The First Choice of
Botulinum Toxin Type A

Neuronox®

Medytox

Biotechnology that Changes The Future

NEURONOX

Medytox is

a global biopharmaceutical company

studying the time of humankind

Neuronox®

The First Choice of Botulinum Toxin Type A

The first company in Korea to develop the BoNT/A product **Neuronox®** [4]

The first company in the world to develop a liquid BoNT/A product, **Innotox®** [6]

The first company in the world to develop the BoNT/A product **Coretox®**, which eliminates the use of non-toxic proteins, HSA, and all animal derived ingredients [7]

The strain used in Medytox is *Clostridium botulinum* type A Hall hyper[1]

C. botulinum type A Hall hyper is a **hypertoxin producer** that creates many high quality toxins in a simple growth medium, and is the strain best suited for use in treatments.[2]

Characteristics of *C. botulinum* type A Hall hyper[3]

Fast production[3]	Produces toxins rapidly over the same time period.
Increased production[3]	Produces the most toxins over the same time period.
Hypertoxigenic strain[3]	Produces toxins with the highest toxicity when cultivated in the same growth medium(TPM).

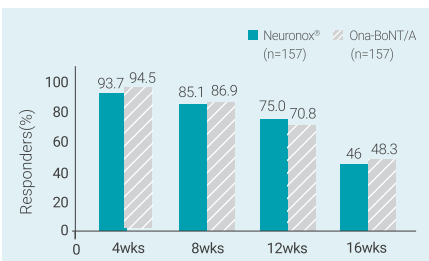
Study design[3]	The kinetics of botulinum toxin gene expression have been investigated in *C. botulinum* type A strains 62A, Hall A-hyper, and type A(B) strain NCTC 2916 during the growth cycle. The analysis were performed in TPGY and type A TPM.

Neuronox® has proven to be safe and effective for **improving glabellar frown lines**[4]

Neuronox® is as safe and effective as Ona-BoNT/A in reducing moderate to severe glabellar frown lines.[4]

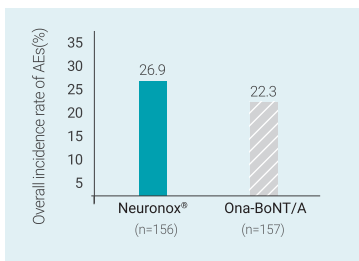
Efficacy Assessment

Responder* rate at maximum frown during Weeks 4, 8, 12, and 16



Safety Assessment

Overall incidence of adverse events



Adapted from Won CH, et al. 2013.

Study design	A double-blind, randomized, active-controlled, Phase III clinical trial. 314 patients were randomly assigned to one of two groups in a 1:1 ratio to receive 20 U of either Neuronox® or Ona-BoNT/A, followed by assessing improvement in the glabellar frown lines with FWS.
Primary Efficacy Endpoint	The responder rate based on the investigator's live assessment on maximum frown lines at Week 4.
Safety Endpoint	AE signs and symptoms reported by the investigator and subject, and the results of physical examinations and laboratory tests.

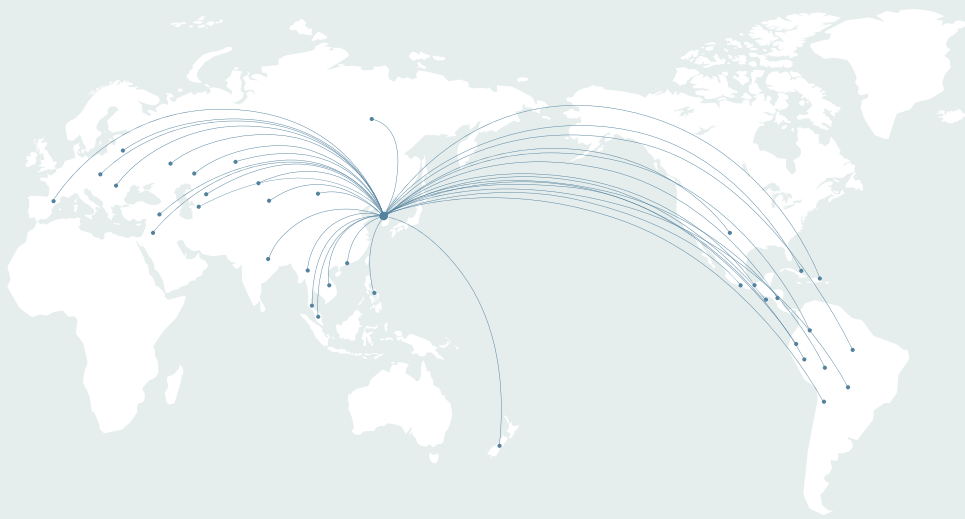
* Responder : A subject whose moderate glabellar line score is improved by at least 1 point, or whose severe glabellar line score is improved by at least 2 points.

BoNT/A, botulinum toxin type A; FWS, facial wrinkle scale; AE, adverse event

World-wide Product,
Neuronox®

Neuronox® is a global product, registered in 29 countries with rapidly growing sales over the world.(2022.12)[5]

Neuronox® registered globally[5]



Neuronox® is also being sold worldwide under different brand names, as **Siax®, Botulift®, Cunox®, Meditoxin® and Acebloc®.**

Detailed Product Description

Neuronox®

(Clostridium botulinum toxin type A)

Appearance

It is lyophilized white powder in a colorless transparent vial

Indication and Usage

1. Treatment of Benign Essential Blepharospasm in patients 18 years of age and older.

2. Treatment of equinus foot deformity due to spasticity in pediatric cerebral palsy patients 2 years of age and older

3. Temporary improvement of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adults over the age of 20 and below the age of 65.

4. Muscle Spasticity: treatment of upper limb spasticity associated with stroke in patient 20 years of age and older.

5. Temporary improvement of moderate to severe lateral canthal lines associated with orbicularis oculi activity in adults over the age of 20 and below the age of 65.

6. Treatment of cervical dystonia in adults

Dosage and Administration

1. Blepharospasm

Reconstitute Neuronox (see Dilution Table) and inject by using a sterile, 28~30 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) for 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. The dose might be increased twice for each injection site in the patients with history of treatments. Dose adjustments might be also done in consideration of spasm or the symptom. However, injecting more than 5.0 U per site appears to have little or no benefit compared to the recommended dose. The total dose of Neuronox administered within a 30-day period must not exceed 200 U.

2. Cerebral palsy in Pediatric Patients

Reconstitute Neuronox (see Dilution Table) and inject by using a sterile, 26-30 gauge needle, to each of the medial and lateral heads of the gastrocnemius muscles. The dosing of Neuronox for pediatric lower limb spasticity is based on Units per kilogram of body weight. The recommended dose is 4 Units/kg for unilateral lower limb injections or 6 Units/kg for bilateral lower limb injections. However, the total dose of Neuronox must not exceed 200 units. Monitor patient for at least 30 minutes for any presence of acute adverse events after administration.

3. Glabellar Lines

Neuronox is reconstituted to make 50U/1.25 mL (4U/0.1 mL) with 0.9% non-preserved sterile saline. Using a 30 gauge needle, 20U Neuronox is injected to two places on the corrugators muscle for each eye and one place on the procerus muscle, total of 5 sites with 0.1 mL per site. To reduce complications of drooping (ptosis) eyelids, injection is avoided in the levator palpebrae superioris vicinity, especially for patients with large corrugator muscles. When administering injection in the medial end of corrugators muscle and in the midpoint between each eyebrow, it must be done in a place at least 1 cm apart from supraorbital ridge.

Neuronox must be injected with caution so that it does not enter the blood vessel. Firmly place a thumb or index finger on the area below the orbital ridge prior to injection to prevent effusion below the orbital ridge. Ensure the injected volume and dose are accurate.

Glabellar facial lines arise from the activity of the corrugator and orbicularis oculi muscles. These muscles move the brow medially, and the procerus and depressor supercilii pull the brow inferiorly. This creates a frown or "furrowed brow". The location, size, and use of the muscles vary markedly among individuals. Lines induced by facial expression occur perpendicular to the direction of action of contracting facial muscles.

The treatment effect of Neuronox for glabellar lines lasts approximately 3-4 months. The safety and effectiveness of frequent injection of Neuronox in has not been clinically evaluated. Thus, frequent injection of Neuronox is not recommended.

In general, the chemical denervation occurs 1 to 2 days after injection and the intensity increases throughout the first week of injection.

4. Upper limb spasticity

Dosing in initial and sequential treatment sessions should be tailored to the individual based on the size, number and location of muscles involved, severity of spasticity, the presence of local muscle weakness, the patient's response to previous treatment. The clinical improvement of muscle spasticity lasts 4 ~ 6 weeks following the treatment.

Dosing by muscle for adult upper limb spasticity in the clinical trial:

Muscle	Total dose	: Number of sites
Biceps brachii	100-200 U	: up to 4 sites
Flexor digitorum profundus	15-50 U	: 1-2 sites
Flexor digitorum sublimis	15-50 U	: 1-2 sites
Flexor carpi ulnaris	10-50 U	: 1-2 sites
Flexor carpi radialis	15-60 U	: 1-2 sites

In the clinical trial, administered dose did not exceeded 360 U and were divided among selected muscle at a given treatment session.

Administer Neuronox using a sterile 24-30 gauge needle for superficial muscles, and a longer needle may be used for deeper musculature. Localization of the involved muscles with techniques such as needle electromyographic guidance or nerve stimulation is recommended.

5. Lateral Canthal Lines (crow's feet lines)

Lateral canthal lines arise largely from the activity of the orbicularis oculi muscles around the eye responsible for blinking and eyelid closure. Forceful contraction of the orbicularis oculi results in lateral and radially oriented folds (crow's feet lines) which originate from the lateral canthus. The distribution of these radial lines differs among patients.

Injections should be given with the needle bevel tip up and oriented away from the eye. Inject 4 Units/0.1 mL of reconstituted Neuronox into 3 sites per side (6 total injection points) in the lateral orbicularis oculi muscle for a total of 24 Units/0.6 mL (12 Units per side).

The safety and efficacy of re-administration interval for the treatment of LCL using Neuronox has not been evaluated in the clinical trial.

6. Cervical Dystonia

Administer Neuronox (see dilution table for recommended dilution) by using an appropriately sized needle (e.g., 25-30 gauge), where the needle size may change depending on the musculature. The administration sites include sternocleidomastoid, levator scapulae, scalene complex, splenius cervicis, trapezius and others (refer to Section 14. Instruction for Physician).

Localization of the involved muscles with electromyographic guidance may be useful. No more than 50 U per site should be administered. Limiting the total dose injected into the sternocleidomastoid muscle to 100 Units or less may decrease the occurrence of dysphagia. In addition, the product should not be injected to both sides of sternocleidomastoid to prevent the occurrence of dysphagia. Total dosing in initial session should not exceed 200 U, and the sequential treatment sessions should be tailored to the individual patient based on the result from the initial session. The total dosing for sequential treatment should not exceed 300 U.

The safety and efficacy of Neuronox in the treatment of cervical dystonia were evaluated for 12 weeks after single treatment session.

Dilution technique

Prior to injection, reconstitute each freeze-dried vial of Neuronox with only sterile, preservative-free 0.9% Sodium Chloride Injection. Draw up the proper amount of diluent in the appropriate size syringe, and slowly inject the diluent into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Gently mix Neuronox with the diluent by rotating the vial. Neuronox should be administered within 24 hours after reconstitution. During this time period, unused reconstituted Neuronox should be stored in a refrigerator (2° to 8°C) for up to 24 hours until time of use. 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. Neuronox vials are for single-dose only. Discard any unused portion.

Dilution table

Diluent Added (0.9 % Sodium Chloride Injection)	Resulting Dose Units (U/0.1 mL)
0.5 mL	10.0 U
1.0 mL	5.0 U
2.0 mL	2.5 U
4.0 mL	1.25 U

Note: These dilutions are calculated for an injection volume of 0.1 mL. A decrease or increase in the Neuronox 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)

How Supplied/Storage and Handling

Unopened vials of Neuronox should be stored in a freezer (-15 ~ -5℃) or refrigerator (2 ~ 8℃). After reconstitution, Neuronox should be stored in a refrigerator (2 ~ 8℃) for up to 24 hours until time of use. For safe disposal, sterilize after dissolving the constituents with water. Used vials or syringes should be sterilized before discarding. Any residuals in vials or syringes should be inactivated using hypochlorite (0.5%).

Manufactured by: Medytox Inc.
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※ Please refer to the local package insert for more information.

Healthcare Professionals Only

Neuronox®

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References **1.** *Yang GH and Jung HH. Dermatol Surg. 2013 Jan;39(1 Pt 2):165-70.* **2.** *Schantz EJ and Johnson EA. Perspect Biol Med. 1997;40(3):317-27.* **3.** *Bradshaw M, et al. Anaerobe. 2004;10(6):321-33.* **4.** *Won CH, et al. Dermatol Surg. 2013;39(1 Pt 2):171-8.* **5.** *Data on file, Medytox Inc.* **6.** *Kim JE, et al. Plast Reconstr Surg. 2015 Mar;135(3):732-741.* **7.** *Lee J, et al. Medicine (Baltimore). 2022 Nov 4;101(44):e31367.*

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