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Wockhardt Regenerative Private Limited,
Wockhardt Regenerative Private Ltd, 8th Floor, Wockhardt Hospitals Limited,
Near Railway Station, Mira Road (E), Mumbai - 401107.

WCK/REGEN/WOCK/PM/113/04/2024 valid upto 13 April 2025

PRODUCT MONOGRAPH

In dynamic wrinkles,

℞ Wocktox

Botulinum Toxin Type A 50 & 100 IU Inj.

EXPRESS WITH CONFIDENCE

Redefine self-expression with Botulinum Toxin from Wockhardt Regenerative.

In dynamic wrinkles,

℞ Wocktox

Botulinum Toxin Type A 50 & 100 IU Inj.

EXPRESS WITH CONFIDENCE

Manufactured by

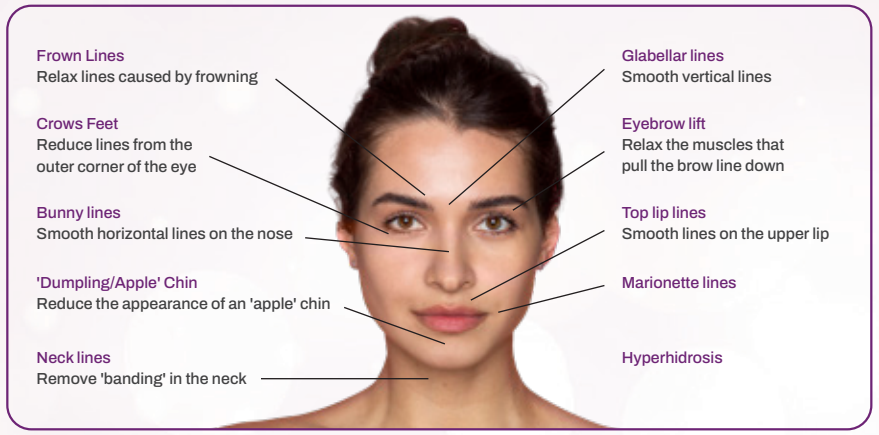
GUFIC BIOSCIENCES LIMITED

In technical collaboration with Prime Bio USA

Marketed by

NEW AGE WOCKHARDT REGENERATIVE | LIFE WINS

NOTES



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WOCKHARDT NEW AGE REGENERATIVE | LIFE WINS

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Contents

Note: For Visit 2 and 4, patients can visit the site within maximum 2 days before or 2 days after the scheduled date of the visit in case of any valid reason. Same window period is applicable for ***telephonic contact.***

References:

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- Visit 1 (Screening on Day 0)
- Unscheduled visit will happen only as per PI's discretion on any day between Day 5- Day 10)
- Visit 2 (Day 30)
- Visit 3-Telephonic contact (Day 60)
- Visit 4 (End of study visit on Day 120

Number of Subjects
Sufficient number of volunteers will be screened to enroll 100 eligible subjects
Study Duration
Four months (120 days)

Study Overview

One hundred subjects with moderate to severe facial wrinkles from the designated hospitals/ clinics (sites) will be included in this multi-center, single arm study. Subjects will complete a screening visit (V1) to determine eligibility for the study based on Inclusion & Exclusion Criteria, medical history and safety measures.

The duration of each patient's participation in the study will be of 4 months (120 days). Scheduled study visits will include:

During Visit 1 (Screening/ Enrolment/ Baseline), informed consent will be obtained before any study procedures take place. After patient has been consented, medical history will then be documented, including the concomitant medications. All subjects will undergo the screening procedure by inclusion and exclusion criteria. Demography, physical examination will be recorded including vital signs and visual assessments. Urine pregnancy test of the female subjects of childbearing age will be carried out. Subject's self-perception of age will be recorded. Treatment will be given to the single/multiple facial zone(s) (as applicable) having wrinkles. Investigator will administer required quantity of Botulinum Toxin Type A through injection. Application of ice packs will be done in case swelling and bruising at the injection site is observed. Adverse reactions and concomitant assessment will be done. Subjects will be monitored for 15 minutes before dismissal. They will be given instructions for the next visit.

If required, at **unscheduled visit,** subjects will visit the site any day between Day 5 to Day10 as per PI's discretion to check the response. If required additional units of injections will be administered. Adverse reactions and concomitant medication assessment will be done.

At Visit 2 (Intermediate visit), subjects will visit the site on Day 30. Photographs of treated facial area are taken. Modified Global Aesthetic Improvement Scale (GAIS) scoring will be done by the Investigator and subjects. Subject's self-perception of age will be recorded. Adverse reaction and concomitant medication assessment will be done. Subjects will be examined prior leaving the site. They will be given instructions for the next visit.

At Visit 3, Telephonic contact: Subjects will be contacted telephonically on Day 60. They will be interviewed about the adverse events, concomitant medications or any other problem.

At Visit 4 (End of study visit), subjects will visit the site on Day 120. Photographs of treated facial area are taken. Modified Global Aesthetic Improvement Scale (GAIS) scoring will be done by the investigator and subjects. Subject's self-perception of age will be recorded. Adverse reactions and concomitant medication assessment will be done.

Executive Summary

1. The German scientist, Dr. Justinus Kerner of Wurttemberg, first explained the disease called botulism (1817 to 1822).
2. Dr. Emile Pierre van Ermengem (Belgium) in 1895 successfully isolated this bacterium, known as Bacillus botulinus.
3. Botulinum Toxin was first used to treat human disease (1980) by Drs. Alan Scott (Opthalmologist) and Edward Schantz, for the indication, strabismus.
4. Botulinum Toxin A has seven serotypes such as A, B, C, C1, C2, D, E, F, and G which are antigenically and serologically distinct but structurally similar.
5. Botulinum Toxin A is a 900kDa complex, wherein 750kDa is the complexing protein and the 150kDa base is broken down into the heavy chain (100kDa) and the light chain (50kDa).
6. Botulinum Toxin A prevents the release of neurotransmitter acetylcholine (ACH) at the neuromuscular junction, by cleaving the Synaptosomal Associated Protein (SNAP) 25.
7. The biological potencies of Formulation of Wocktox- Botulinum Toxin A and originator were well within the ranges of 100 MU+ 25% and 100 MU - 20%, allowed by the European Pharmacopoeia 6.0 109% vs 116%)
8. The Indian Study Ongoing- A Multi-Center, Prospective, Single Arm, Post Market Surveillance Study to Evaluate the Safety & Efficacy of Botulinum Toxin Type A (Formulation of Wocktox- Botulinum Toxin A) in Management of Moderate to Severe Facial Wrinkles (Data on file).
9. The potency of BoNT-A is measured in mouse units (MU). One MU of BoNT-A is equivalent to the amount of toxin that kills 50% of a group of 17- 222 g Swiss-Webster mice of intraperitoneal injection (LD50).
10. There is a consistent batch potency of each batch which is shown by LD50 assay (40 vs 42 *vs.* 43)

History of Botulinum Toxin A. for Medical and Aesthetic Use

Sausage Poisoning

During Napoleonic War (1795– 1815) outbreak of a deadly illness from contaminated foods occurred which was due to smoked blood sausages.

One of the biggest outbreaks occurred in 1793 in Wildebrad, Southern Germany; by 1811, the Department of Internal Affairs of the Kingdom of Wurtemberg named “prussic acid” as the culprit in sausage poisoning. Intrigued, the district medical officer, Dr. Justinus “Wurst” Kerner (1786–1862), began what would become a lifelong quest to uncover the mysteries of the poison. He later was considered as the godfather of Botulinum Toxin (BoNT) research for his dedicated research work.

In 1817 and 1820, Kerner identified and described the first accurate descriptions of botulism (a term coined in 1871 from the Latin botulus, meaning “sausage'.

In 1822, he studied contaminated sausage ingredients and concluded that the toxin must occur in fat, leading him to call the suspicious substance “sausage poison” and published the first complete monograph.

Through animal and self-experimentation, Kerner observed that the toxin developed under anaerobic conditions and was lethal in small doses. Since the effects were similar to atropine, scopolamine, nicotine, and snake venom. Kerner suggested that small amounts of this sausage poison might be used to lower sympathetic nervous system activity associated with movement disorders (i.e., treat St. Vitus' dance or Sydenham's chorea, a disorder characterized by jerky, uncontrollable movements, either of the face or of the arms and legs) and hypersecretion of bodily fluid, as well as to treat ulcers, delusions, rabies, plague, tuberculosis, and yellow fever.

Identification of C. botulinum

Microbiologist Professor Emile Pierre van Ermengem (1851–1922) trained under Robert Koch, who discovered anthrax, tuberculosis, and cholera was the first researcher to prove that microorganisms could cause disease in animals. In 1897, Van Ermengem identified the bacterium Clostridium botulinum (originally called Bacillus botulinus) as the causative agent of botulism after examining postmortem tissue of patients in Belgium who had contracted gastroenteritis and died from eating raw, salted pork. Over the next twenty years, different strains of the bacterium that produced serologically distinct types of toxins were recognized; these were eventually classified alphabetically into seven serotypes (A, B, C1, D, E, F and G). In 1928, Dr. Herman Sommer (University of California, San Francisco) isolated the most potent serotype – BoNT type A (BoNTA) in purified form as a stable acid precipitate, paving the way for future studies.

The Cosmetic Connection

In the mid-1980s, Dr. Jean Carruthers, an ophthalmologist in Vancouver, Canada, noticed that her patients injected with BoNTA for blepharospasm experienced a reduction in glabellar rhytides, and discussed the findings with both Dr. Scott and Dr. Alastair Carruthers, who was attempting to soften the forehead wrinkles of his patients using soft-tissue augmenting agents available.

Carruthers used the toxin experimentally on their receptionist's forehead and subsequently published the first report of BoNTA for the treatment of glabellar frown lines in 1992. Other reports soon followed, including the first double-blind, placebo-controlled study for the treatment of hyperkinetic facial lines.

Measuring the potency labelling of Botox and Formulation of Wocktox in an LD50 assay

Results of comparative study of following formulations of BoNT/A available in market.

Sr.	Product	Batch No.	Mfg. date	Exp. Date	% Assay
1.	Botox	C5389C2	Sept. 18 year	Aug. 21 year	116.4%
2.	Formulation of Wocktox	GI/B8/19/05/A	Dec. 19 year	Nov. 21 year	109.4%
				LIMITS:	80% to 125%

*Data on File

As described in the European Pharmacopoeia the biological potency of BT drugs is measured by a standardized LD50 assay (European Pharmacopoeia 2008) and expressed in mouse units. The biological potencies of both BT drugs were well within the ranges of 100 MU+ 25% and 100 MU - 20%, allowed by the European Pharmacopoeia 6.0.

Indian Study (Ongoing)

A multi-center, prospective, single arm, post market surveillance study to evaluate the safety & efficacy of Formulation of Wocktox - Botulinum Toxin -A in management of moderate to severe facial wrinkles.

STUDY OBJECTIVES AND ENDPOINTS

Study Objectives

Primary Objective:

- To assess the safety of Botulinum Toxin Type A

Primary Objective:

- To evaluate efficacy of Botulinum Toxin A in subjects with moderate to severe facial wrinkles [one or multiple facial zone(s) (as applicable) under treatment]

End Point Primary End Point:

- Evaluation of safety will include assessment of safety of the formulation with respect to adverse events
- Proportion of subjects reported by the investigator at least 'improved' on 'Modified Global Aesthetic Improvement Scale (GAIS)' at the end of study visit

Secondary End Point:

Evaluation of efficacy will include:

- Proportion of subjects self-reported at least 'improved' on 'Modified Global Aesthetic Improvement Scale (GAIS) at the end of study visit
- Comparison of subject's self-perception of age will be done between baseline and end of study visit. The rating will be reported as I look my current age, I look _ years younger, or I look _ years older

3. In fertility studies of BOTULINUM TOXIN A (4, 8, or 16 Units/kg) in which either male or female rats were injected intramuscularly prior to mating and on the day of mating (3 doses, 2 weeks apart for males, 2 doses, 2 weeks apart for females) to untreated animals, reduced fertility was observed in males at the intermediate and high doses and in females at the high dose.

4. The no-effect doses for reproductive toxicity (4 Units/kg in males, 8 Units/kg in females) are approximately 4-8 times the average high human dose for glabellar lines, crow's feet, and forehead lines of 64 Units on a body weight basis (Units/kg).

How is it Supplied/Storage and Handling

BOTULINUM TOXIN A for injection is a Lyophilized powder supplied in a single dose vial in the following sizes: 50 Units,100 Units.

Storage

Unopened vials of BOTULINUM TOXIN A should be stored in a refrigerator 2° to 8°C. Do not use after the expiration date on the vial. Reconstituted BOTULINUM TOXIN A should be stored in a refrigerator 2° to 8°C. After reconstitution BOTULINUM TOXIN A can be stored for 24h in refrigerator.

Clinical trials

Study Title	Sample size	Methods	Conclusion
Phase 3 Study of Botulinum Toxin A Distributed Between Frontalis, Glabellar lines, and Crow's feet for Treatment of Upper Facial Lines (Koenraad.et.al. Dermatol Surg. 2018 Nov;44(11):1437- 1448).	787	Subjects with moderate to severe FHL were randomized (2:2:1) to Botulinum Toxin A 40 U, botulinum toxin A 64 U, or placebo. After 180 days, subjects could receive up to 2 additional open-label botulinum toxin A 64 U treatments.	Botulinum toxin A distributed between the frontalis and glabellar complex, with or without additional CFL injections, was safe and effective for treatment of moderate to severe FHL.
Efficacy of Botulinum Toxin A for the Treatment of Glabellar Frown Lines in Male Subjects: Post-Hoc Analyses From Randomized, Double-Blind Pivotal Studies (Darek et .al. 2017 Nov; Dermatol Surg; 43 Suppl 2:S235-S241).	55	Three Botulinum Toxin A studies were included in post hoc analyses of responder rates: 2 pivotal Phase 3 US registration studies for GFLs (n = 55 males in a pooled analysis) and a European pivotal Phase 3 study for upper facial lines (UFLs; n = 21 males.	Compared with females, males demonstrate lower response rates on wrinkle severity scales in studies on all 3 available botulinum toxins. Variations in treatment response are potentially associated with key male anatomic differences (e.g., muscle mass). Results emphasize the need for customized treatment plans.
Patient Satisfaction and Efficacy of Full-Facial Rejuvenation Using a Combination of Botulinum Toxin Type A and Hyaluronic Acid Filler. (Beatriz et. al; Dermatol Surg; 2015 Dec;41 Suppl 1:S325-32).	13	A 6-month, multicenter, open- label clinical study, using BoNT- A (s.U) and 5 HA fillers to treat up to 13 facial zones. Subject satisfaction questionnaires were administered 3 weeks and 6 months after the last injection. Global aesthetic improvement and improvement on each treated zone as well as safety were evaluated.	The combination of BoNT-A (s.U) and HA fillers results in high patient satisfaction and in an overall improvement of aesthetic outcomes and quality of life.

Year	Discoverer	Discovery
1870	Muller	Derived the name Botulism from the Latin word "Botulus" which means sausage.
1895	Emile Van Ermengem	First isolated C.botulinum from a piece of ham, caused major outbreaks
1944	Dr. Edward Schantz	First isolated botulinum neurotoxin
1949-1950	-	Studied the effect of Botulinum Toxin on the nervous system, which blocks the neuromuscular junction by blocking acetylcholine.
1980	Dr. Alan B. Scott	Used neurotoxin to treat strabismus
1989	-	USFDA approved the use of Botulinum toxin for the treatment of strabismus
2002	-	FDA approved the use of Botulinum Toxin in cosmetic improvement to treat wrinkles, frown lines etc.

Composition

Botulinum Toxin Type A for Injection BP 50/100 Unit Lyophilized	Each vial contains: Clostridium botulinum Toxin Type A... 50/100 Unit excipients.....q.s

Indications and Usage

Botulinum toxin A is indicated in adult patients for the temporary improvement in the appearance of:

1. Moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity
2. Moderate to severe crow's feet associated with orbicularis oculi activity
3. Moderate to severe forehead lines associated with frontalis muscle activity
4. Management of severe hyperhidrosis of the axillae, which does not respond to topical treatment with antiperspirants or antihidrotics

Dosage and Administration

Instructions for Safe Use

In treating adult patients for one or more indications with BOTULINUM TOXIN A, the maximum cumulative dose should generally not exceed 400 Units, in a 3 months interval. The safety and effectiveness of dosing with BOTULINUM TOXIN A for frequency more than every 3 months, have not been clinically evaluated.

The safe and effective use of BOTULINUM TOXIN A depends upon proper storage of the product, selection of the correct dose, proper reconstitution and administration techniques. Physicians administering BOTULINUM TOXIN A must understand the relevant neuromuscular and structural anatomy of the area involved and any alterations to the anatomy due to prior surgical procedures and disease.

Preparation and Dilution Technique

1. BOTULINUM TOXIN A is administered as a single-dose 50 Units and 100 Units per vial. Prior to intramuscular injection, reconstitute each vacuum-dried vial of BOTULINUM TOXIN A with sterile, preservative-free 0.9% Sodium Chloride Injection.
2. Draw up the proper amount of diluent in the appropriate size needle and syringe to obtain a reconstituted solution at a concentration of 4 Units/0.1 mL and a total treatment dose of 20 Units in 0.5 mL for glabellar lines, 24 Units in 0.6 mL for crow's feet, and 40 Units in 1 mL for forehead lines and glabellar lines.
3. Then slowly inject the diluent into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Gently mix BOTULINUM TOXIN A with the saline by rotating the vial. Record the date and time of reconstitution on the space on the label.
4. BOTULINUM TOXIN A should be administered within 24 hours after reconstitution. During this time period, reconstituted BOTULINUM TOXIN A should be stored in a refrigerator (2° to 8°C). BOTULINUM TOXIN A vials are for single-dose only. Discard any remaining solution.

Dilution Instructions for BOTULINUM TOXIN A. Vials (100 Units and 50 Units)

Diluent* Added to 100 Unit Vial	Resulting Dose Units per 0.1 mL	Diluent* Added to 50 Unit Vial	Resulting Dose Units per 0.1 mL
2.5 mL	4 Units	1.5 mL	4 Units

*Preservative-free 0.9% Sodium Chloride Injection Only

Parenteral drug products should be inspected visually for particulate matter.

Potency of Botulinum Toxin

The potency of botulinum toxins is measured in mouse units (MU). One MU of botulinum toxin is equivalent to the amount of toxin that kills 50% of a group of 17- 222 g Swiss-Webster mice of intraperitoneal injection (LD50).

Tests	Batch Number			Specification
	BA-101	BA-102	BA-103	
*Specific activity (LD50 Value)	40.9 Picogram	42.2 Picogram	43.1 Picogram	The specific activity is confirmed in a mouse model of toxicity in by in vivo methods validated with respect to the LD50 assay and expressed in mouse LD50 units per milligram of protein. Specific activity must not be less than 1 x 108 mouse LD units per milligram of 50 protein for the 150000 relative molecular mass neurotoxin and must not be less than 1 x 107 mouse LD 50 units per milligram of protein for the 900000 relative molecular mass neurotoxin complexes.

Pharmacodynamics

Byun et al. compared the pharmacodynamics of three Bont/A formulations, i.e., Botox® (onabotulinumtoxinA), Xeomin® (incobotulinumtoxinA), and Coretox®, following repeated intramuscular (IM) injections in mice. All examined BoNT/A formulations presented identical pharmacological effects.

Kim et al. compared three different preparations: onabotulinumtoxinA (ona-BoNT/A), abobotulinumtoxinA (abo-BoNT/A), and Neuronox (neu-BoNT/A), in a mouse model using a digit abduction scoring (DAS) assay. Studies suggests that Neu-BoNT/A and abo-BoNT/A had similar effects in terms of muscle weakness at significantly lower doses than abo-BoNT/A (IM ED50 41.2-2.4 U/kg; $p < .001$). The safety margin of both BoNT was found comparable. Neu-BoNT/A and ona-BoNT/A also produced comparable patterns of DAS response and body weight recovery by day 29.

Pharmacokinetics

Sharova et al. reviewed pharmacokinetic profile of Botulinum Toxin A, safety, and clinical efficacy.

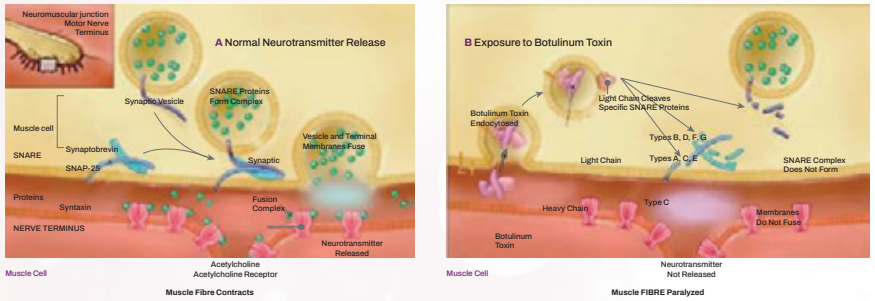
Nonclinical Toxicology

Carcinogenesis, Mutagenesis, Impairment of Fertility

1. Long-term studies in animals have not been performed to evaluate carcinogenic potential of BOTULINUM TOXIN A.
2. BOTULINUM TOXIN A was negative in a battery of in vitro (microbial reverse mutation assay, mammalian cell mutation assay, and chromosomal aberration assay) and in vivo (micronucleus assay) genetic toxicologic assays.

2. When injected intramuscularly at therapeutic doses, BOTULINUM TOXIN A produces partial chemical denervation of the muscle resulting in a localized reduction in muscle activity. In addition, the muscle may atrophy, axonal sprouting may occur, and extrajunctional acetylcholine receptors may develop.

3. There is evidence that re-innervation of the muscle may occur, thus slowly reversing muscle denervation produced by BOTULINUM TOXIN A.



Normal neurotransmission and the impact of Botulinum Toxin. **A,** Release of acetylcholine at the neuromuscular junction is mediated by the assembly of a synaptic fusion complex that allows the membrane of the synaptic vesicle containing acetylcholine to fuse with the neuronal cell membrane. The synaptic fusion complex is a set of SNARE proteins, which include synaptobrevin, SNAP-25, and syntaxin. After membrane fusion, acetylcholine is released into the synaptic cleft and then bound by receptors on the muscle cell. **B,** Botulinum toxin binds to the neuronal cell membrane at the nerve terminus and enters the neuron by endocytosis. The light chain of botulinum toxin cleaves specific sites on the SNARE proteins, preventing complete assembly of the synaptic fusion complex and thereby blocking acetylcholine release. Botulinum toxins types B, D, F, and G cleave synap to brevin; types A, C, and E cleave SNAP-25; and type C cleaves syntaxin. Without acetylcholine release, the muscle is unable to contract. NSF, N-ethylmaleimide-sensitive fusion protein; SNAP-25, synaptosomal-associated protein of 25-kDa; SNARE, soluble NSF-attachment protein receptor.

Botulinum toxins act at four different sites in the body:

- The neuromuscular junction.
- Autonomic ganglia.
- Postganglionic parasympathetic nerve endings.
- Postganglionic sympathetic nerve endings that release acetylcholine.

Stability study

The Reconstituted BOTULINUM TOXIN A is a clear, colorless, and free of particulate matter. The Botulinum Toxin A was found stable up to 14 days at 2-8°C after reconstitution and multiple withdrawal of injection solution from vial.

Administration

Glabellar Lines (GFL)

The muscles involved in GFL are the procerus and the corrugator muscles. An effective dose for facial lines is determined by gross observation of the patient's ability to activate the superficial muscles injected.

In order to reduce the complication of ptosis, the following steps should be taken:
Avoid injection near the levator palpebrae superioris muscles especially in the mid-pupillary line.

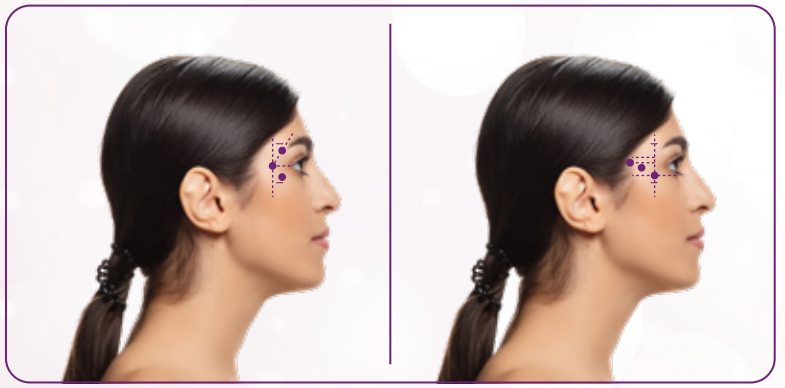
Lateral corrugator injections should be placed at least 1 cm above the bony supraorbital ridge.

Inject 4 Units (0.1 mL) of reconstituted BOTULINUM TOXIN A intramuscularly into each of 5 sites, 2 in each corrugator muscle and one in the procerus muscle for a total dose of 20 Units. Typically, the initial doses of reconstituted BOTULINUM TOXIN A induce chemical denervation of the injected muscles after 3-5 days of injection. The duration of effect of BOTULINUM TOXIN A for glabellar lines is approximately 3-4 months.

Crow's feet

Crows feet arise largely from the activity of the orbicularis oculi muscles around the eye. Forceful contraction of the orbicularis oculi results in lateral and radially oriented folds (crow's feet) which originate from the lateral canthus. Injections should be given with the needle bevel tip up and oriented away from the eye. Inject 4 Units/0.1 mL of reconstituted BOTULINUM TOXIN A into 3 sites per side (4,3,3 or 4,4,4) in the lateral orbicularis oculi muscle for a total of 24 Units/0.6 mL (12 Units per side). The first injection should be approximately 1.5-2.0 cm temporal to the lateral canthus and just temporal to the orbital rim.

For simultaneous treatment with glabellar lines, the dose is 24 Units for crow's feet and 20 Units for glabellar lines, with a total dose of 44 Units.

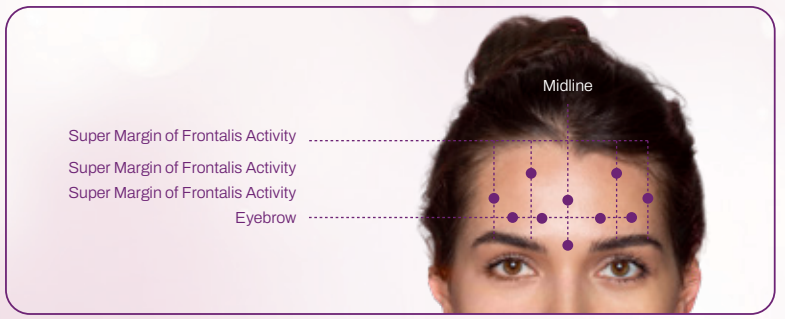


Forehead Lines (FL)

Forehead lines arise largely from the activity of the frontalis muscles. Frontalis contraction causes brow elevation.

Treat forehead lines in conjunction with glabellar lines to minimize the potential for brow ptosis. The recommended total dose for treatment of forehead lines (20 Units/0.5 mL) in conjunction with glabellar lines (20 Units /0.5 mL) is 40 Units (1mL). Inject 1.5-2 inch above the eyebrow.

For simultaneous treatment with crow's feet, the total dose is 64 Units, comprised of 20 Units for forehead lines, 20 Units for glabellar lines, and 24 Units for crow's feet.



Precautions after Botulinum Toxin A injection

1. Patient should be instructed to contract the injected area for approximately 90 minutes to two hours, which will help in the uptake of the toxin.
2. Avoid bending for a few hours after treatment to avoid potential diffusion.
3. One should go home immediately and rest after injection. Avoid strenuous exercise for one or two days.
4. Refrain from laser/IPL treatments, facials and facial massage for one to two weeks after Neuromuscular junction Motor Nerve Terminus A Normal Neurotransmitter Release B Exposure to Botulinum Toxin injections. This is to minimize toxins dislodging and traveling (due to increased blood circulation or direct pressure) to the surrounding muscles.

Therapeutic failure

- Some patients do not respond to injections and, never previously responded, are designated as primary non-responders.
- Patients with rhytids that are not dynamic in origin (eg, photodamage, age-related changes) do not respond.
- Improper injection technique or the denatured toxin may also result into therapeutic failure.
- Some patients may have neutralizing antibodies from prior subclinical exposure, or individual variations in docking proteins may exist.
- Secondary non-responders respond initially but lose the response on subsequent injections. Most of these patients may have developed neutralizing antibodies.

Microbiology

- Botulinum toxin (BTX or BoNT) is produced by Clostridium botulinum, a gram-positive anaerobic, spore forming bacillus.
- Botulinum toxin has seven serotypes such as A, B, C, C1, C2, D, E, F, and G, which are antigenically and serologically distinct but structurally similar.
- Type A is the most potent toxin, followed by types B and F toxin.
- Human botulism is caused mainly by types A, B, E, and (rarely) F. Types C and D cause toxicity only in animals.

Clinical Pharmacology

Mechanism of Action

1. BOTULINUM TOXIN A blocks neuromuscular transmission by binding to acceptor sites on motor nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. This inhibition occurs as the neurotoxin cleaves SNAP-25, a pre-synaptic protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings.

Drug Interactions

1. No formal drug interaction studies have been conducted with BOTULINUM TOXIN A for injection.

2. Aminoglycosides and other agents interfering with neuromuscular transmission

3. Co-administration of BOTULINUM TOXIN A and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated.

4. Anticholinergic drugs use after administration of BOTULINUM TOXIN A may potentiate systemic anticholinergic effects.

5. Muscle relaxants-excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of BOTULINUM TOXIN A.

Use in Specific Populations

Pregnancy (Category C)

There are no studies or adequate data from postmarketing surveillance on the developmental risk associated with use of BOTULINUM TOXIN A in pregnant women. In animal studies, administrations of BOTULINUM TOXIN A during pregnancy resulted in adverse effects on fetal growth (decreased fetal body weight and skeletal ossification) at clinically relevant doses, which were associated with maternal toxicity.

Lactation (Category C)

There are no data on the presence of BOTULINUM TOXIN A in human or animal milk, the effects on the breastfeed child, or the effects on milk production.

Pediatric Use (Vulnerable population)

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

Overdosage

- Excessive doses of BOTULINUM TOXIN A for injection may be expected to produce neuromuscular weakness with a variety of symptoms.
- Should accidental injection or oral ingestion occur or overdose be suspected, these patients should be considered for further medical evaluation and appropriate medical therapy immediately instituted, which may include hospitalization.
- The person should be medically supervised for several weeks for signs and symptoms of systemic muscular weakness which could be local, or distant from the site of injection.
- 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 involve the need for a tracheostomy and/or prolonged mechanical ventilatory support.

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Hyperhidrosis

Primary hyperhidrosis of the axillae
Recommended needle: Sterile 27-30-gauge needle
Administration guidance: The hyperhidrotic

area to be injected may be defined by using standard staining techniques, e.g. Minor´s iodine-starch test.

Recommended dose: 50 Units of Botulinum Toxin A is injected intradermally to each axilla, evenly distributed in multiple sites approximately 1-2 cm apart. The recommended injection volume for intradermal injection is 0.1-0.2 ml.

Maximum dose: Doses other than 50 Units per axilla cannot be recommended.

Additional information: Clinical improvement generally occurs within the first week after injection and persists for 4-7 months. Repeat injection of Botulinum Toxin can be administered when the clinical effect of a previous injection diminishes and the treating healthcare practitioner deems it necessary. Injections should not be repeated more frequently than every 16 weeks.

Contraindications

- Known hypersensitivity to Botulinum Toxin A
- BOTULINUM TOXIN A is contraindicated in individuals with known hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation.

Infection at the Injection Site (s)

BOTULINUM TOXIN A is contraindicated in the presence of infection at the proposed injection site(s).

Warnings and Precautions

Postmarketing safety data from BOTULINUM TOXIN A and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin and may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death related to spread of toxin effects.

Hypersensitivity Reactions

Serious and/or immediate hypersensitivity reactions have been reported. These reactions include anaphylaxis, serum sickness, urticaria, soft tissue edema, and dyspnea. If such a reaction occurs, further injection of BOTULINUM TOXIN A should be discontinued and immediately provide appropriate medical therapy.

Cardiovascular System

There have been reports following administration of BOTULINUM TOXIN A. The adverse reactions involving the cardiovascular system are arrhythmia and myocardial infarction, some with fatal outcomes. Few patients had risk factors including pre-existing cardiovascular disease. Use caution when administering to patients with pre-existing cardiovascular disease.

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Increased Risk of Clinically Significant Effects with Pre-Existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored when given Botulinum Toxin A. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, and severe dysphagia.

Dysphagia and Breathing Difficulties

- Treatment with BOTULINUM TOXIN A and other botulinum toxin products can result in swallowing or breathing difficulties.
- Deaths as a complication of severe dysphagia have been reported after treatment with Botulinum Toxin A. Dysphagia may persist for several months, and require use of a feeding tube to maintain adequate nutrition and hydration. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised.
- Patients treated with botulinum toxin A may require immediate medical attention and they could develop problems with swallowing, speech or respiratory disorders. These reactions can occur within hours to weeks after injection with Botulinum Toxin.

Pre-existing Conditions at the Injection Site

Caution should be used when BOTULINUM TOXIN A treatment is used in the presence of inflammation at the proposed injection site(s), ptosis, or when excessive weakness or atrophy is present in the targeted muscle(s).

Corneal Exposure and Ulceration in Patients Treated with BOTULINUM TOXIN A for Blepharospasm

- Reduced blinking from injection of botulinum toxin products in or near the orbicularis oculi muscle can lead to corneal exposure, persistent corneal epithelial defect, and corneal ulceration, especially in patients with VII nerve disorders.
- Vigorous treatment of any corneal 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.

Dry Eye in Patients Treated with BOTULINUM TOXIN A

Spatial Disorientation, Double Vision or Past-pointing in Patients Treated for Strabismus Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay.

Adverse Reactions

There have been spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin A. There have also been reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. The following adverse reactions by System Organ Class have been identified of BOTULINUM

TOXIN A:

- Fever and flu like symptoms
- Ear and labyrinth disorders, eyelid edema, hypoacusis; tinnitus; vertigo, eyelid ptosis
- Eye disorders-Diplopia; dry eye; lagophthalmos; strabismus; visual disturbances; vision blurred
- Gastrointestinal disorders-abdominal pain; diarrhea; dry mouth; nausea; vomiting
- General disorders and administration site conditions-Denervation; malaise; pyrexia
- Metabolism and nutrition disorders-Anorexia
- Musculoskeletal and connective tissue disorders-Localized muscle twitching/involuntary muscle contractions; muscle atrophy; myalgia
- Nervous system disorders- Headache, Brachial plexopathy; dysarthria; facial palsy; hypoaesthesia; localized numbness; myasthenia gravis; paresthesia; peripheral neuropathy; radiculopathy; syncope, brow ptosis, skin tightness
- Respiratory, thoracic and mediastinal disorders-Aspiration pneumonia; dyspnea; respiratory depression and/or respiratory failure
- Skin and subcutaneous tissue disorders- Facial paresis, alopecia, including madarosis; hyperhidrosis; pruritus; skin rash (including erythema multiforme, dermatitis psoriasiform, and psoriasiform eruption)

In general, adverse reactions occur within the first week following injection of BOTULINUM TOXIN A 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. Needle-related pain and/or anxiety may result in vasovagal responses (including e.g., 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.