Rx Only

NEURONOX® Powder for Solution for Injection
(*Clostridium botulinum* toxin type A)

Composition

Each vial contains

[NEURONOX® 50Units]		
Active ingredient	: Clostridium botulinum toxin type A	50 units(U)
Stabilizer	: Human serum albumin	0.25mg
Isotonic agent	: Sodium chloride	0.45mg
[NEURONOX® 100Units]		
Active ingredient	: Clostridium botulinum toxin type A	100 units(U)
Stabilizer	: Human serum albumin	0.5mg
Isotonic agent	: Sodium chloride	0.9mg
[NEURONOX® 200Units]		
Active ingredient	: Clostridium botulinum toxin type A	200 units(U)
Stabilizer	: Human serum albumin	1.0mg
Isotonic agent	: Sodium chloride	1.8mg

* One unit(U) of NEURONOX® corresponds to the calculated median intraperitoneal lethal dose (LD50) in mice.

Description

Lyophilized white powder for injection in a colorless transparent glass vial.

Indications and Usage

NEURONOX® is indicated for:

- Treatment of benign essential blepharospasm in adult patients.
- Treatment of equinus foot deformity due to spasticity in pediatric cerebral palsy patients 2 years of age and older.
- Treatment of upper limb spasticity associated with stroke in adult patients.
- Temporary improvement of glabellar lines ranging from moderate to severe associated with corrugators muscle and/or procerus muscle activities in adult patients below 65 years of age.

Dosage and Administration

Route of administration: Intramuscular injection

1. Blepharospasm

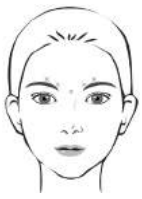
For blepharospasm, reconstituted NEURONOX® (see Dilution Table) is injected using a sterile, 27 - 30 gauge needle without electromyographic guidance. The initial recommended dose is 1.25 - 2.5 U (0.05 mL to 0.1 mL volume at each site) injected into the medial and lateral pre-tarsal orbicularis oculi 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 of the affected lower limbs. 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.
Repeat NEURONOX® treatment may be administered when the effect of a previous injection has diminished, but generally no sooner than 12 weeks after the previous injection. The degree and pattern of muscle spasticity at the time of re-injection may necessitate alterations in the dose of NEURONOX® and muscles to be injected.

3. Glabellar Lines

NEURONOX® is reconstituted to make 50U/1.25mL, 100U/2.5mL and 200U/5.0mL (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 lines. The procerus muscle and depressor supercilii muscle pull the forehead down. Frowning or glabellar lines 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 lines 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. Upper Limb 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.
Repeat NEURONOX® treatment may be administered when the effect of a previous injection has diminished, but generally no sooner than 12 weeks after the previous injection. The degree and pattern of muscle spasticity at the time of re-injection may necessitate alterations in the dose of NEURONOX® and muscles to be injected.

The table below is intended to give dosing guidelines in the treatment of upper limb spasticity associated with stroke:

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, maximum allowable dose was up to 360U
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

Reconstitution should be done with aseptic techniques. Prior to injection, reconstitute freeze-dried NEURONOX® with sterile normal saline without a preservative. 0.9% Sodium chloride Injection. 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 swirling the vial. NEURONOX® should be administered within 24 hours after reconstitution. During this time period, reconstituted NEURONOX® should be stored in a refrigerator (2°C - 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)		
	50U	100U	200U
1.0 mL	5.0 U	10.0 U	20.0 U
2.0 mL	2.5 U	5.0 U	10.0 U
4.0 mL	1.25 U	2.5 U	5.0 U
8.0 mL	0.625 U	1.25 U	2.5 U

Note: These dilutions are calculated for an injection volume of 0.1mL. 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

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.
Neuronox should only be given by physicians with the appropriate qualifications and experience in the treatment of patients and the use of required equipment. The relevant anatomy, and any alterations to the anatomy due to prior surgical procedures, must be understood prior to administering Neuronox and injection into vulnerable anatomic structures must be avoided. The recommended dosage and frequency of administration for NEURONOX® 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.
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) There have been reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes in case of other botulinum toxin treatment. Some of these patients had risk factors including cardiovascular disease.
5) 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.
6) Lack of interchangeability between Botulinum toxin products.
The potency units of biological activity of NEURONOX® can not be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method.
7) Injections In or Near Vulnerable Anatomic Structures
Care should be taken when injecting in or near vulnerable anatomic structures. Serious adverse events including fatal outcomes have been reported in patients who had received other botulinum toxin products injected directly into salivary glands, the oro-lingual-pharyngeal region, esophagus and stomach. Some patients had pre-existing dysphagia or significant debility. (Safety and effectiveness have not been established for indications pertaining to these injection sites.) Pneumothorax associated with injection procedure has been reported following the administration of other botulinum toxin product near the thorax. Caution is warranted when injecting in proximity to the lung, particularly the apices.
8) Pulmonary Effects of botulinum toxin product in Patients with Compromised Respiratory Status Treated for Spasticity.
In Patients with compromised respiratory status treated with other botulinum toxin for upper limb spasticity,reduced lung function and upper respiratory tract infections were reported and patients with Detrusor Overactivityassociated with a Neurologic Condition treated with Botox, reduced lung function was reported.
9) Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity
Bronchitis was reported more frequently as an adverse reaction in patients treated for upper limb spasticity with botulinum toxin, compared to placebo. In patients with reduced lung function treated for upper limb spasticity, upper respiratory tract infections were also reported more frequently as adverse reactions in patients treated with botulinum toxin compared to placebo.
10) 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 theoretical risk of infectious diseases by transmissible agents cannot be completely excluded, though is considered extremely remote. 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.
11) 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.
12) Cerebral Palsy
NEURONOX® treatment is used for local seizure studied in association with the standard treatment; it does not replace these treatment modalities. NEURONOX® does not appear that it will be effective in improving limited movement of joints permanently.
13) Glabellar Lines
In the phase III clinical trial study, those patients who have the history of facial nerve paralysis or the symptoms of eyelid ptosis, history of treatment of glabellar part like face lifting and permanent implant or with scars which may affect the treatment results, satisfactorily not improved with physical method since the lines are not flattened even using hands, they were excluded. Therefore warnings should be given. The interval between administrations of NEURONOX® should not be less than 3 months, and the minimum effective dose must be used.
14) Muscle Spasticity
NEURONOX® is used only for treating localized spasticity studied in association with typical standard treatment. NEURONOX® is not effective in improving the range of movement in joints affected by fixed limitation.

1. Contraindications
NEURONOX® must not be administered to the following patients;
1) Known Hypersensitivity to Botulinum Toxin
2) Infection at the Injection Sites
3) Diagnosed with myasthenia gravis or Lambert-Eaton Syndrome

2. Adverse reactions
Clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.
In general, adverse reactions occur within the first week following injection of NEURONOX® and, while generally transient, may have a duration of several months or longer. Localized pain, infection, inflammation, tenderness, swelling, erythema, and/or bleeding/bruising may be associated with the injection. Symptoms associated with flu-like symptoms (e.g., nausea, fever, myalgia) have been reported after treatment from other approved botulinum toxin. Needle-related pain and/or anxiety may result in vasovagal responses (including syncope, hypotension), which may require appropriate medical therapy.
Local weakness of the injected muscle(s) represents the expected pharmacological action of botulinum toxin. However, weakness of nearby muscles may also occur due to spread of toxin

1) Blepharospasm
In a randomized, double -blind, active-controlled phase 3 clinical trial of blepharospasm patients aged 18-75 years who received up to 60 units of NEURONOX® or other botulinum toxin treatment, Proportion of patients who had experienced at least one adverse event was 16.13% in NEURONOX® group and 27.59% in control group.

A total of 12 cases were considered to possibly be related with study drug. Incidence rate of adverse reaction was 16.13% in NEURONOX®group and 24.14% in control group. The most frequent adverse reactions were eyelid ptosis and foreign sensation in eye in NEURONOX® group. The reported adverse reactions following treatment appear in Table.

Table. Adverse Reactions in the Double-blind, Active-controlled, Phase 3 Clinical Trials in Adult Patients with Blepharospasm

SOC / PT	NEURONOX® (N=31)	CONTROL (N=29)
Eye disorders		
Eyelid ptosis	2 (6.45%)	3 (10.34%)
Foreign body sensation in eyes	2 (6.45%)	-
Eye pruritus	1 (3.23%)	-
Eyelid oedema	-	2 (6.90%)
Dry eye	-	1 (3.45%)
Eye pain	-	1 (3.45%)

2) Pediatric cerebral palsy

Safety of NEURONOX® for the treatment of equinus foot deformity due to spasticity in pediatric cerebral palsy patients was evaluated in a phase 3 clinical trial. Total 119 patients aged 2~10 years enrolled in double-blind, active-controlled study, received up to 200 units NEURONOX® or other botulinum toxin. 9 patients in NEURONOX® group (15.00%) and 9 patients in control group (15.25%) reported adverse events.

There was one adverse reaction of mild intensity from control group.

Table. Adverse Reaction in the Double-blind, Active-controlled, Phase 3 Clinical Trials in Pediatric Patients with Lower Limb Spasticity

SOC / PT	NEURONOX® (N=60)	CONTROL (N= 59)
Musculoskeletal and connective tissue disorders		
Muscular weakness	-	1 (1.69%)

3) Glabellar Lines

In a randomized, double-blind active-controlled phase 3 clinical Trial, total 313 patients aged 20~65 years enrolled and received 20 units of NEURONOX® or other botulinum toxin for treatment of glabellar lines. Proportion of patients who had experienced at least one adverse event was 26.92% in NEURONOX® group and 22.29% in control group.

Proportion of patients who had experienced at least one adverse reaction was 7.05% in NEURONOX® group and 4.46% in control group. The most frequent adverse reaction was eyelid ptosis in NEURONOX® group. The reported adverse reactions following treatment appear in table.

Table. Adverse Reaction in the Double-blind, Active-controlled, Phase 3 Clinical Trials in Adult Patients with Glabellar Lines

SOC / PT	NEURONOX® (N=156)	CONTROL (N=157)
Eye disorders		
Eyelid ptosis	5 (3.21%)	3 (1.91%)
Conjunctivitis	1 (0.64%)	-
Dry eye	1 (0.64%)	-
Extraocular muscle disorder	1 (0.64%)	4 (2.55%)
Eye pain	1 (0.64%)	-
Eyelid disorder	1 (0.64%)	1 (0.64%)
Eyelid oedema	1 (0.64%)	-
Vision blurred	1 (0.64%)	-
General disorders and administration site conditions		
Injection site discomfort	1 (0.64%)	-
Injection site pruritus	1 (0.64%)	-
Local swelling	1 (0.64%)	1 (0.64%)
Face oedema	-	1 (0.64%)
Skin and subcutaneous tissue disorders		
Periorbital oedema	1 (0.64%)	-
Pruritus	-	1 (0.64%)
Gastrointestinal disorders		
Sensitivity of teeth	-	1 (0.64%)
Infections and infestations		
Pharyngitis	-	1 (0.64%)
Musculoskeletal and connective tissue disorders		
Spinal column stenosis	-	1 (0.64%)
Psychiatric disorders		
Insomnia	1 (0.64%)	-
Renal and urinary disorders		
Urethral discharge	1 (0.64%)	-
Respiratory, thoracic and mediastinal disorders		
Cough	1 (0.64%)	-
Productive cough	1 (0.64%)	-

4) Upper Limb Spasticity

Total 196 patients over the age of 20 years enrolled in double-blind active-controlled phase 3 clinical trial, received up to 360 Units of NEURONOX® or other botulinum toxin for treatment of upper limb spasticity. Percentage of subjects who had experienced at least one adverse event was found 39.80% in NEURONOX group and 41.84% in control group.

Adverse Reactions occurred in 4.08% of NEURONOX® group patients and 8.16% of control group patients. The most frequent adverse reactions was injection site haematoma in NEURONOX® group. The reported adverse reactions following treatment appear in Table.

Table. Adverse Reaction in the Double-blind, Active-controlled, Phase 3 Clinical Trials in Adult Patients with Upper Limb Spasticity

SOC / PT	NEURONOX® (N=98)	CONTROL (N=98)
General disorders and administration site conditions		
Injection site haematoma	2 (2.04%)	1 (1.02%)
Oedema peripheral	1 (1.02%)	-
Pyrexia	-	1 (1.02%)
Nervous system disorders		
Convulsion	-	1 (1.02%)
Headache	-	2 (2.04%)
Hemiparesis	-	1 (1.02%)
Partial seizures	-	1 (1.02%)
Investigations		
Alanine aminotransferase increased	-	1 (1.02%)
Liver function test abnormal	-	1 (1.02%)
Musculoskeletal and connective tissue disorders		
Tendonitis	1 (1.02%)	-
Muscular weakness	-	1 (1.02%)

5) Post-Marketing Experience There have been the post marketing surveillance and phase IV trials in 641 patients with Benign Essential Blepharospam for 6 years in Korea. It has been reported that rate of adverse reaction was 12.5% (80/641, 116 cases), in which 7.8% (50/641, 57 cases) cases could not be excluded by causality with the drug and ptosis was reported 3.9% (25/641, 25 cases). Other treatment-related adverse events reported by ≦ 1% were as follows : facial swelling (6 cases), ocular abnormality (4 cases), rash(3 cases), itching, paresthesia, lid leg, abnormal tear secretion, ophthalmalgia (2 cases), corneal ulcer, diplopia, arrhythmia, periorbital swelling, oculomotor nerve palsy, headache, paralysis, dizziness, and purpura (1 case). The rate of serious adverse events was reported 3 of 641 patients (0.5%, 5 cases) : spinal stenosis (2 cases), melosalgia (1 case), myocardial infarction (1 case), and arrhythmia (1 case).

-Unexpected adverse drug reactions were reported in 11 of 641 patients(1.7%), but there was no unexpected serious adverse event among them. The unexpected and non-serious adverse drug reactions were reported as follows : facial swelling (6 cases), ocular abnormality (2 cases), headache, paresthesia, dizziness (1 case).

In PMS (Post Marketing Surveillance) study in 210 patients with equinus foot deformity due to cerebral palsy in Korea, it has been reported that the rate of adverse event was 21.4% (45/210, 84 cases). Among them, the rate of adverse drug reaction which could not be excluded by causality was 1.4% (3/210 patients, 3 cases) and the rate of inflammation of injection site was 1% (2/210 patients, 2 cases). Another adverse drug reaction, myalgia was reported ≦ 1%. The rate of serious adverse event was reported 1.4% (3/210 patients, 3 cases) by 2 cases of pneumonia and 1 case of urinary tract infection. However, there was no reported unexpected serious adverse event among them.

Post marketing surveillance in 812 patients with glabellar lines ranging from moderate to severe for 4 years (from 20 SEP 2011 to 19 SEP2015) in Korea reported that the rate of adverse events was 1.60% (13/812, 14 cases). The rate of adverse event of which causality of drug could not be excluded was 0.49% (4/812, 5 cases) and the adverse events were as follows: headache 0.25% (2/812, 2 cases), eye pain 0.12% (1/812, 1 case), injection site pruritus 0.12% (1/812, 1 case) and injection site rash 0.12% (1/812, 1 case). No serious adverse events and adverse drug reactions have been reported.

The rate of unexpected adverse events reported was 0.74% (6/812, 6 cases), and the adverse events were as follows: psoriasis, herpes zoster, common cold, injection site rash, phlebitis and peptic ulcer (0.12%, 1/812, 1 case each). The rate of unexpected adverse drug reactions reported was 0.12% (1/812,1 case) and the adverse drug reaction was injection site rash. No unexpected serious adverse events and unexpected adverse drug reactions have been reported.

An evaluation was done between the adverse events cases and spontaneous reports(side effects) collected during the “re-examination period (from 20SEP2011 to 19SEP2015)” of glabellar lines ranging from moderate to severe of NEURONOX® in the Republic of Korea, and adverse events reported during the post marketing surveillance for all pharmaceutical products registered in Republic of Korea (1989~DEC 2015). When comparing the adverse reaction case that are reported with significant statistical difference in NEURONOX® to all pharmaceutical products at the time of end of re-evaluation period, no new adverse reactions were found.

There have been the post marketing surveillance in 607 patients with upper spasticity related to stroke for 4 years in Korea. It has been reported that rate of adverse reaction was 6.26% (38/607, 62 cases), in which 1.81% (11/607, 12 cases) could not be excluded by causality with the drug. Adverse drug reactions were as follows: injection site tenderness 0.82% (5/607, 5 cases), Common cold 0.33% (2/607, 2 cases), Injection site rash 0.33% (2/607, 2 cases), Convulsions 0.16% (1/607, 1 case), Myalgia 0.16% (1/607, 1 case), Pain neck/shoulder 0.16% (1/607, 1 case).

The rate of serious adverse events was 0.66% (4/607, 5 cases) and the adverse events were as follows: Weakness generalized, Aspiration pneumonitis, Haemoptysis, Cholangitis, Cerebral infarction 0.16% (1/607, 1 case each). No serious adverse drug reactions have been reported.

The rate of unexpected adverse events reported was 5.11% (31//607, 41 cases), and the adverse events were as follows: Common cold 0.99% (6/607, 7 cases), Injection site pain 0.82% (5/607, 5 cases), Aspiration pneumonitis 0.49% (3/607, 3 cases), Injection site rash, Pruritus 0.33% (2/607, 2 cases each), Tinea pedis, Cystitis, Urinary Tract infection, Reflux oesophagitis, Gingivitis, Convulsions, Abnormal eye movements, Cachexia, leg pain, Otitis externa, Depilation, Heamoptysis, Respiratory disorder, Pain neck/shoulder, Sleep disturbed, Depression, Somnolence, Cholangitis, Hypokalaemia, Appetite decreased, Cerebral infarction, Abrasion nos 0.16% (1/607, 1 case each). The rate of unexpected adverse drug reactions reported was 1.65% (10/607, 11 cases) and the adverse drug reaction was Injection site pain 0.82% (5/607, 5 cases), Common cold, Injection site rash 0.33% (2/607, 2 cases each), Convulsions, Pain neck/shoulder 0.16% (1/607, 1 case each).

The rate of unexpected serious adverse events reported was 0.66% (4/607, 5 cases): Cachexia, Aspiration pneumonitis, Heamoptysis, Cholangitis, Cerebral infarction 0.66% (1/607, 1 case each). No unexpected serious adverse drug reactions have been reported.

3. 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. Continuous concomitant use of NEURONOX® with aminoglycosides or spectinomycin is contraindicated. Use of polymyxin, tetracycline, or lincomycin for patients taking NEURONOX® should be done with caution.

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.

4. Pregnancy and lactation

Safety in pregnant women and nursing mothers has not been established in this drug.

5. Pediatric use

Blepharospasm

Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

Upper Limb Spasticity

Safety and effectiveness in patients below the age of 20 years have not been established.

Lower Limb Spasticity in Pediatric patients

Safety and efficacy in pediatric patients with lower limb spasticity below 2 years of age have not been evaluated.

Glabellar Lines

Safety and effectiveness in pediatric patients below the age of 20 years have not been established.

6. Carcinogenesis, mutagenesis, impairment of fertility, Animal toxicity

Carcinogenesis, mutagenesis, impairment of fertility, Animal toxicity studies have not been conducted for NEURONOX®.

7. 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 miss injection. The antitoxin will not reverse any botulinum toxin induced muscle weakness effects already appeared by the time of antitoxin administration.

If the musculature of the oropharynx and esophagus are affected, aspiration may occur which may lead to development of aspiration pneumonia. If the respiratory muscles become paralyzed or sufficiently weakened, intubation and assisted respiration may be necessary until recovery takes place. Supportive care could invol ve the need for a tracheostomy and/or prolonged mechanical ventilation, in addition to other general suppo rtive care.

8. Precaution in use

Unopened vials of NEURONOX® should be stored at (2~8°C). After reconstitution, NEURONOX® should be stored in a refrigerator (2~8°C) for up to 24 hours. Equipment used with the drug (such as syringes) should also be sterilized. The residual NEURONOX® should be inactivated using dilute hypochlorite solution (0.5%).

9. Information for patients

Swallowing, Speaking or Breathing Difficulties, or Other Unusual Symptoms

Advise patients to inform their doctor or pharmacist if they develop any unusual symptoms (including difficulty with swallowing, speaking, or breathing), or if any existing symptom worsens

Ability to Operate Machinery or Vehicles

Advise patients that if loss of strength, muscle weakness, blurred vision, dizziness, or drooping eyelids occur, they should avoid driving a car or engaging in other potentially hazardous activities.

Ophthalmic Adverse Reactions

Inform patients that NEURONOX® injection may cause ocular symptoms including eye dryness, eye pain, eye irritation, or photosensitivity, or changes in vision. Advise patients to report these symptoms to the prescribers.

10. Nonclinical studies

In pharmacodynamic comparison study, NEURONOX® showed similar dose ratio to that of other botulinum toxin type A product(comparator) for muscle weakening efficacy (IM ED50 value) , lethality (IM LD50 value), and the duration of recovery was also comparable between the two products.

According to the investigated single dose intramuscular toxicity and the repeated intramuscular dose toxicity of NEURONOX®, it was concluded that the single intramuscular dose of NEURONOX® produced clinical signs including weakening, decrease of locomotor activity, eyelid closure, lacrimation, reddish tear, nasal discharge, paralytic gait, ananastasia, and decrease of body weight or attenuation of body weight gain. The LD50 values of the test article were estimated to be 70.71 ng/kg for males and 97.63 ng/kg for females.

The target organ of 4-weeks, repeated, intramuscular dose toxicity study of NEURONOX® in SD rats was the skeletal muscle around the administered region. The NOEL in this test could not be determined because the expected pharmacological effects of the test article were atrophy and paralysis of muscle around the administered region. The NOAEL in this test for both male and female was determined to be 1 ng/kg because no significant changes were found at gross necropsy and clinical chemistry at this dose although a weak muscle atrophy was observed in histopathological study.

Storage

The unopened vial should be stored in a refrigerator (2-8°C).

After reconstitution, NEURONOX® should be stored in refrigerator (2 -8 °C) for up to 24 hours.

How supplied

NEURONOX® is supplied in a single use vial.

Expiration

Refer to the Outer Carton of the Product

Manufactured by: Medytox Inc.
78, Gangni 1-gil, Ochang-eup, Cheongwon-gu,
Cheongju-si, Chungcheongbuk-do,
Republic of Korea