Cosmetic
Anti-Aging TOP Secret

BTXA™
Botulinum Toxin Type A

Therapeutic
Back to the healthy me

Hugh Source (International) Limited
**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

- Dr. Scott developed Oculinum®.
- Oculinum® was manufactured by Oculinum Inc. and distributed by Allergan Inc. in late 1970s.
- The Allergan Inc. bought Oculinum Inc. from Dr. Scott in 1991 and changed the brand name of Oculinum® to the American brand.

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

- Dr. Scott
- Prof. Sugiyama
- Oculinum®
- Dr. Yinchun Wang
- The American brand
- BTXA

- Dr. Scott & Prof. Hiroshi Sugiyama did research in the University of Wisconsin, USA. Dr. Yinchun Wang was a visit scholar in this university.
- Prof. Sugiyama from University of Wisconsin donated the Clostridium botulinum bacteria type A Hall Strain to Dr. Yinchun Wang in 1984.
- 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.
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, 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.

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

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.

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

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

3 days 14 days 45 days 90 days 180 days

76% 94% 92% 82% 50%

References:
Cosmetic
Anti-Aging TOP Secret
**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 hypertrophy (each side) | Man | 10 - 13 U | 3 - 4 | 30 - 40 U | IM: 2 – 3 cm
Masseter muscle 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**

- Frontalis m.
- Nasalis m.
- Levator labii superioris alaeque nasi m.
- Levator labii superioris m.
- Zygomaticus minor m.
- Zygomaticus major m.
- Depressor septi m.
- Depressor anguli oris m.
- Depressor labii inferioris m.
- Mentalis m.
- Corrugator superciliaris
- Corrugator m.
- Orbicularis oculi m.
- Procerus m.
- Lev. labii superioris m.
- Zygomaticus minor m.
- Zygomaticus major m.
- Levator anguli oris m.
- Masseter m.
- Parotid gland
- Parotid duct
- Buccal fat pad
- Buccinator m.

**Injection depth**

- Deep
- Middle
- Superficial
Treatment of Masseter Muscle Hypertrophy

- 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

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

Treatment of Calf Muscle Hypertrophy

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

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)
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

<table>
<thead>
<tr>
<th>Location</th>
<th>Dose</th>
<th>Concentration</th>
<th>Total injection sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palms</td>
<td>50-100 U / palm</td>
<td>2-2.5 U / 0.1 ml / site</td>
<td>Depends on the size of the hyperhidrotic area</td>
</tr>
<tr>
<td>Soles</td>
<td>50-100 U / sole</td>
<td>2-2.5 U / 0.1 ml / site</td>
<td></td>
</tr>
<tr>
<td>Axillae</td>
<td>50 U / axilla</td>
<td>2.5 U / 0.1 ml / site, 5 U / 0.2 ml / site</td>
<td>10-15 sites / axillae</td>
</tr>
</tbody>
</table>

Palms
- Inject intradermally
- Approximate depth of 3 mm
- 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

Soles
- Inject intradermally
- Approximate depth of 3 mm
- Avoid intramuscular injections
- 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

Axillae
- Inject intradermally
- Approximate depth of 3 mm and at a 45° to the skin surface
- Avoid intramuscular injections
- 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:

<table>
<thead>
<tr>
<th>Storage condition</th>
<th>Before reconstitution</th>
<th>After reconstitution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Storage temperature</td>
<td>2°C to 8°C or -20°C to -5°C</td>
<td>2°C to 8°C, do not freeze</td>
</tr>
<tr>
<td>Shelf life</td>
<td>2 or 3 years after lyophilization</td>
<td>Use within 4 hours ideally</td>
</tr>
</tbody>
</table>

Dilution table:

<table>
<thead>
<tr>
<th>Concentration (U / 0.1 ml)</th>
<th>Volume of diluents (ml) added</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50 U vial</td>
</tr>
<tr>
<td>10.0 U / 0.1 ml</td>
<td>0.5 ml</td>
</tr>
<tr>
<td>5.0 U / 0.1 ml</td>
<td>1.0 ml</td>
</tr>
<tr>
<td>4.0 U / 0.1 ml</td>
<td>/</td>
</tr>
<tr>
<td>2.5 U / 0.1 ml</td>
<td>2.0 ml</td>
</tr>
<tr>
<td>1.25 U / 0.1 ml</td>
<td>4.0 ml</td>
</tr>
</tbody>
</table>

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
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

Most side effects are transient and will disappear spontaneously after 1-2 weeks
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 halophilic Clostridium botulinum grown in a medium containing trehalose and yeast extract. A series of purifying procedures were taken to form a crystalline complex consisting of the active high molecular weight toxin protein and an associated haptoglobin. After re-dissolving and depyrogenating, the crystalline toxin is an aqueous solution of the active (60% of the dry weight) toxoid protein and a low molecular weight haptoglobin (less than 5%).

Each vial of BTXA contains 100-500 units (10-50 mg) of botulinum toxin type A, 5 mg of gelatin, 25 mg of calcium and 20 mg of sucrose. Dilute with sterile normal saline according to different needs before using. The white-disk product form is stable in a dry state for at least one month. After reconstitution, the lyophilized BTXA crystalline complex disperses in water and returns to an aqueous solution containing 25-2.5 mg/ml of BTXA with 50 U/ml of haptoglobin and 0.1 mg/ml of gelatin. The lyophilized BTXA crystalline complex will disperse in saline and therefore cause local muscle fasciculations. INSTRUCTIONS: BTXA is indicated for the treatment of the muscle spasm of blepharospasm, hemifacial spasm, and abductor spasms. For blepharospasm, the injection should be made directly into the orbicularis oculi muscle at several points of upper and lower lid, 1 mg to 0.5 mg of injection into a single site for the treatment of horizontal hemifacial spasm. For hemifacial spasm, the toxin is injected into the muscle area around the upper jaw, upper lid, and the lower jaw respectively. For blepharospasm, the injection consists of at least 3 sites in total. The distances between injection sites is about 1 cm. The dosage volume of each injection should be less than 0.1 ml. For patients having insufficient responses, supplementary injection could be given. To reduce incident, the dose can be increased gradually. But for each muscle the maximum dose should be less than 5 U/ml. The Dilution of BTXA: The dilution of BTXA with sterile normal saline should be done carefully on the basis of each need. Following is a reference table of dilution to be recommended:

<table>
<thead>
<tr>
<th>Concentration (U/0.1 ml)</th>
<th>Volume of Solution (ml) Adder</th>
<th>50 U vial</th>
<th>100 U vial</th>
</tr>
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<tr>
<td>10.0 U/0.1 ml</td>
<td>0.5 ml</td>
<td>0.5 ml</td>
<td>1.0 ml</td>
</tr>
<tr>
<td>5.0 U/0.1 ml</td>
<td>1.0 ml</td>
<td>1.0 ml</td>
<td>2.0 ml</td>
</tr>
<tr>
<td>2.5 U/0.1 ml</td>
<td>2.0 ml</td>
<td>2.0 ml</td>
<td>4.0 ml</td>
</tr>
<tr>
<td>1.25 U/0.1 ml</td>
<td>4.0 ml</td>
<td>4.0 ml</td>
<td>8.0 ml</td>
</tr>
</tbody>
</table>

Shaking the vials gently after adding sterile normal saline to the complete solution. The recombinant BTXA should be used once or stored in refrigerator at 2° C to 8° C and used to be within 4 weeks. The container and the syringes used with the drug as well as the reconstituted BTXA solution should be disposed after each use. SIDE EFFECTS: For some people, the local discomfort of the lower eyelid around the injection site, muscle fasciculations, weakness of facial muscles, may occur in the patients who received BTXA therapy for blepharospasm and hemifacial spasm. However, if all the symptoms will disappear without any therapy within 3 to 5 weeks. Temporary and different degree of closure of the eyelids, facial swelling and redness, which related to the injection of the toxin to the muscle area, may occur in some patients who received BTXA therapy for strabismus. The symptoms will disappear without any therapy within a few weeks. CONTRAINDICATIONS: (1) BTXA is contraindicated in individuals with amyloidosis and known hypersensitivity to this preparation. (2) BTXA may be used cautiously in children and adolescent with amyloidosis and known hypersensitivity to this preparation. (3) BTXA is contraindicated in the presence of malignancy. (4) BTXA may be used cautiously in the presence of malignancy. The injection process should be taken after the patients who have been treated for active infections or any other infections. This group of drugs should not be taken during the administration of BTXA. BTX A is in low effect or without any effect in the patients in the following situations: (1) severe glaucoma, (2) severe glaucoma, (3) severe systemic infections, (4) severe systemic infections, (5) severe systemic infections, (6) severe systemic infections. 11,000 patients 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. CONTACTING THE MANUFACTURER: Biologics Products Sole Agent - Hugh Source (International) Ltd. Tel: (852) 2771 9022 Fax: (852) 2782 5249. Email: hughsource.com

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