**INDICATIONS AND USAGE**

BLOXIVERZ, a cholinesterase inhibitor, is indicated for the reversal of the effects of non-depolarizing neuromuscular blocking agents (NMBAs) after surgery (1).

**DOSEAGE AND ADMINISTRATION**

1. **Important Dosage Information**

   - **BLOXIVERZ** is a cholinesterase inhibitor indicated for the reversal of the effects of non-depolarizing neuromuscular blocking agents after surgery. 
   - **BLOXIVERZ** is for intravenous use only and should be injected slowly to avoid an excessively rapid decrease in blood pressure. 
   - **BLOXIVERZ** should be administered by trained healthcare providers familiar with the use, actions, characteristics, and complications of neostigmine and anticholinergic agents. 
   - An anticholinergic agent, e.g., atropine sulfate or glycopyrrolate, should be administered concurrently with BLOXIVERZ [see Dosage and Administration (2.4)].

2. **DOSAGE in Adult Patients**

   a. Peripheral nerve stimulation devices capable of delivering a train-of-four (TOF) stimulus are essentially to effect a neuromuscular blockade in adult patients. 
   b. There must be a twitch response to the first stimulus in the TOF of at least 0.9 of baseline amplitude, i.e., the response prior to NMBA administration, prior to the administration of BLOXIVERZ. 
   c. Prior to administration of BLOXIVERZ, the time of initiation of the NMBA should be recorded and the neuromuscular blockade should be determined. Onset and time of return to baseline twitch responses should be noted to determine the need for additional doses. 
   d. BLOXIVERZ should be administered only and should be injected slowly over a period of at least 1 minute. The BLOXIVERZ dose is weight-based [see Dosage and Administration (2.3)].

3. **Dosage in Pediatric Patients, including Neonates**

   a. Prior to administration, visually inspect BLOXIVERZ for particulate matter and discoloration. 
   b. There must be a twitch response to the first stimulus in the TOF of at least 0.9 of baseline amplitude, i.e., the response prior to NMBA administration, prior to the administration of BLOXIVERZ. 
   c. Prior to administration of BLOXIVERZ, the time of initiation of the NMBA should be recorded and the neuromuscular blockade should be determined. Onset and time of return to baseline twitch responses should be noted to determine the need for additional doses. 
   d. BLOXIVERZ should be administered only and should be injected slowly over a period of at least 1 minute. The BLOXIVERZ dose is weight-based [see Dosage and Administration (2.3)].

4. **CONTRAINDICATIONS**

   BLOXIVERZ 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, fever, rash, bronchospasm, bradycardia and anaphylaxis).
   - Perinatal or mechanical obstruction of the intestinal or urinary tract.

5. **WARNINGS AND PRECAUTIONS**

   5.1. Bradycardia 

   Bradycardia has been associated with BLOXIVERZ. Atropine sulfate or glycopyrrolate should be administered prior to BLOXIVERZ to lessen the risk of bradycardia [see Dosage and Administration (2.4)]. 

   5.2. Serious Adverse Reactions in Patients with Certain Coexisting Conditions 

   BLOXIVERZ should be used with caution in patients with coronary artery disease, cardiac arrhythmias, recent acute coronary syndrome or myocardial infarctions. 

   5.3. Hypersensitivity

   Hypersensitivity to neostigmine methylsulfate is characterized by exaggerated pharmacological effects, in particular, atropine-like reactions, such as cardiac arrhythmias, hypotension, bradycardia, tachycardia, hypotension, and gastrointestinal disturbances. 

   5.4. Neuromuscular Dysfunction

   Neuromuscular dysfunction due to non-depolarizing neuromuscular blocking agents may be increased when BLOXIVERZ administered in the recovery from neuromuscular blockade is administered. 

   5.5. Neuroleptic Malignant Syndrome

   BLOXIVERZ should be used with caution in patients who have a history of neuroleptic malignant syndrome (NMS). 

   5.6. Tissue Disorders

   Tissue disorders include severe edema, erythema multiforme, urticaria, urticaria papulosa, angioedema, and anaphylaxis. 

   5.7. Respiratory Disorders

   Respiratory disorders include bronchospasm and/or dyspnea, which may be accompanied by increased respiratory rate, hypoxia, and respiratory failure. 

6. **ADVERSE REACTIONS**

   6.1. Clinical Trials Experience

   Drug-related adverse events associated with the use of BLOXIVERZ were similar to those associated with other cholinesterase inhibitors. 

   6.2. Post Marketing Experience

   BLOXIVERZ is available as:

   - Injection: 0.5 mg/mL and 1 mg/mL in 10 mL multiple-dose vials (3) 
   - 0.07 mg/kg dose is recommended for: 
   - 0.03 mg/kg dose is recommended for: 
   - The 0.07 mg/kg dose is recommended for: 
   - Should be administered by trained healthcare providers (2.1) 
   - The recommended maximum total dose is 0.07 mg/kg or up to a total of 5 mg, whichever is less. 
   - An anticholinergic agent, e.g., atropine sulfate or glycopyrrolate, should be administered prior to or concurrently with BLOXIVERZ. 

   7. **DRUG INTERACTIONS**

   7.1. Pregnancy 

   For BLOXIVERZ. BLOXIVERZ™ (Neostigmine Methylsulfate Injection), HIGHLIGHTS OF PRESCRIBING INFORMATION

   www.fda.gov/medwatch. 

   8. **USE IN SPECIFIC POPULATIONS**

   8.1. Pregnancy 

   8.2. Labor and Delivery 

   8.3. Nursing Mothers 

   8.4. Pediatric Use 

   8.5. General Use 

   8.6. Rash/Erupption 

   8.7. Hepatic Impairment 

   9. **OVERDOSAGE**

   9.1. Description 

   9.2. Clinical Pharmacology 

   9.3. Pharmacodynamics 

   9.4. Pharmacokinetics 

   9.5. Nonclinical Toxicology 

   9.6. Clinical Studies

   9.7. How Supplied/Storage and Handling

   Sections or subsections omitted from the full prescribing information are not listed.

   10. **ADVERSE REACTIONS**

   10.1. General 

   BLOXIVERZ, a cholinesterase inhibitor, should be administered prior to BLOXIVERZ to lessen the risk of bradycardia [see Dosage and Administration (2.4)].

   10.2. Serious Adverse Reactions in Patients with Certain Coexisting Conditions 

   BLOXIVERZ should be used with caution in patients with coronary artery disease, cardiac arrhythmias, recent acute coronary syndrome or myocardial infarctions. 

   10.3. Hypersensitivity 

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

   10.4. Neuromuscular Dysfunction 

   Neuromuscular dysfunction due to non-depolarizing neuromuscular blocking agents may be increased when BLOXIVERZ administered in the recovery from neuromuscular blockade is administered. 

   10.5. Neuroleptic Malignant Syndrome

   BLOXIVERZ should be used with caution in patients who have a history of neuroleptic malignant syndrome (NMS). 

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   Tissue disorders include severe edema, erythema multiforme, urticaria, urticaria papulosa, angioedema, and anaphylaxis. 

   10.7. Respiratory Disorders

   Respiratory disorders include bronchospasm and/or dyspnea, which may be accompanied by increased respiratory rate, hypoxia, and respiratory failure. 

   11. **WARNINGS AND PRECAUTIONS**

   11.1. Bradycardia 

   Bradycardia has been associated with BLOXIVERZ. Atropine sulfate or glycopyrrolate should be administered prior to BLOXIVERZ to lessen the risk of bradycardia [see Dosage and Administration (2.4)].

   11.2. Clinical Pharmacology 

   11.3. Pharmacodynamics 

   11.4. Pharmacokinetics 

   11.5. Nonclinical Toxicology 

   11.6. Clinical Studies

   11.7. How Supplied/Storage and Handling

   Sections or subsections omitted from the full prescribing information are not listed.
7. 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 BLOXIVERZ with other drugs which may alter the metabolic enzymes involved in its metabolism.

8. USE IN SPECIFIC POPULATIONS
8.1. Pregnancy
Teratogenic Effects: Pregnancy Category C. It is not known whether neostigmine methylsulfate can cause harm when administered to a pregnant woman or can affect reproductive capacity. BLOXIVERZ should be given to a pregnant woman only if clearly needed.

8.2. Labor and Delivery
Neostigmine methylsulfate is a competitive anticholinesterase agent. Cholinergic crisis may occur if anticholinesterase drug therapy is discontinued abruptly in patients maintained on anticholinesterase drugs. Overdose of BLOXIVERZ can cause cholinergic crisis, which is characterized by increased bronchial and salivary secretions, and bradycardia. May appear with overshoot of BLOXIVERZ when used for intubation. Use with caution when using BLOXIVERZ with other drugs which may alter the metabolic enzymes involved in its metabolism.

8.3. Neonates
For the treatment of neonatal respiratory failure, BLOXIVERZ may be administered to neonates of less than 1 year of age. It is important that the patient’s individual needs be considered because the pharmacokinetics of neostigmine methylsulfate in neonates have not been studied.

8.4. Pediatric Use
The dose of BLOXIVERZ required to reverse neuromuscular blockade in pediatric patients of all ages.

8.5. Geriatric Use
Because elderly patients are more likely to have decreased renal function, use of BLOXIVERZ should be monitored for a longer period in elderly patients. The duration of action of neostigmine methylsulfate is similar to that of the elderly; however, elderly patients also experience slower spontaneous recovery from neuromuscular blockade. Therapy should be avoided if the patient is not able to cooperate.

8.6. Renal Impairment
Elimination half-life of neostigmine methylsulfate was prolonged in patients with renal insufficiency compared to normal controls. Elimination half-life for normal and transplant and anephric patients were 79.8 ± 48.6, 0.12 and 1.4 L/kg. Protein binding of neostigmine methylsulfate to human serum albumin ranges from 15 to 25%. Neostigmine methylsulfate volume of distribution is reported between 3 and 11 L/kg.

8.7. Hepatic Impairment
The pharmacokinetics of neostigmine methylsulfate in patients with hepatic impairment have not been studied. Neostigmine methylsulfate is metabolized by microsomal enzymes in the liver. Neostigmine methylsulfate volume of distribution is reported between 3 and 11 L/kg.

8.8. Overdose
Muscular symptoms (nausea, vomiting, diarrhea, sweating, increased bronchial and salivary secretions, and bradycardia) may appear with overshoot of BLOXIVERZ when used for intubation. Use with caution when using BLOXIVERZ with other drugs which may alter the metabolic enzymes involved in its metabolism.

10. OVERDOSE
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