BOTOX – WHAT IT IS AND HOW IT WORKS

Botox toxin is a neurotoxin that has been utilized since 30 years in the field of ophthalmic interventions for the cure of strabismus, and in neurology for muscular spasms. The Botox toxin (BoNT) is manufactured thru anaerobic growth from Clostridium botulinum. Seven different types are known, classified by letter from A to G; currently, only the BoNT types A and B are authorized and utilized for medical treatment.

In referring to Botox, therapeutic treatments should be distinguished from the esthetic ones.

Action mechanism
The Botox toxin intervenes at the neuro-muscular conjunction level (motility plaque) blocking the release and effects of acetylcholine, the neurotransmission agent both for the Central Nervous System (CNS) as the Peripheral Nervous System (PNS). Acetylcholine normally is released in the synaptic space, thru an action potential that runs through the neuron axon, at the last terminal of the arborization of the axon, thus causing the release of the calcium ducts. The calcium ions penetrate within the synaptic button and give way to the release of acetylcholine in the synaptic space where it binds to specific receptors (ACh-receptors), placed on the post-synaptic cell membrane of the muscle cell. The neurotransmitter, in interacting with the Ach-receptors, produces its effects causing the muscle to contract. Immediately then, the acetylcholine is hydrolyzed by the acetylcholinesterase. By inhibiting the release of acetylcholine, the botox toxin interferes with the nervous impulse determining a characteristic flaccid paralysis of the muscle. The botox toxin is, effectively a recognized muscle relaxant.

BoNT-A is currently permitted in Italy for esthetic specialist use in treating glabellar and periocular lines, with the commercial denomination: Vistabex®. Other prescriptions currently authorized in Italy for esthetic use are: Azzalure® and Bocouture®. BoNT-A is approved in Italy also for the following indications:

- focal spasticity;
- dynamic deformity of the equine foot, due to spasticity in pediatric patients ambulating with cerebral paralysis, aged ≥ 2 years;
- hand or pulse disability due to ictus;
- blepharospasm;
- facial hemispasm and related focal dystonia;
- spasmodic stiff neck;
- severe persistent primary hyperhidrosis of the axilla, interfering with normal daily activity and resistant to topical treatment.

In the last 20 years though, BoNT-A has been used in a wide range of off-label therapeutic indications in the fields of neurology, dermatology, and gastroenterology. Botox toxin is classified as C in the “Pregnancy Category Definitions” of the Food and Drug Administration, warning against its use in pregnancy and breast feeding.
AUTHORIZATION OF BOTOX TOXIN TYPE A FOR ESTHETIC INTERVENTIONS

In 2004, AIFA has authorized the use of type A botox toxin for esthetic interventions, with the indication: “Temporary improvement of vertical lines, of moderate to severe degree, between the eyebrows while frowning, in adults aged under 65, when the severity of such lines determines a relevant psychological impact on the patient.”

February 15, 2014 the Italian Official Gazette on behalf of AIFA, published the authorization for the use of OnabotulinumtoxinA for the temporary treatment of lateral canthal lines (crow’s foot) from moderate to severe, observable at the maximum extension of the smile. These lines may be treated either alone or together with the glabellar lines. Therefore use of the toxin for treatment of other facial areas, in injection sites differing from those approved, is considered off-label.

OFF-LABEL USE OF BOTOX TOXIN FOR FACIAL LINES

We may repeat as stated in the previous paragraph that the use of Type A Botox toxin for treatment of facial areas in injection sites differing from those approved is OFF-LABEL. The use of BoNT-A is consented for:

- **Glabellar lines (approved)**
  Glabellar lines highlight naturally with facial movements and are the result of the skin traction caused by the underlining muscles. The muscles involved are the procerus and the eyebrow corrugators. BoNT-A is injected in these muscles in 5 focal points: 1 for the procerus, and 2 for each eyebrow corrugators, slowly infusing directly into the muscle a specific dosage.

- **Periorbital Lines (approved)**
  The muscle involved in the formation of the periorbital lines (crow’s foot) is the orbicularis oculi. The injection sites are basically 3 and must be singled out among the eye lines, after having required the patient to laugh exaggeratedly.

- **Forehead Lines**
  Forehead lines are due to the traction of the frontal muscle. This muscle, besides corrugating the forehead is also deputed to lifting the eyebrow. BoNT-A is injected into the muscle body, in specific sites depending on the lines and according to the symmetry of personal mimics.

- **Upper lip**
  Perioral injection of micro-dosage quantities of BoNT-A in the orbicularis oris muscle, above the vermilion, may relieve the small vertical lines of the upper lip border. For gummy smiles it may be used to relax the lift muscles of the upper lip that covers the gum.

- **Chin**
  Hyperkinesis of the chin muscle may cause a pronounced horizontal line or even a chin with a “cobblestone” effect. Such imperfections may be treated with a single BoNT-A injection at the peak of the chin, sent deep into the muscle.

- **Mouth corners**
  BoNT-A can be used to correct the folds that form at the corners of the mouth (marionette folds). To treat these imperfections, side specific dosages of BoNT-A are injected into the depressor anguli oris muscle, exactly on the border of the jaw, on the crossing point of a line drawn from the corner of the nose to that of the mouth.
• Imperfections of the neck
The plastima muscle, with its subsidence due to aging, is often cause of unpleasant horizontal lines and mostly of prominent vertical bands. Treatment with BoNT-A, injected in this muscle, may settle such imperfections and improve the tension of the neck bands. The most consistent collateral effects are the diffusion of the toxin to the laryngeal muscles or to the sternocleidomastoid muscle, causing dysphagia or weakness in the neck.

ADVERSE REACTIONS TO BOTOX IN ESTHETIC MEDICINE
The onset of possible complications is always and anyway a transitory event, entirely reversible. From the study of available literature, no episode of death, nor severe threats to patients’ health, associated to the esthetic use of botox, nor permanent damages clinically distinguishable, have ever been reported. If used appropriately, complying with approved indications and recommended dosages, BoNT-A shows a low rate of complications, having only moderate severity. The most frequent complication, associated to the off-label use of BoNT-A in esthetic treatment, as for all esthetic treatments described in literature, is caused by the local diffusion of the toxin (lack of localized expressivity); and no episodes of systemic diffusion have been reported with this specific treatment.

Reactions may be:

• GENERAL: nausea; fatigue; general malady; flu symptoms; skin rashes; metal taste in the mouth; allergic reactions; anaphylactic shock (the event, described only recently, and of the rarest chance, is due to the presence of albumin in some of the preparations and does not differ from what may occur with any injectable solution containing such protein)(1,2).

• LOCAL: bother upon the injection site; edema; erythema; ecchymosis (bruising is the most common complaint, due to the needle entrance in the derma and the rupture of a small capillary); migraine (not infrequent, it may arise 2-3 hours after inoculation and last up to 6 hours); diplalia (double vision); ptosis (lowering of the eyelid); lowering of the eyebrow.

With an important information notice (3) the AIFA recalled attention on the risk of diffusion related to the use of BoNT-A, concluding that, with the indications currently approved, the risk-benefit factor is favorable; and that to reduce to the minimum the risk of severe reactions due to the effect of systemic diffusion of BoNT-A, it is essential that practitioners rigorously attain to the dosages, warnings and precautions reported on the Product Specifications.
Unconditional contraindications

- Known hypersensitivity to any component of the formulation (Botox, human albumin, sodium chloride).
- General muscular activity disorder (myasthenia gravis, Lambert–Eaton syndrome).
- Patients treated with amynoglicoside antibiotics, cyclosporine.
- Patients treated by muscle relaxants, calcium channel blockers, magnesium sulfate, lincosamides, anticholinergic drugs.
- Infection or inflammation on the injection site.
- Pregnancy or breast feeding.