The First Choice of Botulinum Toxin Type A

Purified Botulinum Toxin Type A Complex

Neuronox®

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Purified Botulinum Toxin Type A Complex

Medytox

The First Choice of Botulinum Toxin Type A

Proven Efficacy & Safety

The efficacy and safety of Neuronox® are proved and verified to be comparable to OnabotulinumtoxinA's in clinical studies.

Global Product

Global Product, Neuronox® has been sold in over 26 countries, since its first launch in 2004. Neuronox® is being sold worldwide under different brand names, such as Siax®, Botulift® and Meditoxin®.

Various choices

Neuronox® line up is consisted of 50, 100 and 200 units, offering various choices according to the application. physicians find it easier to use and the patients more economical.

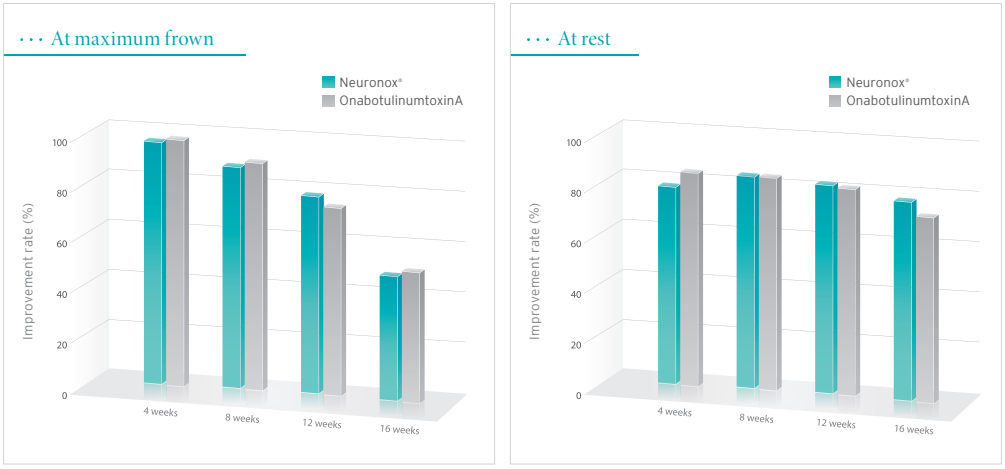
Proven Efficacy & Safety

The efficacy and the Safety of Neuronox® are proved to be comparable to OnabotulinumtoxinA in various clinical studies.

I. Glabellar Frown Lines

Comparative clinical study for **Glabellar Frown Lines** with Neuronox® vs. OnabotulinumtoxinA[1]

: **Percentage of responder based on physician's live assessment**



Methodology Multi-center, double blinded, randomized, active controlled, parallel designed, phase Ⅲ clinical study.

Subjects 314 healthy adult patients(aged between 20 to 65) with moderate or severe glabellar lines at maximum frown.

Results The efficacy of Neuronox® was not inferior to that of Onabotulinumtoxin A. No difference was noted in the frequency of adverse events. Neuronox® can be safely used as an alternative to botox treatment at an equivalent ratio of 1:1.

- Adverse Event Rate(%)
  The common (>1%) treatment-related AEs were eyelidptosis (5/156, 3.2% NBoNT group; 3/157, 1.9% OBoNT group) and extraocularmuscle disorder (1/156, 0.6% NBoNT group; 4/157, 2.6% OBoNT group). All other related AEs had a total incidence of <1%. No statistical differenes in the incidence and severity of AEs between the two groups were observed.

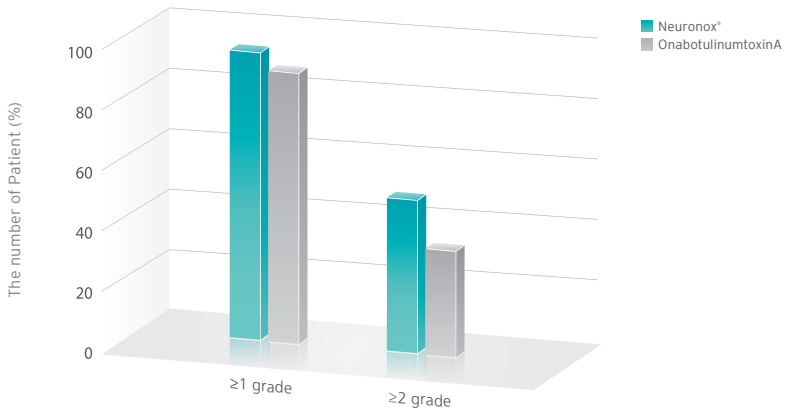
Reference 1. CH Huh et al. Efficacy and Safety of a Novel Botulinum Toxin Type A Product for the Treatment of Moderate to Severe Glabellar Lines: A Randomized, Double-Blind, Active-Controlled Multicenter Study. Dermatol Surg 2013;39:171-178

Proven Efficacy & Safety

II. Essential Blepharospasm

Comparative clinical study for **Essential Blepharospasm** with Neuronox® vs. OnabotulinumtoxinA[2]

··· Improvement in the Severity of Spasm Score



Methodology Multi-center, double blinded, randomized, active controlled, parallel designed, phase Ⅲ clinical study

Subjects 60 patients diagnosed with an essential blepharospasm.
(Neuronox® n=31 / Botox® n=29)

Results The efficacy of Neuronox® was not inferior to Botox® in this clinical study. No difference was noted in the frequency of adverse events. Neuronox® can be safely used as an alternative to botox treatment at an equivalent ratio of 1:1.

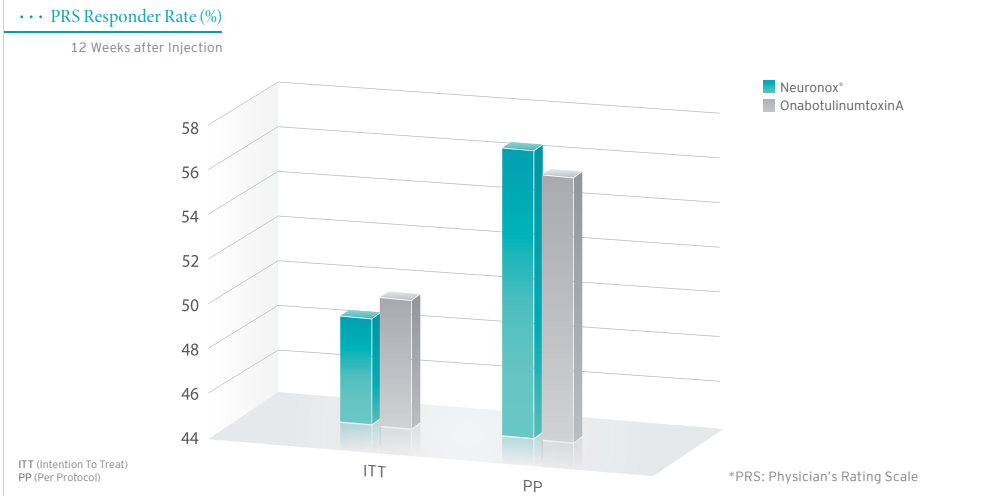
- Adverse Event Rate(%)
16.1% of patients(treated with Neuronox) and 27.6% of patients(treated with OnabotulinumtoxinA) experienced adverse events. As the results did not show any significant differences between the two groups, they were proven to have similar safety profiles.

Reference 2. Yoon JS et al. Double-Blind, Randomized, Comparative Study of Meditoxin® Versus Botox® in the Treatment of Essential Blepharospasm. Korean Journal of Ophthalmology 2009;23:137-141

Proven Efficacy & Safety

III. Cerebral Palsy

Comparative clinical study equinus deformity in **Cerebral Palsy** with Neuronox® vs. OnabotulinumtoxinA[3]



Methodology Multi-center, double blinded, randomized, active controlled, parallel designed, phase Ⅲ clinical study

Subjects 119 pediatric patients diagnosed with spastic cerebral palsy with equinus foot deformity (Neuronox® n=60 / Botox® n=59)

Results Neuronox® was not inferior to Botox® in this clinical study. No difference was noted in the frequency of adverse events. Neuronox® can be safely used as an alternative to botox treatment at an equivalent ratio of 1:1

- Adverse Event Rate(%)
A total of 34 adverse events were reported in 18 out of 119 participants (15.1%): Nine children in the Neuronox group experienced a total of 15 AEs and nine children in the BOTOX group experienced a total of 19 AEs. As the results did not show any significant differences between the two groups, they were proven to have similar safety profiles.

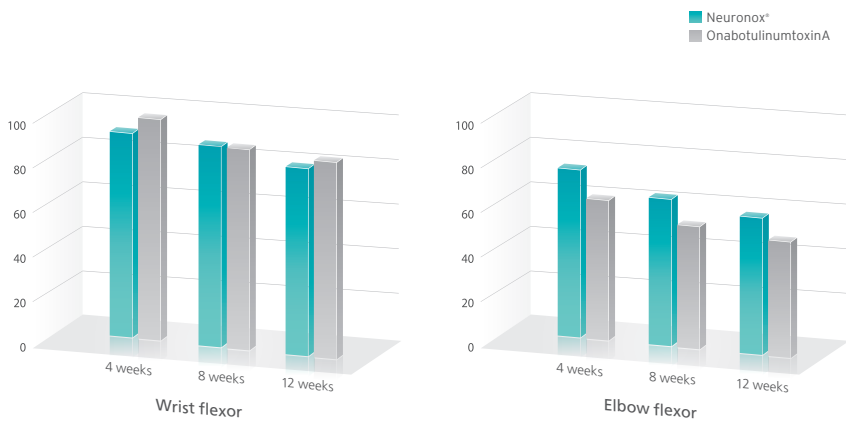
Reference 3. MS Bang et al. Meditoxin® Versus Botox® for spastic equinus gait in children with cerebral palsy Double-Blind, Randomized, Controlled multicenter clinical trial Developmetn Medicine & Child Neurology 2011;53:239-244

Proven Efficacy & Safety

IV. Post-Stroke Upper Limb Spasticity

Comparative clinical study for **Post-Stroke Upper Limb Spasticity** with Neuronox® vs. OnabotulinumtoxinA[4]

··· MAS improvement Rate (%)



Methodology Multi-center, double blinded, randomized, active controlled, parallel designed, phase Ⅲ clinical study

Subjects 196 adult patients with ≥2 points in the focal spasticity of wrist flexor and ≥1 points at least one of elbow flexor and finger flexor as measured on MAS(Diagnosed with stroke at least 6 weeks before the study enrollment).

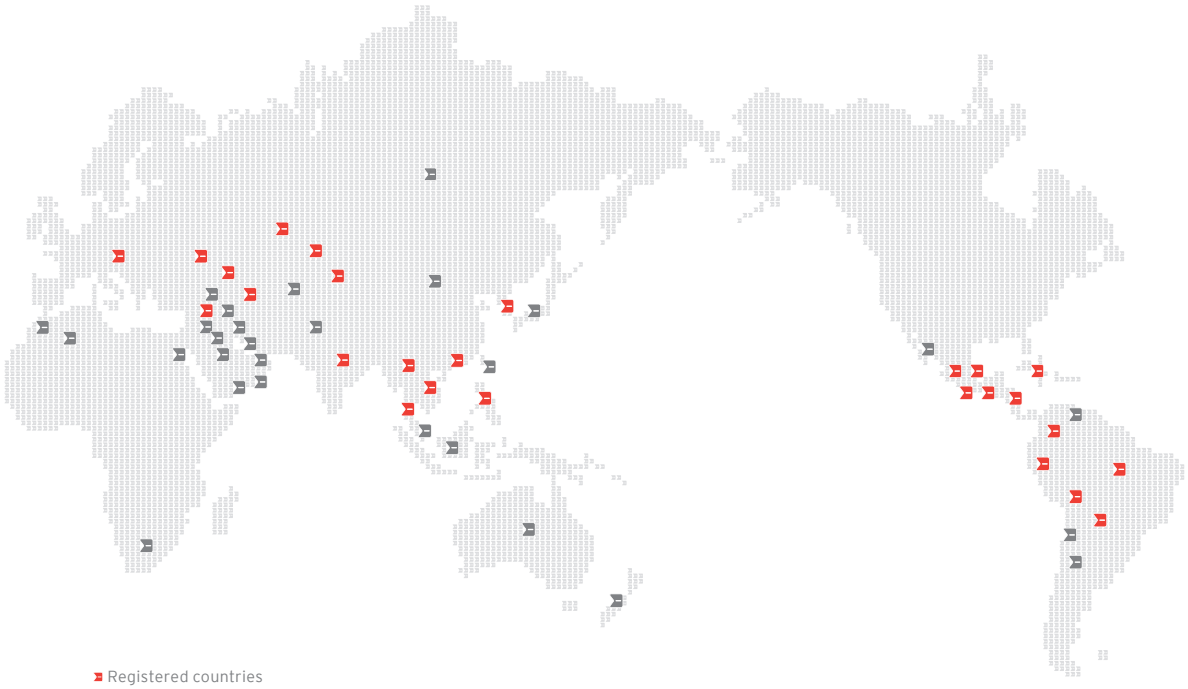
Results The efficacy of Neuronox® was not inferior to OnabotulinumtoxinA in this clinical study. No difference was noted in the frequency of adverse events. Neuronox® can be safely used as an alternative to botox treatment at an equivalent ratio of 1:1.

- **Adverse Event Rate(%)**
  39.8% of patients(treated with Neuronox) and 41.84% of patients(treated with OnabotulinumtoxinA experienced adverse events. As the results did not show any significant differences between the two groups, they were proven to have similar safety profiles.

Reference 4. Clinical trial Report. A randomized, double blind, multi-center, active drug controlled, phase III clinical trial to compare the efficacy and safety of MEDITOXIN® versus BOTOX® in treatment of post stroke upper limb spasticity. Data on file. Medytox.Inc

World-wide Product

Neuronox® is registered in 26 countries including Korea, Brazile, India, Hong Kong, Ukraine, Thailand and panama. Currently, it is in the process of registration in 30 additional countries.



Registered countries
Registration in progress

Registered countries*

AZERBAIJAN
BOLIVIA
BRAZIL
CHILE
COLOMBIA
PARAGUAY
COSTARICA
DOMINICA REP
EL SALVADOR
GEORGIA
GUATEMALA
HONGKONG
INDIA
IRAN
KAZAKHSTAN
KOREA
KYRGYZSTAN
LEBANON
NICARAGUA
PANAMA
PERU
PHILIPPINES
THAILAND
UKRAINE
UZBEKISTAN
VIETNAM

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

Various Choice of products

Neuronox® offers various choices according to the application. Physicians find it easier to use and the patients more economical.

Product	 Neuronox® 50U	 Neuronox® 100U	 Neuronox® 200U
Manufacturer	Medytox Inc.	Medytox Inc.	Medytox Inc.
Drying Method	Freeze-dried	Freeze-dried	Freeze-dried
Potency per vial	50U	100U	200U
Composition	50Units of Clostridium botulinum toxin type A complex	100Units of Clostridium botulinum toxin type A complex	200Units of Clostridium botulinum toxin type A complex
	0.25mg of human serum albumin	0.5mg of human serum albumin	1.0mg of human serum albumin
	0.45mg of sodium chloride	0.9mg of sodium chloride	1.8mg of sodium chloride

Dilution Information	Diluent Added (0.9% sodium chloride)	Resulting Dose Units (Units /0.1mL)	Diluent Added (0.9% sodium chloride)	Resulting Dose Units (Units /0.1mL)	Diluent Added (0.9% sodium chloride)	Resulting Dose Units (Units /0.1mL)
	0.5mL	10.0U	1.0mL	10.0U	1.0mL	20.0U
	1.0mL	5.0U	2.0mL	5.0U	2.0mL	10.0U
	2.0mL	2.5U	4.0mL	2.5U	4.0mL	5.0U
	4.0mL	1.25U	8.0mL	1.25U	8.0mL	2.5U
Storage	Freezer(blow −5℃) or refrigerator (2~8℃).		Feezer(blow −5℃) or refrigerator (2~8℃).		Refrigerator (2~8℃).	

Detailed Product Description

Neuronox® 50·100·200units

(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 18 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. Clinical improvement may be expected within 4 weeks after injection. Injections may be repeated when the effect of a previous injection has diminished, but generally no sooner than 12 weeks.

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 patients with large corrugators 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® is injected with caution so that it does not enter the 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 thesemuscles. 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 36months from the manufacturing date.

Manufactured by: Medytox Inc.

※Please refer to the package insert for more information.

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www.medytox.com

MT-13041