Neuronox® Injection

(Clostridium botulinum toxin type A)

Forms and Presentation

Neuronox®: 50 U, Lyophilized powder for injection, Box of 1 vial

Neuronox®: 100 U, Lyophilized powder for injection, Box of 1 vial

Neuronox®: 200 U, Lyophilized powder for injection, Box of 1 vial

Composition

Neuronox®: 50 U, Each vial contains Clostridium Botulinum Toxin type A 50 units (U)

Neuronox®: 100 U, Each vial contains Clostridium Botulinum Toxin type A 100 units (U)

Neuronox®: 200 U, Each vial contains Clostridium Botulinum Toxin type A 200 units (U)

Excipients: Human Serum albumin, Sodium Chloride.

One unit(U) of Neuronox® corresponds to the calculated median interperitoneal lethal dose (LD_{50}) in mice.

Description

It appears as a lyophilized white powder for injection in a colorless transparent vial.

Indication

It is indicated for the treatment of benign essential blepharospasm in patients 18 years of age and above.

Dosage and administration

■ Blepharospasm

For blepharospasm, reconstituted Neuronox® (see Dilution Table) is injected using a sterile , 27 – 30 gauge needle without electromyographic guidance. The initial recommended dose is 1.25 – 2.5 U (0.05 mL to 0.1 mL volume at each site) injected into the medial and lateral pre-tarsal orbicularis oculi of the upper lid and into the lateral pre-tarsal orbicularis oculi of the lower lid. In general, the initial effect of the injections is seen within three days and reaches a peak at one to two weeks post-treatment. Each treatment lasts approximately three months, following which the procedure can be repeated. At repeat treatment sessions, the dose may be increased up to two-fold if the response from the initial treatment is considered insufficient-usually defined as an effect that does not last longer than two months. However there appears to be little benefit obtainable from injecting more than 5.0 U per site. Some tolerance may be found when the drug is used in treating blepharospasm if treatments are given any more frequently than every three months, and is rare to have the effect be permanent.

The cumulative dose of Neuronox® treatment in a 30-day period should not exceed 200 U.

■ Dilution Technique

Prior to injection, reconstitute freeze-dried Neuronox® with sterile normal saline without a preservative. 0.9% Sodium Chloride Injection is the recommended diluent.

Draw up the proper amount of diluent in the appropriate size syringe. Since the drug is denatured by bubbling or similar violent agitation, the diluent should be injected gently into the vial. Discard the vial if vaccum does not pull the diluent into the vial. Record the date and time of reconstitution on the space on the label. Neuronox® should be administered within four hours after reconstitution. During this time period, reconstituted Neuronox® should be stored in a refrigerator (2 - 8°C). Reconstituted Neuronox® should be clear, colorless and free of particulate matter. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Because the drug and diluent do not contain any preservative, one vial of Neuronox® should be used for a single patient.

Dilution Table

Diluent added (0.9% Sodium Chloride Injection)	Resulting dose (U/0.1 mL)
1.0 mL	10.0U
2.0 mL	5.0U
4.0 mL	2.5U
8.0 mL	1.25U

Note: These dilutions are calculated for an injection volume of 0.1 mL. A decrease or increase in dose is also possible by administering a smaller or larger injection volume - from 0.05 mL (50% decrease in dose) to 0.15 mL (50% increase in dose).

Precautions

1.Warnings

Since the active constituent in this drug is Clostridium botulinum toxin type A neurotoxin which is derived from *Clostridium botulinum*, the recommended dosages and frequency of administration should be observed with a full understanding of the precautions in use. Physicians administering the drug must understand the relevant neuromuscular and/or orbital anatomy of the area involved and any alterations to the anatomy due to prior surgical procedures. An understanding of standard electromyographic techniques is also required for the administration of the drug. The recommended dosage and frequency of administration for Neuronox® should not be exceeded.

1) Hypersensitivity reactions

Serious and/or immediate hypersensitivity reactions have been rarely reported with other botulinum toxin injections. These reactions include anaphylaxis, urticaria, soft tissue edema and dyspnea. One fatal case of anaphylaxis has been reported in which lidocaine was used as a diluent but the causal agent cannot be reliably determined. If such a reaction occurs, further injection of the drug should be discontinued and appropriate medical therapy should be immediately instituted.

2) Pre-existing neuromuscular disorders

Individuals with peripheral motor neuropathic diseases (e.g., amyotrophic lateral sclerosis, or motor neuropathy) or neuromuscular junctional disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) may be at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of botulinum toxin injection. P

Published medical literature with other botulinum toxin injection has reported rare cases of administration of a botulinum toxin to patients with known and unrecognized neuromuscular disorders where the patients have shown extreme sensitivity to the systemic effects of typical clinical doses. In some of these cases, dysphagia has lasted several months and required placement of a gastric feeding tube.

3) Dysphagia

Dysphagia is a commonly reported adverse event following treatment of cervical dystonia patients with all botulinum toxins. In these patients, there are reports of rare cases of dysphagia severe enough to warrant the insertion of a gastric feeding tube. There are also rare case reports where subsequent to the finding of dysphagia a patient developed aspiration pneumonia and died.

4) There have also been rare reports of adverse events with other botulinum toxin injection involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including cardiovascular disease.

2. Contraindications

Neuronox® should not be administered when;

1) The patients have known hypersensitivity to any ingredient in the formulation of Neuronox®.

2) The patients have neuromuscular junctional disorders (e.g., myasthenia gravis, Lambert-Eaton syndrome or amyotrophic lateral sclerosis). (The diseases may be exacerbated due to the muscle relaxation activity of the drug.)

3) The drug is used for the treatment of cervical dystonia in the patients with severe respiratory disorder.

4) The patients are pregnant women, women of childbearing potential, or mothers under lactation.

3. Precautions

Neuronox® should be administered with caution in;

1) Patients under treatment by other muscle relaxant (e.g., tubocurarine chloride, dantrolene sodium, etc.) [Muscle relaxation may be potentiated or risks of dysphagia may be increased].

2) Patients under treatment by drugs with muscle relaxing activity, e.g., spectinomycin HCl, aminoglycoside antibiotics (gentamicin sulfate, neomycin sulfate, etc.), polypeptide antibiotics (polymixin B sulfate, etc.), tetracycline antibiotics, lincomycin antibiotics (lincosamides), muscle relaxants (baclofen etc.), anti-cholinergic agents (scopolamine butylbromide, trihexylphenidil HCl, etc.), benzodiazepine and the similar drugs (diazepam, etizolam, etc.), benzamide drugs (thiapride HCl, sulpiride, etc.). [Muscle relaxation may be potentiated or risks of dysphagia may be increased].

4. Adverse reactions

1) General

There have been rare spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin.

There have also been rare reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. The exact relationship of these events to the botulinum toxin injection has not been established.

The following events have been reported with other botulinum toxin injection and a causal relationship to the botulinum toxin injected is unknown: skin rash (including erythema multiforme, urticaria and psoriasiform eruption), pruritus, and allergic reaction. In general, adverse events occur within the first week following injection of the drug and while generally transient may have a duration of several months.

Local pain, tenderness and/or bruising, traction, swelling, hot feeling or hypertonia at injection site or adjacent muscles may be associated with the injection. Local weakness of the injected muscle(s) represents the expected pharmacological action of botulinum toxin. However, weakness of adjacent muscles may also occur due to spread of toxin. When injected in patients with blepharospasm or cervical dystonia, some distant muscles from injection site can show increased electrophysiologic jitter (rapid variation in a waveform) which is not associated with clinical weakness or other types of electrophysiologic abnormalities.

2) Strabismus

Extraocular muscles adjacent to the injection site can be affected, causing ptosis or vertical deviations, especially with higher doses of the drug. The incidence rates of these adverse effects with other botulinum toxin injections were as follows; in 2058 adults who received a total of 3650 injections for horizontal strabismus, ptosis were observed in 15.7% of the patients and vertical deviations were in 16.9%.

Inducing paralysis in one or more extraocular muscles may produce spatial disorientation, double vision, or past-pointing. Covering the affected eye may alleviate these syndromes.

The incidence of ptosis was 0.9% after inferior rectus injection and 37.7% after superior rectus injection.

Ptosis (0.3%) and vertical deviation greater than two prism diopters (2.1%) were reported to persist for over six months in 5587 injections of horizontal muscles in 3104 patients with other botulinum toxin injection. In these patients, the injection procedure itself caused nine scleral perforations. A vitreous hemorrhage occurred in one case and later cleared. No retinal detachment or visual loss occurred in any case. Sixteen retrobulbar hemorrhage occurred without visual loss. Decompression of the orbit after five minutes was done to restore retinal circulation. Five eyes had pupillary change consistent with ciliary ganglion damage (Adie's pupil).

One patient developed anterior segment ischemia after receiving other botulinum toxin injection into the medial rectus muscle under treatment for esotropia.

3) Blepharospasm

In a study of blepharospasm patients who received an average dose per eye of 33 U (injected at 3 to 5 sites) of other botulinum toxin injections, the most frequently reported treatment-related adverse reactions were ptosis (20.8%), superficial punctuate keratitis (6.3%) and eye dryness (6.3%). All of these events were mild to moderate except for one case of ptosis which was rated severe.

Other events reported in prior clinical studies with other botulinum toxin injections in decreasing order of incidence include: irritation , tearing , lagophthalmos , photophobia , ectropion , keratitis, diplopia and entropion, diffuse skin rash and local swelling of the eyelid skin lasting for several

days following eyelid injection .
In two cases of VII nerve disorder (one case of an aphakic eye) reduced blinking from other botilunum toxin injections of the orbicularis muscle led to serious corneal exposure, persistent epithelial defect, and corneal ulceration. Perforation occurred in the aphakic eye and required corneal grafting.
A report of acute angle closure glaucoma one day after receiving an injection of botulinum toxin for blepharospasm was received, with recovery four months later after laser iridotomy and trabeculectomy.
Focal facial paralysis, syncope and exacerbation of myasthenia gravis have also been reported after treatment of blepharospasm. Frequently, anopia or conjunctivitis has been reported, which required appropriate measures be taken.
In 660 patients with other botulinum toxin injections (for 6 years in korea), a total of 41 patients (6.2%) showed adverse reactions . Adverse reactions included ptosis in 17 patients (2.6%), local swelling in 5 (0.8%), lacrimal disorders in 3 (0.5%), bulbar irritation in 3 (0.5%) lagophtalmos in 3 (0.5%), muscle weakness in 3 (0.5%), eye dryness in 3. Adverse reactions obscure in causality included traction at injection site in 2 patients (0.3%) conjunctival congestion in 2 (0.3%), and eye pain in 1 (0.2%).
4) Cervical dystonia
The most frequently reported adverse events with other botilunum toxin injections in the treatment of spasmodic torticollis included pain and soreness at injection sites, local weakness, symptomatic general weakness and fatigue . However , fatigue was also reported in patients treated with placebo. Dysphagia and local weakness may be attributable to an extension of the pharmacology of botulinum toxin resulting from the spread of the toxin from injected muscles. Since the adverse reactions associated with dosage are more frequently observed in female patients, muscle mass should be taken into consideration when selecting the appropriate dose. Other adverse events include; nausea, dizziness, headache, numbness, stiffness, and bruising.
5) Pediatric cerebral palsy
Safety tests of Neuronox® for the treatment of dynamic equinus foot deformity due to spasticity in pediatric cerebral palsy patients was performed. As is expected for any intramuscular injection procedure, localized pain was associated with the injection in the patients. All treatment-related adverse events were mild-to-moderate in severity.
The adverse reactions most frequently reported as related to treatment include recession, leg pain, leg (local) weakness, and general weakness. The percentage of patients who experienced these events at least once during the study are summarized below:

	Neuronox® , n=215
Recession	9.3 %
Leg pain	2.3 %
Weakness, local	2.3 %
Weakness, general	2.3 %

Recession may be attributable to a change in ankle position and gait pattern and/or local weakness. Local weakness represents the expected pharmacological action of botulinum toxin.
Other treatment-related adverse reactions reported in 1% of patients were: leg cramps, fever, knee pain, ankle pain, pain at the injection site post-treatment, and lethargy.
5. General precautions
1) This drug contains albumin, a derivative of human blood. When a medicinal product derived from human blood or serum is administered in human body, the potential of infectious diseases by transmissible agents cannot be completely excluded. It may include any pathogenic agent that is still unknown. In order to decrease the risks of infection by transmissible agents, particular cares including appropriate assay methods are given to the controls of the donors and donation site, to the manufacturing process and to the virus removal/inactivation process.
2) Due to the nature of the disease being treated, the effects of the drug on the ability to drive or to operate machines cannot be predicted.
3) During the administration of other botilunum toxin injection for the treatment of strabismus, retrobulbar hemorrhages sufficient to compromise retinal circulation have occurred form needle penetrations into the orbit . It is recommended that appropriate instruments to decompress the orbit be accessible. Ocular (globe) penetrations by needles have also occurred. An ophthalmoscope to diagnose this condition should be available. Inducing paralysis in one or more extraocular muscles may produce spatial disorientation, double vision or past pointing. Covering the affected eye may alleviate these symptoms.
4) Blepharospasm
Reduced blinking from botulinum toxin injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defect and corneal ulceration, especially in patients with VII nerve disorders. One case of corneal perforation in a aphakic eye requiring corneal grafting has occurred because of this effect. Careful testing of corneal sensations in eyes previously operated upon, avoidance of injection into the lower lid area to avoid ectropion, and vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.
6. Drug interactions
1) The effect of botulinum toxin may be potentiated by aminoglycoside antibiotics or other drugs that interfere with neuromuscular transmission e.g. tubocurarine-type muscle relaxants. Concomitant use of Neuronox® with aminoglycosides or spectinomycin is contraindicated.
Polymyxins, tetracyclines and lincomycin should be used with caution in the Neuronox® - treated patient.
2) The effect of administering different botulinum neurotoxin serotypes at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.
7. Pregnancy and lactation
Safety in pregnant women and nursing mothers has not been established in this drug.
Other botulinum toxin injection has been shown to produce abortions and effects at daily doses of 0.125 U/kg/day and at 2 U/kg and higher in rabbits; whereas in rats and mice, no abortions or effects were observed when up to 4 U/kg of botulinum toxin were injected. Doses of 8 and 16 U/kg in rats and mice have been shown to be associated with reduced fetal body weight and/or delayed ossification of the hyoid bone, which may be reversible.
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Neuronox® is administered to a nursing woman.
Neuronox® is contraindicated in pregnancy and lactation.
8. Pediatric use
Safety and effectiveness in children below the age of 18 have not been established.
9. Carcinogenesis, mutagenesis, impairment of fertility
Long term studies in animals have not been performed to evaluate carcinogenic potential of botulinum toxin.
10. Overdosage
Signs and symptoms of overdose are not apparent immediately post-injection. Should accidental injection or oral ingestion occur, the person should be medically supervised for up to several weeks for signs or symptoms of systemic weakness or muscle paralysis.
An antitoxin is available in the event of immediate knowledge of an overdose or misinjection. The antitoxin will not reverse any botulinum toxin induced muscle weakness effects already appeared by the time of antitoxin administration.
11. Precaution in use
Unopened vials of Neuronox® should be stored under refrigeration (2~8°C). After reconstitution, Neuronox® should be stored in a refrigerator (2~8°C) for up to 4 hours prior to use.
For safe disposal, unused vials should be sterilized after melting it with a little amount of water. Equipment used with the drug (such as syringes) should also be sterilized. The residual Neuronox® should be inactivated using dilute hypochlorite solution (0.5%).
12. Information for patients
Patients with blepharospasm may have been extremely sedentary for a long time. Such patients should be cautioned to resume activity slowly and carefully after the administration of Neuronox®.
Neuronox® blocks neuromuscular transmission binding to acceptor sites on motor nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine.When injected intramuscularly at therapeutic doses, Neuronox® produces partial chemical denervation of the muscle resulting in a localized muscle activity reduction. In addition, the muscle may atrophy, axonal sprouting may occur, and extra junctional acetylcholine receptors may develop. There is evidence that reinnervation of the muscle may occur, thus slowly reversing muscle denervation produced by Neuronox®.
The paralysis activity of botulinum toxin is effective for the relief of excessive abnormal contraction associated with blepharospasm.
When injected into neck muscles, other botulinum toxin injection acts to provide relief from both objective signs and subjective symptoms of spasmodic torticollis (cervical dystonia). These improvements may include reduced head rotation, reduced shoulder elevation, decreased size and strength of hypertrophic muscles.
The efficacy of another botulinum toxin product in deviations over 50 prism diopters, in restrictive strabismus, in Duane's syndrome with lateral rectus weakness, and in secondary strabismus caused by prior surgical over-recession of the antagonist has not been established or repeated injections may be required for the treatment.
Botulinum toxin is ineffective in chronic paralytic strabismus and only surgical repair is effective to reduce antagonist contracture.
Presence of antibodies to botulinum toxin type A may reduce the effectiveness of botulinum toxin therapy. In clinical studies, reduction in effectiveness due to antibody production has occurred in one patient with blepharospasm receiving 3 doses of botulinum toxin over a 6 week period totaling 92 U, and in several patients with torticollis who received multiple doses experimentally, totaling over 300 U in a one month period. For this reason, the dose of Neuronox® for strabismus and blepharospasm should be kept in any case below 200 U in a one month period.

Storage

The unopened lyophilized vial should be stored at 2°C - 8°C or at -15°C ~ -5°C .

How supplied

Neuronox® is supplied in a single use vial.

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Benta S.A.L , Dbayeh - Lebanon
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This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

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