NEURONOX

Global Botulium Toxin Type A

Neuronox®

Medytox

Medytox is
a global biopharmaceutical company
studying time of humankind.

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

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

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

The strain used in Medytox is *Clostridium botulinum* Hall A 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, 4]

Fast production[3]	Produces more toxins over the same time period.
Higher toxicity[4]	Produces toxins with the highest potency over the same time period.
Hypertoxigenic strain[4]	Produces the most toxins when cultivated in the same growth medium (TPM).

Study design[4]: 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.

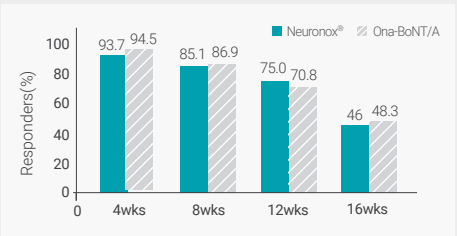
C. Botulinum, clostridium botulinum; BoNT, botulinum toxin; BoNT/A, botulinum toxin type A; HSA, human serum albumin; TPM, toxin production media; TPGY, trypticase peptone glucose yeast.

Neuronox® has proven to be safe and effective for **improving glabellar frown lines** [5]

- Neuronox® is as safe and effective as Ona-BoNT/A in reducing moderate to severe glabellar frown lines.[5]

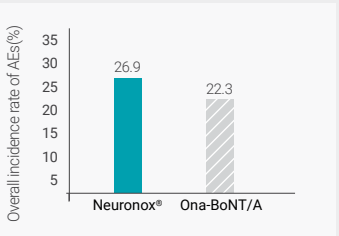
Efficacy Assessment

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



Safety Assessment

Overall incidence of adverse events



- **Study Methodology** — 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.

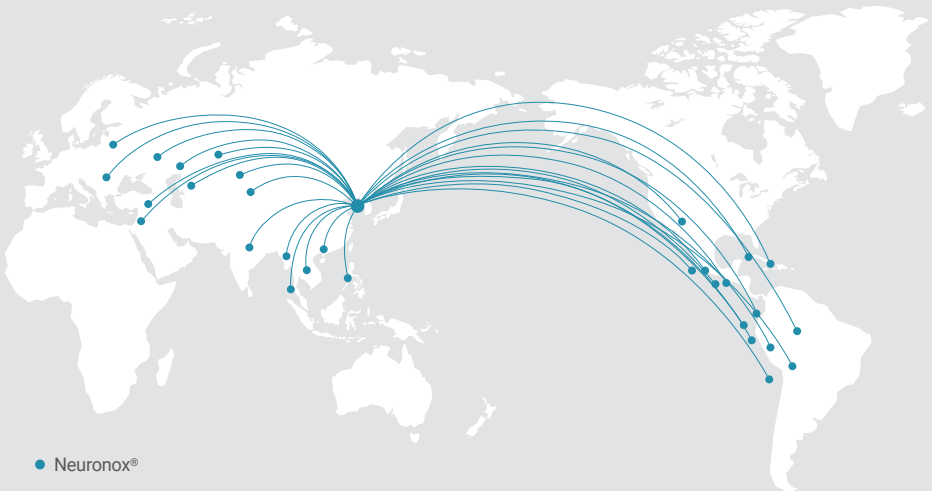
* Responder : A subject whose moderate glabellar line score is improved by at least 1 point, or whose severe glabellar line score is improved by at least 2 points.

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

World-wide Product

Neuronox® is registered in 31 countries including Korea, Brazil, India, Hong Kong, Ukraine, Thailand and Mexico. Currently, it is in the process of registration in 30 additional countries.

- Neuronox® registered globally [1]



- Neuronox®

Registration Status of Neuronox®
(2018. 02)

Asia	Korea HongKong India Iran Kazakhstan Kyrgyzstan Lebanon Mongolia Myanmar Philippines Thailand Uzbekistan Vietnam Syria
America	Bolivia Brazil Chile Colombia Costa Rica Dominican Republic Ecuador El Salvardor Guatemala Mexico Nicaragua Panama Paraguay Peru Trinidad and Tobago
Europe	Belarus Georgia

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)

Description

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

Indication and Usage

1. NEURONOX® is indicated for the treatment of benign essential blepharospasm in patients 18 years of age and older.

2. NEURONOX® is indicated for the treatment of equinus foot deformity due to spasticity in pediatric cerebral palsy patients 2 years of age and older.

3. Temporary improvement of serious glabellar wrinkles ranging from moderate to severe associated with corrugators muscle and/or procerus muscle activities in adults over the age of 20 and below the age of 65.

4. Muscle spasticity : NEURONOX® is indicated for the treatment of upper limb spasticity associated with stroke in patient 20 years of age and older.

Dosage and Administration

1. 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.

2. Pediatric cerebral palsy

For the pediatric cerebral palsy, reconstituted NEURONOX® (see Dilution Table) is injected using a sterile,26-30 gauge needle. It is recommended to inject to each of the medial and lateral heads of the gastrocnemius muscles. A total dose of 4U/kg bodyweight is recommended for the affected gastrocnemius muscle in patients with hemiplegia. And in patients with diplegia, the recommended dose is 6U/kg bodyweight divided between both legs. The maximum dose administered must not exceed 200U/patient at a time. After injection, patient should be monitored for at least 30 minutes for any presence of acute adverse event.

3. Glabellar Wrinkles

NEURONOX® is reconstituted to make 100U/2.5mL (4U/0.1 mL) with 0.9% non-preserved sterile saline.

Using a 30 gauge needle, 20U of 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 pat ient s with large corrugators muscles. When administering inject ion 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® is inj e c ted wi th c a u t i o n s o t h a t i t do e s n o t ent e r t he blood vessel, and to prevent effusion from the area below the orbital ridge, firmly place a thumb or an index finger on the area below the orbital ridge prior to injection. During injection, the needle should point upward toward the center and injection dose must be measured accurately. The corrugators muscle and orbicularis oculi muscle move the center of the forehead and generate the glabellar facial wrinkles. The procerus muscle and depressor supercilii muscle pull the forehead down. Frowning or glabellar wrinkles are produced by these muscles. Because the position, size, and use of these muscles are different for individuals, an effective dose is determined based on general observations on the patient's ability to move the injected superficial muscles. The treatment effect of NEURONOX® for glabellar wrinkles lasts approximately 3-4 months. Frequent injection of NEURONOX® has not been clinically evaluated for safety and effectiveness, and it is not recommended. In general, the first NEURONOX® injection induces chemical denervation in the injected muscles 1 to 2 days after injection and its intensity increases during the first week.

4. Muscle Spasticity

The exact dosage and the number of injection should be tailored to the individual based on the size, the number and location of the muscles involved, the severity of spasticity, presence of local muscle weakness, and the patient's response to previous treatment. Clinical improvement in muscle tone is seen four to six weeks following treatment.

In controlled clinical trials, the following doses are administered:

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

In the clinical trial, doses are not over 360U, injected into individual muscles.

Reconstituted NEURONOX® is injected 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 electromyographic guidance or nerve stimulation techniques is recommended.

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. The diluent should be injected gently into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Gently mix NEURONOX® with the saline by rotating the vial. NEURONOX® should be administered within 24 hours after reconstitution. During this time period, reconstituted NEURONOX® should be stored in a refrigerator(2 - 8℃). 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	10.0 U
2.0 mL	5.0 U
4.0 mL	2.5 U
8.0 mL	1.25 U

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).

How supplied

NEURONOX® is supplied in a single use vial.

Expiration

The shelf-life of NEURONOX® is 36 months from the manufacturing date.

Manufactured by: Medytox Inc.

※ Please refer to the package insert for more information.

Healthcare Professionals Only

Studying the Time of Humankind

Medytox

Contact Information

Medytox Global Business Center
Medytox Bldg,626,Teheran-ro, Gangnam-gu, Seoul, Korea
internationalsales@medytox.com

www.medytox.com
www.medytoxacademy.com

References. ***1***. *K. A. Foster, Ch2. Botulinum Toxin as a Clinical Product:Manufacture and Pharmacology. Clinical Applications of Botulinum Neurotoxin, 7 Current Topics in Neurotoxicity 5 © Springer Science+Business Media New York 2014.* ***2.*** *Perspectives in Biology and Medicine 1997;40:317-327* ***3.*** *Dermatol Surg 2013; 39: 165-170.* ***4.*** *Anaerobe 2004; 10: 321–333.* ***5.*** *Dermatologic surgery 2013;39:171-178.*