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Anti-Aging TOP Secret
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Tòxina Botulìnica Tipo A
Therapeutic
Back to the healthy me
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BTXA
Лантокс
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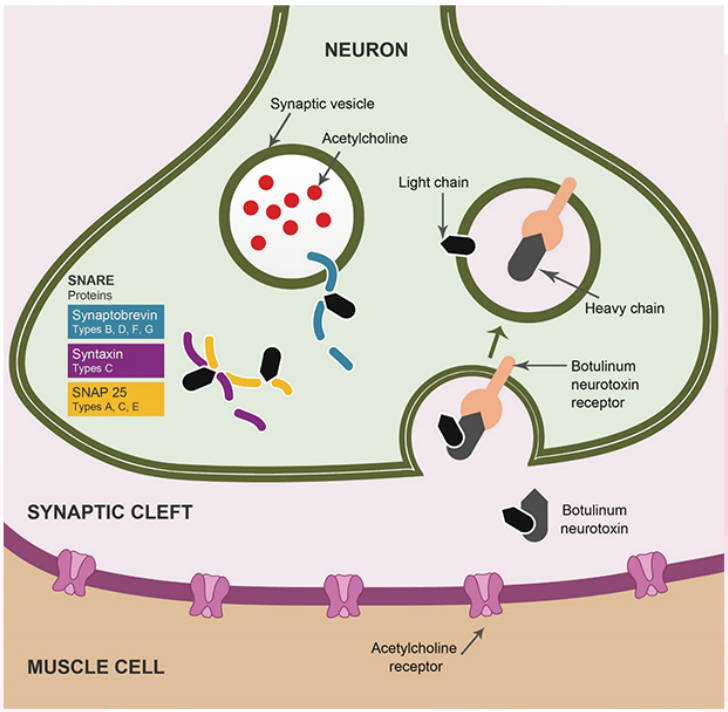
Mode of Action



BTXA, Botulinum Toxin Type A, inhibits release of acetylcholine at presynaptic membrane of nerve terminals, resulting in muscular flaccid paralysis.

History of BTXA

History of BTXA - BTXA and the American brand share the same *Clostridium botulinum* bacteria type A Hall Strain

University of Wisconsin, USA
Same *Clostridium botulinum* bacteria type A Hall Strain

Dr. Scott & Prof. Hiroshi Sugiyama did research in the University of Wisconsin, USA. Dr. Yinchun Wang was a visit scholar in this university.

Dr. Scott developed Oculinum®.

Dr. Scott

Prof. Sugiyama

Prof. Sugiyama from University of Wisconsin donated the *Clostridium botulinum* bacteria type A Hall Strain to Dr. Yinchun Wang in 1984.

Oculinum® was manufactured by Oculinum Inc. and distributed by Allergan Inc. in late 1970s.

Oculinum®

Dr .Yinchun Wang

Dr. Wang is the developer of BTXA in the Lanzhou Institute of Biological Product of China with the bacteria Hall Strain obtained from the University of Wisconsin. **The package inserts of Oculinum ® as well as the American brand nowadays still quoted Dr. Yinchun Wang's research paper as their references.**

The Allergan Inc. bought Oculinum Inc. from Dr. Scott in 1991 and changed the brand name of Oculinum® to the American brand.

The American brand

BTXA

Evidence on the Clinical Efficacy and Safety of BTXA Compared to the American Brand

The treatment with BTXA is considered the golden standard in both Blepharospasms (BS) and Hemifacial spasm (HS).

In *A double-blind, randomized, crossover study of BTXA versus the American brand in patients with blepharospasms and hemifacial spasm*[1], the selected patients, all with HS or idiopathic BS, were followed in two periods for at least three months.

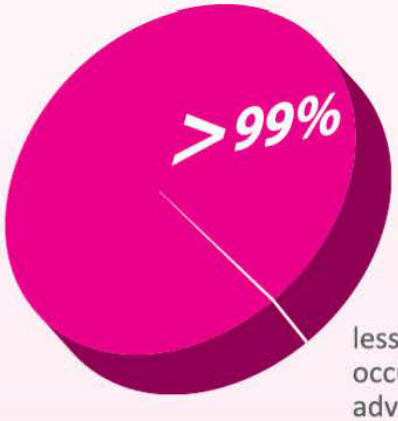
The study evaluated the subjective global improvement, response onset, efficacy duration, and incidence and severity of adverse events.

In all analyzed parameters, there were no significant differences between the two drugs. It has been concluded that BTXA and the American brand are comparable with respect to efficacy and safety for the treatment of blepharospasm and hemifacial spasm.

Safety Assessment

A more than five years' continuous safety monitoring on BTXA application was carried out in Brazil and respective Periodic Safety Update Report (PSUR) was issued in Jan 2009[2].

During the period covered (Jun 2003- Dec 2008), about 300,000 cases had been treated with BTXA



Reported satisfactory safety result

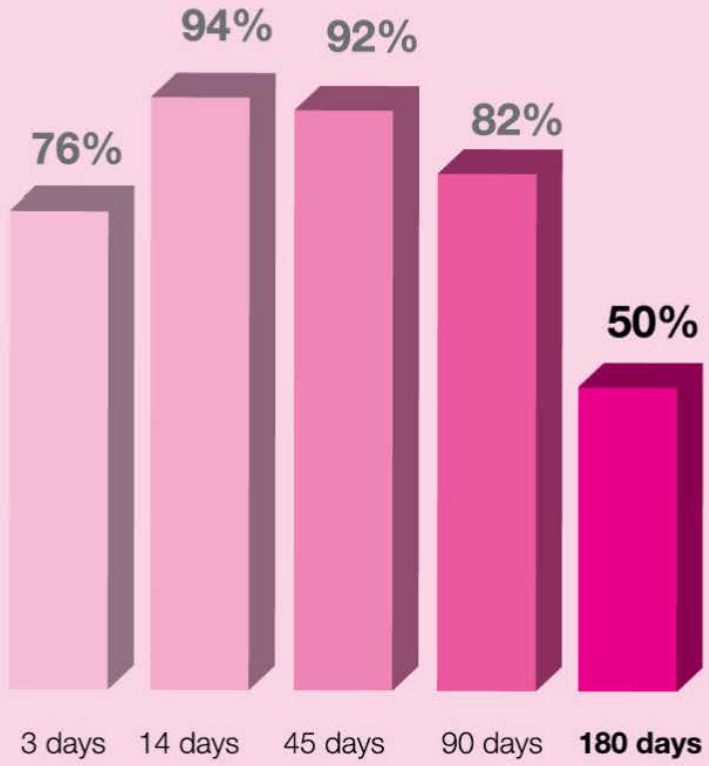
less than 1 % occurence of adverse events

Overall adverse event rate is classified as uncommon. Most of the reported scenarios were also expected in other brands of botulinum toxin type A.

BTXA treatment is continuously under Safety monitoring of Health Authorities

Botulinum Toxin Type A injections were the #1 non-surgical cosmetic procedure and the #1 cosmetic procedure overall for the sixth year in a row[3].

Efficacy vs Long - lasting Effects of BTXA in Facial Wrinkles Treatment



- The satisfactory rate reached more than 90% in 14 days after injection[4]
- 50% patients maintained satisfactory result **up to 6-month period**[4]
- Only 1% of the patients reported much pain or burning upon the injection and no patients reported significant post-injection pain[4]
- Conclusion: BTXA was deemed safe, well tolerated and reached good satisfactory levels[4]

References:

1. Costa J, Rieder C, ***et al***. A double-blind, randomised, crossover study of Prosigne versus Botox in patients with blepharospasm and hemifacial spasm. Clin Neuropharmacol. 2007;30:39-42.
2. Drug Safety Report-Prosigne ® (Botulinum Toxin Type A), Jan 2009, Hugh Source (Int'l) Ltd. Data on file.
3. 2007 American Society of Aesthetic Plastic Surgery (ASAPS) Cosmetic Surgery National Data Bank Statistics.
4. Talarico S, Bgatin E, Pecora CS, Ferreira LM, Orofino R, Godoy A, ***et al***. Open-Label, Prospective, Multicenter, Multidisciplinary Phase III Study to Evaluate the Efficacy and Tolerability of Prosigne (Botulinum Toxin Type A) in the Aesthetic Treatment of the Upper third of the Face in Patients with Facial Wrinkles. Data on file.

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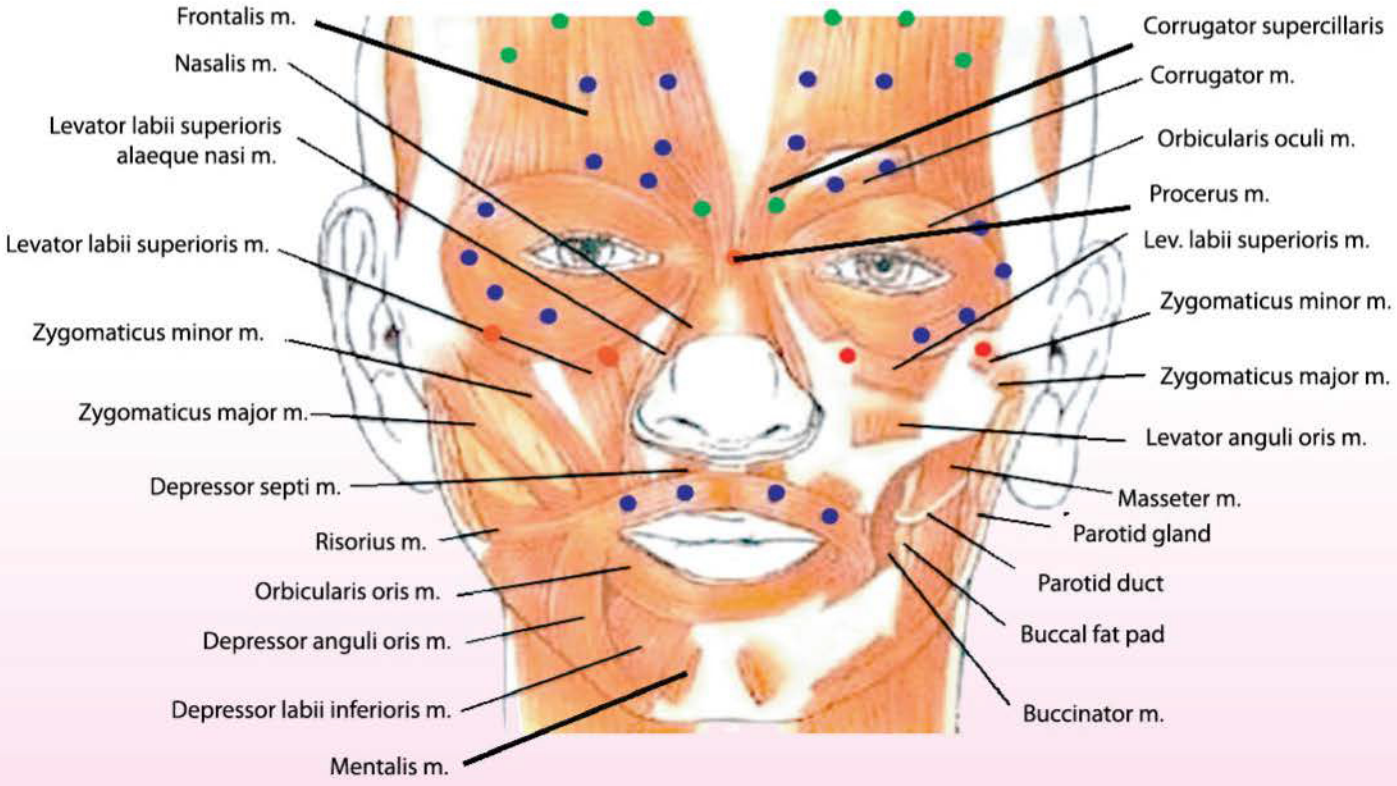
Injection Dosage (for reference)

Application areas		Dose per site	No. of sites	Total dose	Injection depth
Forehead lines		2 - 4 U	5 - 10	10 – 20 U	SC / IM
Vertical glabellar lines		4 U	4	16 U	SC / IM
Horizontal glabellar lines		4 U	1	4 U	SC / IM
Crow's feet (each side)		2 U	3 – 6	6 -12 U	SC
Perioral rhytides		1 - 2 U	4	4 -8 U	Superficial
Horizontal platysmal bands (each band)		3 - 5 U	3	12-15 U	IM
Masseter muscle	Man	10 – 13 U	3 – 4	30 – 40 U	IM: 2 – 3 cm
hypertrophy (each side)	Woman	7 – 10 U	3 – 4	20 – 30 U	IM: 1 – 1.5 cm
Calf muscle hypertrophy (each side)		5 U	20 – 30	100 – 150 U	IM: ~2 cm

Facial Injection Sites



Injection depth ● Deep ● Middle ● Superficial

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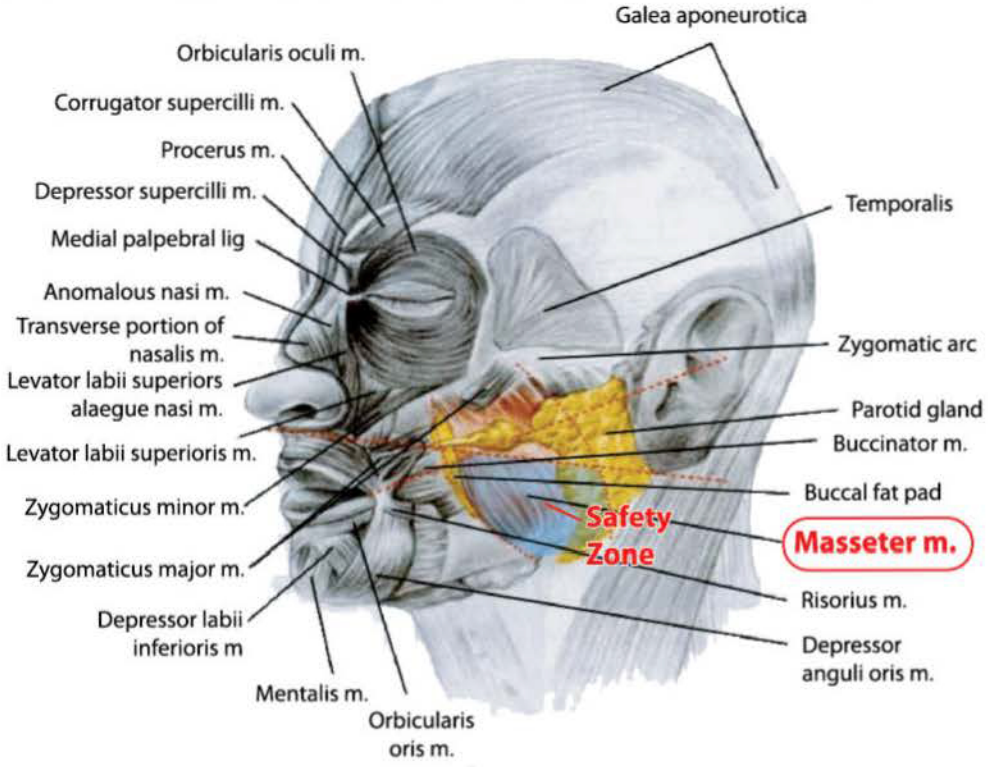
Treatment of Masseter Muscle Hypertrophy

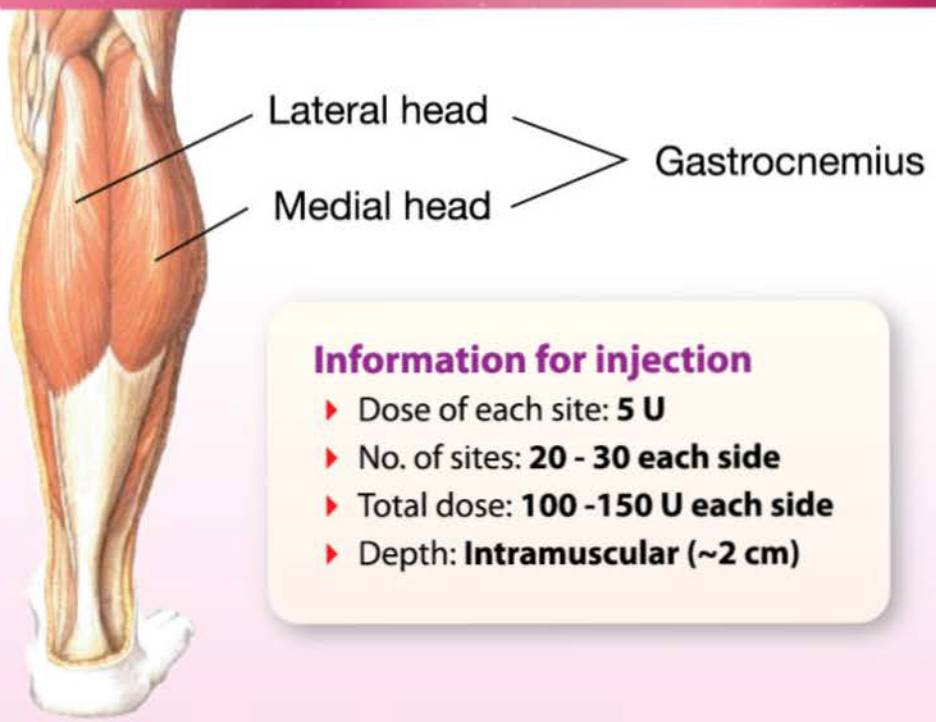


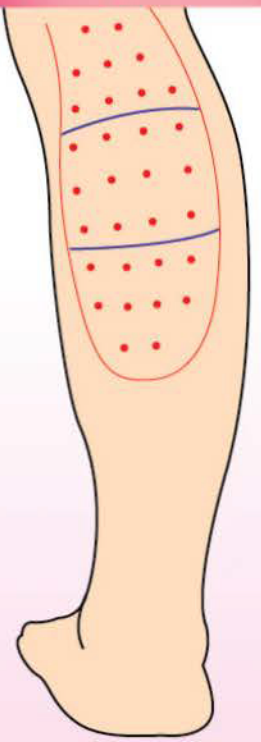
Information for injection

- Dose of each site:
  - Man: **10 – 13 U**
  - Woman: **7 – 10 U**
- No. of sites: **3 – 4 each side**
- Total dose for each side:
  - Man: **30 – 40 U**
  - Woman: **20 – 30 U**
- Depth: Intramuscular
  - Man: **2 – 3 cm**
  - Woman: **1 – 1.5 cm**

- Ask the patient to close the jaw tightly to show the masseter muscle
- Use 23G needle to inject at the deeper portion of muscle
- Avoid injection to the origin site and upper portion to prevent cheek depression
- Space the injections 2 cm apart

Treatment of Calf Muscle Hypertrophy





Information for injection

- Dose of each site: **5 U**
- No. of sites: **20 - 30 each side**
- Total dose: **100 -150 U each side**
- Depth: **Intramuscular (~2 cm)**

- Carry out intravenous sedation with Ketamine
- Mark the outline contour of calf muscle when the patient is raising heel for tip-toeing

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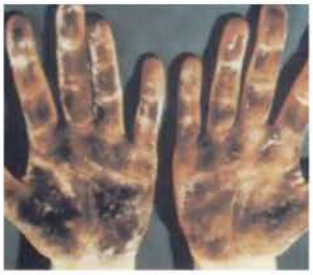
Treatment of Hyperhidrosis

Classical locations of hyperhidrosis: face, underarm, hands and feet



Before injection:

An iodine starch test can be performed to ascertain the injection areas

Steps:
1. The areas to be evaluated are covered with castor oil & iodine in a 1:9 proportion
2. The areas are sprinkled by potato starch
3. The areas of active sweating turn black

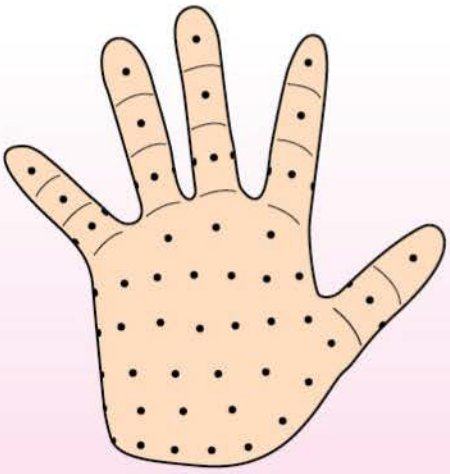
- This test should be carried out prior to regional nerve blocks or the use of topical anaesthetics
- It is helpful to draw a grid on the skin to mark the injection fields

For palms and soles:

- The dose varies from patient to patient and depends on the size of the hyperhidrotic area to be injected
- In plantar hyperhidrosis, the lateral and medial edges of the foot may need additional injections
- The main limitation is that most patients find the injections painful and may require regional anesthesia via median and ulnar nerve blocks for palms and sural and posterior tibial nerve block for soles
- Alternatively, the area can be rendered relatively pain free by prior application of anesthetic cream under occlusion, iontophoretic application of lidocaine, or cryospray

Location	Dose	Concentration	Total injection sites
Palms	50-100 U / palm	2- 2.5 U / 0.1 ml / site	Depends on the size of the hyperhidrotic area
Soles	50-100 U / sole	2- 2.5 U / 0.1 ml / site	
Axillae	50 U / axilla	2.5 U / 0.1 ml / site 5 U / 0.2 ml / site	10-15 sites / axillae

Palms	Soles	Axillae
Inject intradermally	Inject intradermally	Inject intradermally
Approximate depth of 3 mm	Approximate depth of 3 mm	Approximate depth of 3 mm and at a 45° to the skin surface
Avoid intramuscular injections	Avoid intramuscular injections	Avoid intramuscular injections
Injections are scattered every 1.5 - 2 cm on the palm of the hand and on the fingertips, tips and webs of hand	Injections are scattered every 1.5 - 2 cm on the sole, sides of the sole and will be placed in the webs between the toes and on the tips of the toes	Injection to multiple sites approximately 1.5 - 2 cm apart



- If injection sites are marked in ink, do not inject BTXA directly through the ink mark to avoid a permanent tattoo effect

User Tips for Injection

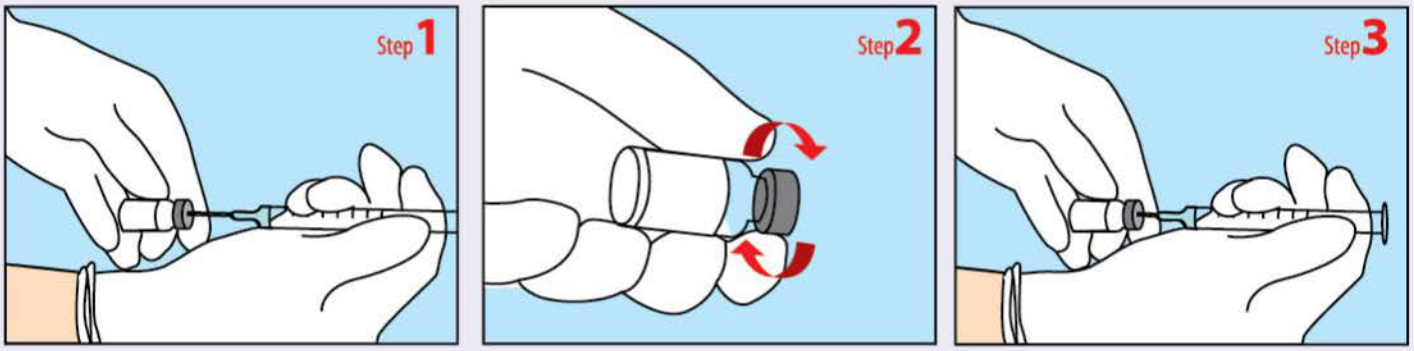
Storage condition:

	Before reconstitution	After reconstitution
Storage temperature	2°C to 8°C or -20°C to -5°C	2°C to 8°C, do not freeze
Shelf life	2 or 3 years after lyophilization	Use within 4 hours ideally

Dilution table:

Concentration (U/ 0.1 ml)	Volume of diluents (ml) added	
	50 U vial	100 U vial
10.0 U / 0.1 ml	0.5 ml	1.0 ml
5.0 U / 0.1 ml	1.0 ml	2.0 ml
4.0 U / 0.1 ml	/	2.5 ml
2.5 U / 0.1 ml	2.0 ml	4.0 ml
1.25 U / 0.1ml	4.0 ml	8.0 ml

Reconstitution techniques:



Step 1: Use a 21G needle and an appropriately sized syringe to draw up appropriate amount of 0.9% sterile saline without preservative. Insert the needle into glass vial gently and slowly inject to avoid bubble formation. Discard the vial if a vacuum does not pull the diluents into vial.

Step 2: **Gently rotate the vial** (do not vigorously shake the vial) to avoid bubble formation which may affect the potency of toxin.

Step 3: Draw the mixture back into the syringe. Inject the mixture into muscle by using appropriate needle tip for injection.

Basic injection techniques:

- Remove any make-up on the patient's skin and wipe the sites with alcohol swab. Allow to dry
- Evaluate the bulk of muscle contraction at the proposed injection site
- After aspiration of BTXA solution, remove the 21G needle tip and attach a 30G needle tip in order to minimize discomfort to patient
- Clear the air bubble from the syringe using minimal agitation before injection
- Advise the patient to relax during injection

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Post-injection:

- Press on the site with a tissue immediately after the injection for minutes to minimize bruising
- Any bruising that occurs should be treated immediately with ice pack
- No other treatments or massage unless otherwise specified
- Advise patient to take rest for 15 minutes before returning to normal activity

Contraindications:

- ✗ Pregnant and breast feeding women
- ✗ Hypersensitive patients
- ✗ Heavy forehead furrows with slight ptosis
- ✗ Redundant facial skin
- ✗ Unrealistic goal and expectations
- ✗ Infection or tumor at the proposed injection sites
- ✗ Long-term usage of anticoagulant or patients with dysfunction of blood coagulation
- ✗ Unstable mental state
- ✗ Patients who are taking aspirin, aminoglycosides antibiotics (eg: gentamicin), aminoquinolines, cyclosporine, D-penicillamine within two weeks prior to injection

How to avoid antibody formation?

- Use minimum effective dose
- Keep at least 2 to 3 months interval between injections
- Avoid booster injection
- Inject no more than 300 units in 3 months

Effectiveness:

- The onset time is 1 to 2 days for most of the patients
- Best effect will usually be attained 1 to 4 weeks after injection
- After 3 to 4 months, effectiveness will gradually fade, but the overall efficacy of BTXA can be maintained for 6 to 8 months
- According to many reports, the duration of effectiveness increased after repeated injections
- Younger patients with more elastic skin will have a longer effect

Potential risks:

Among all the cases of BTXA cosmetic applications, severe adverse reaction was rarely reported.

- Bruising—resolve in 7 to 10 days
  - Avoided by not taking aspirin prior to injection
- Ptosis—resolve within a few weeks
  - Avoided by injection at least 1 cm above the eyebrow and no massage after injection
- Ecchymosis & oedema
- Tightening of forehead
- Mild nausea
- Pain at the injection sites
- Erythema
- Cyanosis
- Unnatural facial expression

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Most side effects are transient and will disappear spontaneously after 1-2 weeks

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BTXA (BOTULINUM TOXIN TYPE A) **DESCRIPTION** BTXA (Botulinum Toxin Type A) is a sterile, lyophilized form of purified botulinum toxin type A, produced from the crude toxin of the culture of the Hall strain of Clostridium botulinum grown in a medium containing trypticase and yeast extract. A series of purifying procedure were taken to form a crystalline complex consisting of the active high molecular weight toxin protein and an associated hemagglutinin. After re-dissolved and dialyzed the crystalline toxin, an accurate amount of the sterile filtered (0.2 microns) toxin were added to a solution containing gelatin-dextran-sucrose, then lyophilized. Each vial of BTXA contains 100 or 50 units (U) of C. botulinum toxin type A, 5 mg of gelatin, 25 mg of dextran and 25 mg of sucrose. Dilute with sterile normal saline according to different needs before using. The white loose product turns to be colorless or yellowish transparent solution after the reconstitution. One unit (U) of BTXA corresponds to 1 LD50 of Botulinum Toxin Type A while being intraperitoneally injected into mouse. BTXA could block neuromuscular conduction by inhibiting the release of acetylcholine and therefore causes local muscle flaccid paralysis. **INDICATIONS** BTXA is indicated for the treatment of blepharospasm, hemifacial spasm in adults and some types of strabismus, especially for acute paralytic strabismus, comitant strabismus, strabismus caused by endocrine myopathy and strabismus which can not be corrected through operation. **USAGE AND DOSAGE Position for injection** For blepharospasm: the injection should be taken intramuscularly at several points of upper and lower lids, i.e., taking 4 to 5 points of injection into orbicularis oculi of medial and lateral or lateral canthus temporal. For hemifacial spasm: besides the points mentioned above, three other points on middle, lower face and cheek should be given intramuscularly. BTXA may be given at the points of two sides of eyebrow, upper lip or the lower jaw according to the diseases. For strabismus: the BTXA is injected using a coaxial electrode needle with electromyographic guidance or amplifier under topical anesthesia of 0.5% Decarine. The injections into extraocular muscles are selected according to the type and position of strabismus. **Dosage** For blepharospasm and hemifacial spasm: the injection could be given following above instructions. The initial dose of each point is 2.5 U / 0.05 ml or 2.5 U / 0.1 ml. If the initial treatment is considered insufficient one week later, a supplementary injection may be given. Double dose of 5 U / 0.1 ml could be given to recrudescent patients. But the limitation of total dose of 55 U for one injection and 200 U for one month should not be exceeded. For strabismus: for vertical and horizontal muscle strabismus of less than 20 prism diopters, the initial dose into each muscle is 1.25-2.5 U; for horizontal strabismus of 20-40 prism diopters, the initial dose into each muscle is 2.5 U; for horizontal strabismus of 40-50 prism diopters, the initial dose into each muscle is 2.5 U and can be increase (to 5.0 each time) depending on the response; for persistent VI cranial nerve paralysis lasted for more than one month, 1.25-2.5 U dose could be injected into medial rectus. The injecting volume into each muscle should not exceed 0.1 ml. To patients, having insufficient response, supplementary injection could be given. To recrudescent patients, the dose can be repeated or increased irregularly. But for each muscle the maximum dose should be less than 5 U / inj. **The Dilution of BTXA** The dilution of BTXA with sterile normal saline should be done carefully on the basis of real needs. Following is a reference table of dilution to be recommended:

Concentration (U / 0.1 ml)	Volume of Diluent (ml) Added	
	50 U vial	100 U vial
10.0 U / 0.1 ml	0.5 ml	1.0 ml
5.0 U / 0.1 ml	1.0 ml	2.0 ml
2.5 U / 0.1 ml	2.0 ml	4.0 ml
1.25 U / 0.1 ml	4.0 ml	8.0 ml

Shaking the vial gently after adding sterile normal saline to the complete dissolving. The reconstituted BTXA should be used at once or stored in refrigerator at 2 to 8°c and to be used within 4 hours. The container and the syringe used with the drug as well as the residual BTXA solution should be disposed after sterilization. **SIDE EFFECTS** Temporary ptosis of the eyelid, drawback of the lower eyelid, reduced blinking, eyelid close incompletely, weakness of facial muscles, etc. may occur to a few patients who received BTXA therapy for blepharospasm and hemifacial spasm. However, all the symptoms will disappear without any therapy within 3 to 8 weeks. Temporary and different degree of ptosis of the eyelid, vertical deviation and rarely mydriasis, which related to the diffusion of the toxin to the muscles adjacent, may occur to some patients who received BTXA therapy for strabismus. The symptoms will disappear without any therapy within a few weeks. **CONTRAINDICATIONS** BTXA is contraindicated in individuals with anaphylactic constitution and known hypersensitivity to this preparation. **PRECAUTIONS** BTXA must be kept, issued, registered by special person and administered only to the patients with above indications. Physicians administering especially during the treatment of strabismus, have to be trained prior, know extraocular and facial muscles anatomy and be good at lectromyographic amplifier technique. The injection procedure should be taken later to patients who have fever, acute infectious diseases and carefully to the patients with heart, liver, lung diseases, active tuberculosis, blood diseases and pregnant women. Botulinum toxin may be potentiated by aminoglycoside antibiotics (such as gentamicin). This kind of drugs should not be taken during the administration of BTXA. BTXA is in low effect or without any effect to the patients in the following situations: strabismus above 50 prism diopters, fixed strabismus, Duane's syndrome due to weak lateral rectus, strabismus caused by excessively corrected operation, chronic paralysis strabismus, chronic VI or III cranial nerve paralysis, serious muscle fiber contracture. 1:1000 adrenaline should be prepared in case of occasional accident. Short period of observation is recommended to the patients who just received BTXA injection. **HOW SUPPLIED** 100 U / Vial, 50 U / Vial **SHELF LIFE** 3 years from the date of lyophilization. **STORAGE** Store at temperature of -5 to -20°c (23 to -4°c). **MANUFACTURER** Lanzhou Institute of Biological Products **SOLE AGENT** Hugh Source (International) Ltd. Tel: (852) 27716822 Fax: (852) 27825249 Email: hughs@hughsource.com

HUGH
Hugh Source (International) Limited

Flat 1311-1312, 13/F, New East Ocean Centre,
9 Science Museum Road, Tsim Sha Tsui, Kowloon, Hong Kong.
Tel: 852-2771 6622 Fax: 852-2782 5249
http://www.btxa.com Email: hughs@hughsource.com

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