulfate injection, the interval for re-dosing the neuromuscular blocking agent during the surgical procedure may be useful in determining whether, and to what extent, post-operative monitoring needs to be extended.

## Hepatic Impairment

The pharmacokinetics of neostigmine methylsulfate in patients with hepatic impairment have not been studied. Neostigmine is metabolized by microsomal enzymes in the liver so neostigmine concentration may increase in patients with impaired hepatic functions. Although no adjustments to the dosing of neostigmine methylsulfate injection appear to be warranted in patients with hepatic insufficiency, patients should be carefully monitored for a longer period of time.

If hepatically cleared neuromuscular blocking agents were used during the surgical procedure, their duration of action may also be prolonged by hepatic insufficiency. This could result in the effects of the neuromuscular blocking agent outlasting those of neostigmine methylsulfate injection. In this regard, the interval for re-dosing the neuromuscular blocking agent during the surgical procedure may be useful in determining whether, and to what extent, post-operative monitoring needs to be extended.

## DOSAGE AND ADMINISTRATION

### Important Dosage and Administration Instructions

- Neostigmine should be administered by trained healthcare providers familiar with the use, actions,

characteristics, and complications of neuromuscular blocking agents (NMBA) and neuromuscular block reversal agents.

- Prior to neostigmine methylsulfate injection administration and up until complete recovery of normal ventilation, the patient should be well ventilated and a patent airway maintained.
- Use a peripheral nerve stimulator capable of delivering a train-of-four (TOF) stimulus to evaluate the extent of recovery of neuromuscular function, and to determine the time of the first dose and the need for additional doses of neostigmine methylsulfate injection.
- Prior to the administration of neostigmine methylsulfate injection, there must be a twitch response to the first stimulus in the TOF of at least 10% of its baseline level (i.e., the response prior to NMBA administration).
- Dose selection should be based on the extent of spontaneous recovery at time of injection, half-life of the neuromuscular blocking agent (NMBA) to be reversed, and need for rapid NMBA reversal.
- Patients should continue to be monitored for adequacy of reversal of the effect of NMBAs for a period of time that would assure full recovery based on the patient's medical condition and the pharmacokinetics of neostigmine and the NMBA used.
- Neostigmine methylsulfate injection is administered by intravenous bolus injection. Additional, carefully adjusted bolus doses are administered according to the patient's response.
- An anticholinergic agent (e.g., atropine or glycopyrrolate) should be administered prior to or concomitantly with neostigmine methylsulfate injection.
- TOF monitoring alone should not be relied upon to determine the adequacy of reversal of neuromuscular blockade. Satisfactory recovery should be judged by the patient's ability to maintain a patent airway, adequacy of ventilation, and skeletal muscle tone.

### **Recommended Dosage in Adults**

- The recommended dose range of neostigmine methylsulfate injection is 0.03 mg/kg to 0.07 mg/kg administered as an intravenous bolus.
- A dose less than 0.04 mg/kg is recommended for reversal of the effect of NMBAs with shorter half-lives (e.g., rocuronium), or when the first twitch response to the TOF stimulus is substantially greater than 10% of baseline, or when a second twitch is present.
- A dose of 0.07 mg/kg is recommended for the reversal of the effect of NMBAs with longer half-lives (e.g., vecuronium or pancuronium), or when first twitch response is not substantially greater than 10% of baseline, or if there is need for more rapid recovery.
- Additional doses may be required. The recommended maximum total dose is 0.07 mg/kg or up to a total of 5 mg, whichever is less.

### **Recommended Dosage in Pediatric Patients, including Neonates**

Adult guidelines should be followed when neostigmine methylsulfate injection is administered to pediatric patients. Pediatric patients require neostigmine methylsulfate injection doses similar to those for adult patients.

### **Concomitant or Pre-Administration of Anticholinergic Agents**

An anticholinergic agent (e.g., atropine sulfate or glycopyrrolate) should be administered intravenously several minutes prior to or with neostigmine methylsulfate injection administration using separate syringes. For bradycardic patients, the anticholinergic agent should be administered prior to neostigmine methylsulfate injection.

### **OVERDOSAGE**

Muscarinic symptoms (nausea, vomiting, diarrhea, sweating, increased bronchial and salivary secretions, and bradycardia) may appear with overdosage of neostigmine methylsulfate, 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 may also cause a cholinergic crisis, which is characterized by increasing muscle weakness, and through involvement of the muscles of respiration, may result in death if not promptly treated.

The treatment of an overdose of neostigmine includes immediate withdrawal of all anticholinergic medication and immediate use of atropine is also recommended. Assistance of ventilation may be required if respiration is severely depressed.



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 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.

## INDICATIONS AND USAGE

Neostigmine methylsulfate injection, a cholinesterase inhibitor, is indicated for reversal of the effects of nondepolarizing neuromuscular blocking agents (NMBA) after surgery.

## HOW SUPPLIED/STORAGE AND HANDLING

Neostigmine Methylsulfate Injection, USP is supplied as a colorless liquid in a pre-filled syringe as follows:

Unit of Sale	Strength	Each
NDC 0641-6240-10	3 mg per 3 mL	NDC 0641-6240-01
Unit of 10	(1 mg per mL)	3 mL single-dose prefilled syringe

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Discard unused portion.

## ENDING INFORMATION

For additional information, please refer to the [Package Insert](#) for full prescribing information, available on [www.hikma.com](http://www.hikma.com).

To report SUSPECTED ADVERSE REACTIONS, contact Hikma Pharmaceuticals USA Inc. at 1-877-845-0689 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

Manufactured by:  
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**Document Identification Number: HK-2077-v1**