Cunox®

The First Choice of Botulinum Toxin Type A

Purified Botulinum Toxin Type A Complex

Medytox

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Botulinum Toxin Type A

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Cunox®

Purified Botulinum Toxin Type A Complex

Proven efficacy

The efficacy of Cunox® is proved to be comparable to Botox (Allergan Inc.)'s in clinical studies.

Verified safety

The safety of Cunox® is verified through clinical studies and field usages. Since the first launch in 2004, Cunox® has been sold in more than 30 countries.

Various choices

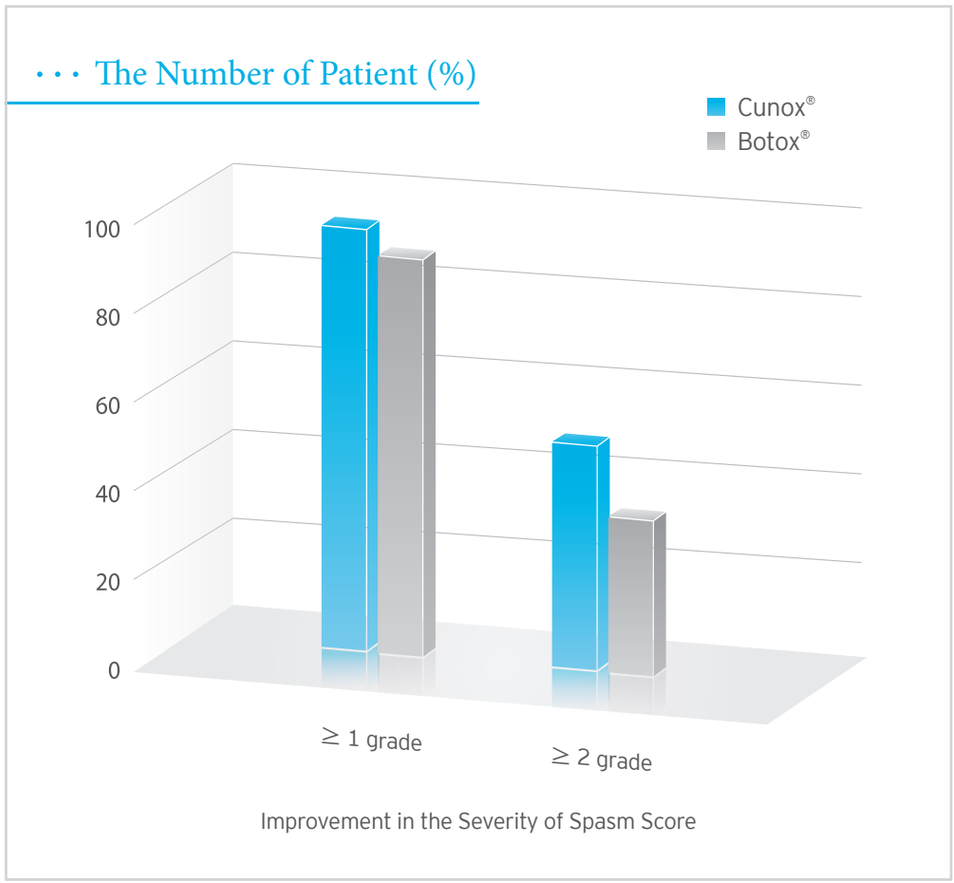
Cunox® consists of 50, 100, and 200 units, offering various choices according to the application. It is easier to use for doctors, and more economical for patients.

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

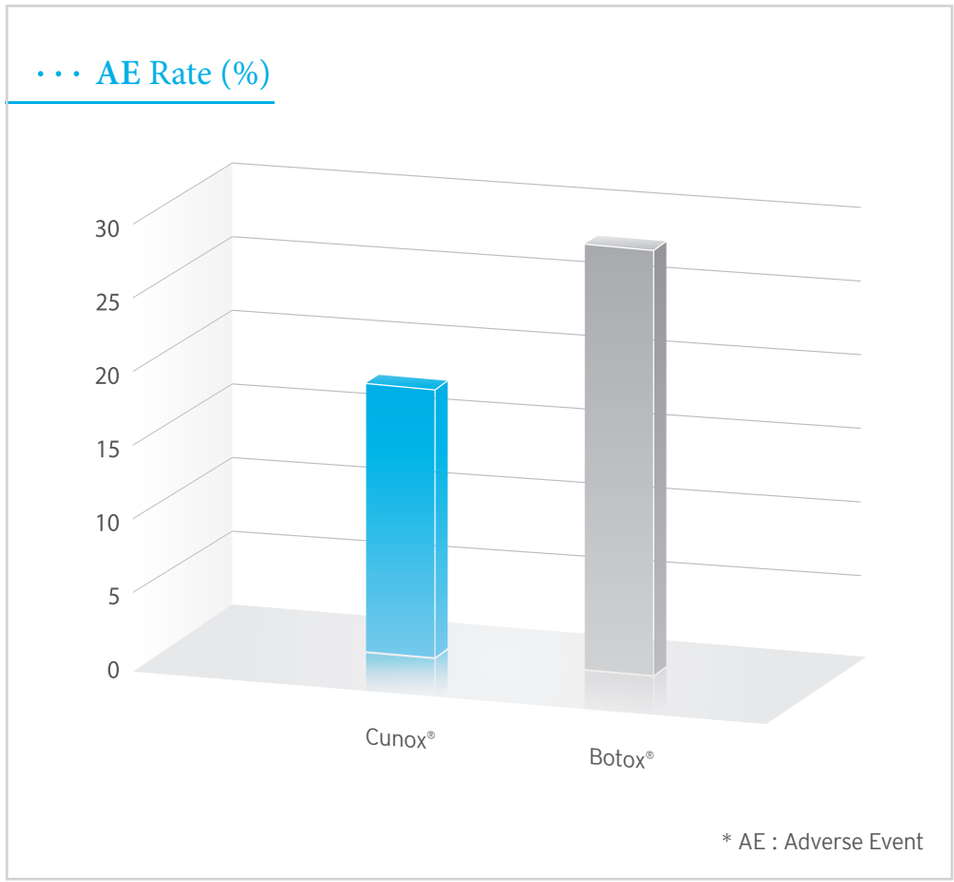
Proven Efficacy & Safety

The efficacy and the safety of Cunox® are proved to be comparable to Botox(Allergan Inc.)'s in various clinical studies.

Comparative clinical study for essential blepharospasm[1] with Cunox® vs. Botox®



Improvement in the Severity of Spasm Score



* AE : Adverse Event

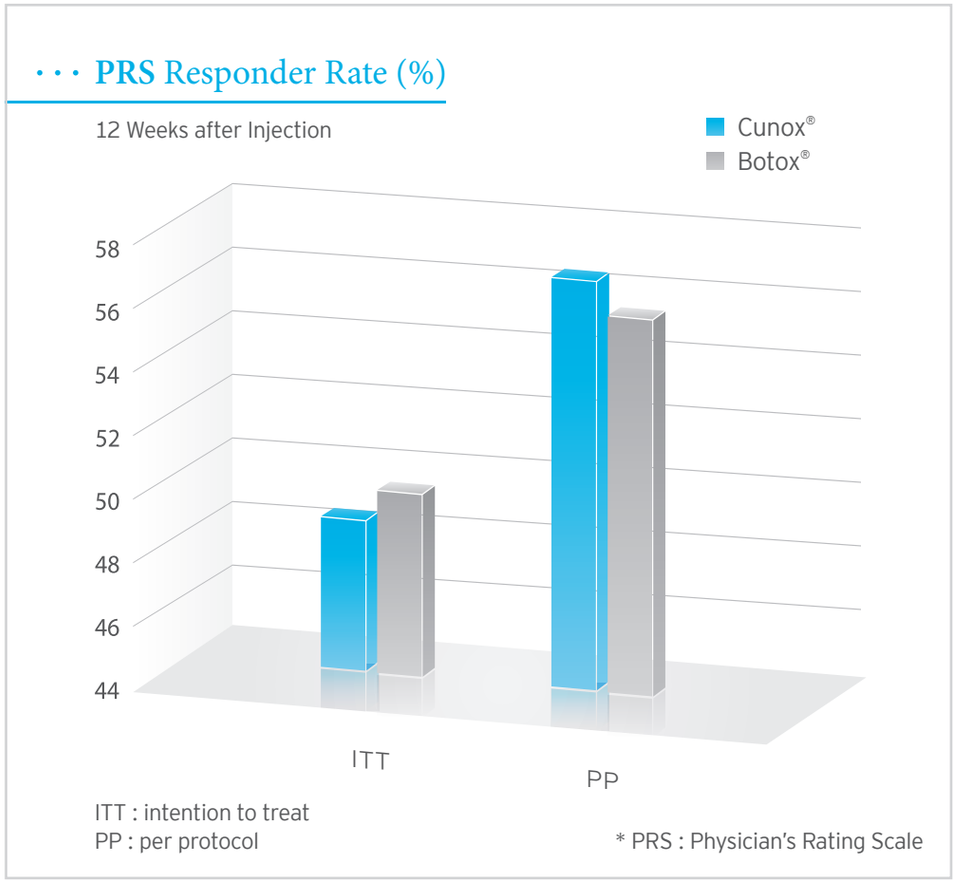
Methodology Multi-center, double blinded, randomized, active controlled, parallel designed, phase Ⅲ clinical study

Subjects 60 patients diagnosed as essential blepharospasm (Cunox® n=31 / Botox® n=29)

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

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

Comparative clinical study for equinus deformity in cerebral palsy[2] with Cunox® vs. Botox®



ITT : intention to treat
PP : per protocol

* PRS : Physician's Rating Scale

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

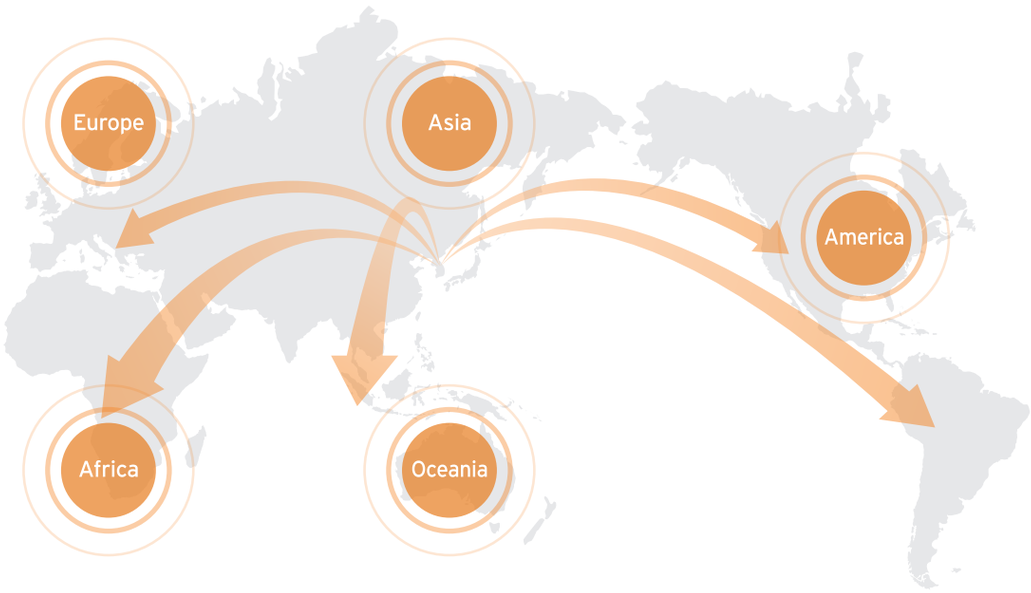
Subjects 119 pediatric patients diagnosed as spastic cerebral palsy with equinus foot deformity (Cunox® n=60 / Botox® n=59)

Results Cunox® was not inferior to Botox® in this clinical study. No differences were noted in the frequency of adverse event. Cunox® can be safely used as an alternative to Botox® treatment.

2) Moon Suk 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 2010.

Globalized Product

Cunox® is registered in 23 countries including Korea, Brazil, India, Hong Kong, Ukraine, Thailand and Panama, and is in the process of registration in other 30 countries.



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

Various Choice of products

Cunox®50U, Cunox®100U and Cunox®200U

Subject	Cunox® 50U	Cunox® 100U	Cunox® 200U
Manufacturer	Medytox Inc.	Same as left	Same as left
Drying Method	Freeze-dried	Same as left	Same as left
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

Cunox® Injection 100units

(Clostridium botulinum toxin type A)

Composition

Each vial contains

Active ingredient	: Clostridium botulinum toxin type A (Korean Minimum Requirement for Biopharmaceutical Product)	100 units(U)
Stabilizer	: Human serum albumin (Korean Minimum Requirement for Biopharmaceutical Product)	0.5mg
Isotonic agent	: Sodium chloride (EP)	0.9mg

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

Description

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

Indication

1. Cunox® is indicated for the treatment of benign essential blepharspasm in patients 18 years of age and above.
2. Cunox® is indicated for the treatment of equinus foot deformity due to spasticity in pediatric cerebral palsy patients 2 years of age and above.

Dosage and administration

1. Blepharospasm

For blepharospasm, reconstituted Cunox® (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 Cunox® treatment in a 30-day period should not exceed 200 U.

2. Pediatric cerebral palsy

For the pediatric cerebral palsy, reconstituted Cunox® (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. Dilution technique

Prior to injection, reconstitute freeze-dried Cunox® 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 Cunox® with the saline by rotating the vial. Cunox® should be administered within 24 hours after reconstitution. During this time period, reconstituted Cunox® should be stored in a refrigerator(2 - 8℃). Reconstituted Cunox® 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 Cunox® 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).

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 anatomy of the area involved and any alterations to the anatomy due to prior surgical procedures. An understanding of standard electromyogrphic techniques is also required for the administration of the drug. The recommended dosage and frequency of administration for Cunox® should not be exceeded.

1) Spread of toxin effect

In some cases, botulinum toxin effect may be observed beyond the site of local injection. The symptoms may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. Swallowing and breathing difficulties can be life threatening and there have been reports of death related to spread of toxin effects. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions. Symptoms with spread of toxin effect have been reported as doses comparable to or lower than doses used to treat cervical dystonia.

2) Hypersensitivity reactions

Serious and/or immediate hypersensitivity reactions have been rarely reported with other botulinum toxin products. These reactions include anaphylaxis, urticaria, soft tissue edema and dyspnea. One fatal case of anaphylaxis with other botulinum toxin product 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.

3) 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. Published medical literature with other botulinum toxin product has reported rare cases of administration of a botulinum toxin to patients with known or 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.

4) Corneal exposure and ulceration in patient treated with botulinum toxin products for 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 an aphakic eye requiring corneal grafting has occurred because of this effect. Careful testing of corneal sensation 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.

5) Lack of interchangeability between Botulinum toxin products.

The potency units of biological activity of Cunox® can not be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method.

2. Contraindications

Cunox® must not be administered to the following patients ;

1) Patients with hypersensitivity reactions to any ingredients of Cunox®

2) Patients with systemic neuromuscular junctional disorders (severe myasthenia gravis, Lambert-Eaton syndrome, amyotrophic lateral sclerosis, etc) (The muscle relaxing effect of this drug can worsen the disease.)

3) Patients with severe respiratory dysfunction while using Cunox® for cervical dystonia

4) Women who are pregnant or may be pregnant and nursing mothers

3. Cunox® should be administered with caution for the following patients ;

1) Patients who are taking a muscle relaxant (Sodium Tubocurarine, Dantrolen Sodium, etc.) [may be at risk of developing dysphagia or increasing muscle relaxing effect.]

2) Patients who are taking Spectinomycin Hydrochloride, aminoglycoside antibiotics (Gentamycin Sulfate, Neomycin Sulfate, etc.), polypeptide antibiotics (Polymixin B Sufate, etc.), tetracycline antibiotics, lincosamide antibiotics, muscle relaxant (Baclofen, etc.), anticholinergics (Butylscopolamine Bromide, Trihexyphenidyl Hydrochloride, etc.), benzodiazepines and similar drugs (Diazepam, Etizolam, etc.), benzamides (Tiapride Hydrochloride, Sulpiride, etc.), and such drugs with muscle relaxing effect may be at risk of developing dysphagia or increasing muscle relaxing effect.

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 products 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) 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 botulinum 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.

3) Pediatric cerebral palsy

Safety of Cunox® for the treatment of equinus foot deformity due to spasticity in pediatric cerebral palsy patients was evaluated in a clinical trial in Korea. In this clinical trial, 60 patients who injected Cunox® showed common adverse reactions(>1%) such as nasopharyngitis(5%), upper respiratory tract infection (1.67%), pyrexia(3.3%), gait disturbance(1.67%), pain in extremity(1.67%), musculoskeletal and connective tissue disorders(1.67%), febrile convulsion(1.67%), constipation(1.67%), and lower limb fracture(1.67%). Additionally the common adverse reactions(>1%) which are shown from 59 patients who injected the control medicine at the comparison clinical trials are as follows; nasopharyngitis(5.08%), haemophilus infection(1.69%), pneumonia(1.69%), pyrexia(5.08%), asthenia(1.69%), joint contracture(1.69%), muscular weakness(1.69%), unequal limb length(1.69%), conjunctivitis(1.69%), headache(1.69%), and anaemia(1.69%). These kinds of adverse reactions may be occurred depending on the patient's characteristics. In the literatures about other botulinum toxin products, similar adverse reactions which are related to the use of botulinum toxin are mentioned such as respiratory infection, brochitis, nasopharyngitis, asthma, muscular weakness, urinary incontinence, falling down, convulsion, pyrexia, pain and others.

Storage

The unopened lyophilized vial should be stored in a freezer(blow -5℃) or refrigerator (2~8℃).

How supplied

Cunox® is supplied in a single use vial.

Expiration

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

Manufactured by: Medytox Inc.

NNX100-EN-03I

Cunox®

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