BOTOX® (Botulinum Toxin Type A)

Purified Neurotoxin Complex

Distant Spread of Toxin Effect.

Postmarketing safety data from BOTOX® and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The symptoms that are consistent with the mechanism of action of botulinum toxin have been reported hours to weeks after injection, and may include muscular weakness, ptosis, diplopia, blurred vision, facial weakness, swallowing and speech disorders, constipation, aspiration pneumonia, difficulty breathing and respiratory depression. The risk of symptoms is probably greatest in children treated for spasticity, but symptoms can also occur in patients who have underlying conditions and comorbidities that would predispose them to these symptoms including adults treated for spasticity and other conditions, and are treated with high doses. Swallowing and breathing difficulties can be life threatening and death has been reported, although a definitive causal association to BOTOX® has not been established.

1. PRESENTATION

BOTOX® is available in 50, 100 and 200 unit (U) sterile vials of *Clostridium botulinum* toxin type A in a vacuum-dried form without a preservative. One Allergan unit (U) corresponds to the calculated median lethal dose (LD_{50}) in mice using reconstituted BOTOX® and injected intraperitoneally.

The quantities of the ingredients in each vial are listed below:

Ingredients	50 Allergan U Vial	100 Allergan U Vial	200 Allergan U Vial
Clostridium botulinum toxin type A neurotoxin complex (900kD)	50 U	100 U	200 U
Human Serum Albumin	0.25 mg	0.5 mg	1.0 mg
Sodium Chloride	0.45 mg	0.9 mg	1.8 mg

2. USES

BOTOX® is indicated for the treatment of blepharospasm associated with dystonia, including benign essential blepharospasm, hemifacial spasm or VIIth nerve disorders in patients 12 years or older.

BOTOX® is indicated for the correction of strabismus in patients 12 years of age or older.

BOTOX® is indicated for the treatment of spasmodic torticollis (cervical dystonia) in adults.

BOTOX® is indicated for the treatment of dynamic equinus foot deformity due to spasticity in paediatric cerebral palsy patients, two years of age or older.

BOTOX® is indicated in the management of focal spasticity, of the upper limbs associated with stroke in adults.

BOTOX® is indicated in the management of focal spasticity, of the lower limbs associated with stroke in adults.

BOTOX® is indicated for the treatment of severe, primary axillary hyperhidrosis that is inadequately managed by topical agents. The objective of treatment is to reduce sweating to a physiologically normal level which patients find tolerable. Anhidrosis is not the target.

BOTOX® is indicated for the temporary treatment of glabellar lines associated with corrugator and/or procerus muscle activity and crow's feet associated with orbicularis oculi muscle activities in adult patients below 65 years of age.

BOTOX® is indicated for the temporary improvement in the appearance of moderate to severe forehead lines in adults.

BOTOX® is indicated for the prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine).

BOTOX® is indicated for the treatment of overactive bladder with symptoms of urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

BOTOX® is indicated for the treatment of urinary incontinence due to neurogenic detrusor overactivity e.g., spinal cord injury (SCI) or multiple sclerosis (MS) in adults who have an inadequate response to or are intolerant of anticholinergic medications.

3. DOSAGE AND ADMINISTRATION

General:

The use of one vial for more than one patient is not recommended because the product and diluent do not contain a preservative. Once opened and reconstituted, store in a refrigerator and use within twenty four hours. Discard any remaining solution. Do not freeze reconstituted BOTOX®.

Reconstituted BOTOX® is injected with the purpose of reaching the motor endplate region of the muscle to be treated.

Route of Administration:

Intramuscular injection. May be subcutaneous injection for blepharospasm. Intradermal for primary hyperhidrosis of axillae. Intradetrusor for neurogenic detrusor overactivity.

Reconstitution of vial: *Dilution Technique:*

Prior to injection, reconstitute vacuum-dried BOTOX® with sterile normal saline **without** a preservative; 0.9% Sodium Chloride is the recommended diluent.

It is good practice to perform vial reconstitution and syringe preparation over plastic-lined paper towels to catch any spillage. Remove the flip-off plastic seal from the BOTOX® vial. An appropriate amount of diluent (see dilution table below, or for specific instructions for intradetrusor injections for neurogenic detrusor activity, refer to DOSAGE AND ADMINISTRATION, Neurogenic Detrusor Overactivity) is drawn up into a syringe. The exposed portion of the rubber septum of the vials is cleaned with alcohol (70%) prior to insertion of the needle. Draw up the proper amount of diluent in the appropriate size syringe, and slowly inject the diluent into the vial. Since BOTOX® is denatured by bubbling or similar vigorous agitation, inject the diluent gently into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Gently mix BOTOX® with the saline by rotating the vial. Record the date and time of reconstitution on the space on the label. BOTOX® should be administered within twenty four hours after reconstitution. This product is for single use only and any unused solution should be discarded.

During this time period, reconstituted BOTOX® should be stored in a refrigerator (2 to 8°C). Reconstituted BOTOX® should be clear, colourless and free of particulate matter. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration and whenever the solution and the container permit. For safe disposal, unused vials should be reconstituted with a small amount of water and then autoclaved. Any used vials, syringes and spillages etc. should be autoclaved, or the residue BOTOX® inactivated using dilute hypochlorite solution (0.5%) for 5 minutes.

Dilution Tables:

Amount of Diluent Added to 50 U/Vial (0.9% Sodium Chloride Injection)	Resulting dose (U per 0.1 ml)
0.5 ml	10 U
1 ml	5 U
2 ml	2.5 U
4 ml	1.25 U

Amount of Diluent Added to 100 U/Vial (0.9% Sodium Chloride Injection)	Resulting dose (U per 0.1 ml)
0.5 ml	20 U
1 ml	10 U
2 ml	5 U
4 ml	2.5 U
8 ml	1.25 U

Amount of Diluent Added to 200 U/Vial (0.9% Sodium Chloride Injection)	Resulting dose (U per 0.1 ml)
0.5 ml	40 U
1 ml	20 U
2 ml	10 U
4 ml	5 U
8 ml	2.5 U

A decrease or increase in the BOTOX® dose is possible by administering a smaller or larger injection volume.

The "unit" by which the potency of preparations of BOTOX® is measured should be used to calculate dosages of BOTOX® only and is not transferable to other preparations of botulinum toxin.

Doses recommended for BOTOX® are not interchangeable with other preparations of botulinum toxin.

Blepharospasm:

For blepharospasm, reconstituted BOTOX® (see Dilution Table) is injected using a sterile, 27 - 30 gauge needle with or without electromyographic guidance. The initial recommended dose is 1.25 - 2.5 U in (0.05 - 0.1 mL volume at each site) injected into the medial and lateral orbicularis oculi of the upper lid and into the lateral orbicularis oculi of the lower lid.

Injection placement may vary based on the patient's presentation. Avoiding injection near the levator palpebrae superioris may reduce the complication of ptosis. Avoiding medial lower lid injections and thereby reducing diffusion into the inferior oblique, may reduce the complication of diplopia. Ecchymosis occurs easily in the soft eyelid tissues. This can be prevented by applying pressure at the injection site immediately after the injection. The hazard of ectropion may be reduced by avoiding injection into the lower lid area.

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 indefinitely. 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. The initial dose should not exceed 25 U per eye. Normally no additional benefit is conferred by treating more frequently than every three months. It is rare for the effect to be permanent.

In the management of blepharospasm total dosing should not exceed 100 U every 12 weeks.

Hemifacial spasm:

Patients with hemifacial spasm or VIIth nerve disorders should be treated as for unilateral blepharospasm, with other affected facial muscles each being injected as needed. Further injections may be necessary into the corrugator, zygomaticus major, orbicularis oris and/ or other facial muscles according to the extent of the spasm. Electromyographic control may be necessary to identify affected small circumoral muscles.

The cumulative dose of BOTOX® for treatment of hemifacial spasm in a 2 month period should not exceed 200 U.

Strabismus:

BOTOX® is intended for injection into extraocular muscles utilizing the electrical activity recorded from the tip of the injection needle as a guide to placement within the target muscle. Injection without surgical exposure or electromyographic guidance should not be attempted. Physicians should be familiar with electromyographic techniques.

BOTOX® is ineffective in chronic paralytic strabismus except to reduce antagonist contracture in conjunction with surgical repair. The efficacy of BOTOX® in deviations over 50 prism diopters, in restrictive strabismus, in Duane's syndrome with lateral rectus weakness, and in secondary strabismus caused by prior surgical over-recession of the antagonist is doubtful. In order to enhance efficacy, multiple injections over time may be required.

To prepare the eye for BOTOX® injection, it is recommended that several drops of a local anesthetic and an ocular decongestant be given several minutes prior to injection. Note: The recommended volume of BOTOX® injected for treatment of strabismus is 0.05 mL to 0.15 mL per muscle.

I. Initial doses in units (abbreviated as U). Use the lower listed doses for treatment of small deviations. Use the larger doses only for large deviations.

A. For vertical muscles, and for horizontal strabismus of less than 20 prism diopters: 1.25 U to 2.5 U in any one muscle.

B. For horizontal strabismus of 20 prism diopters to 50 prism diopters: 2.5 U to 5.0 U in any one muscle.

C. For persistent VIIth nerve palsy of one month or longer duration: 1.25 U to 2.5 U in the medial rectus muscle.

II. Subsequent doses for residual or recurrent strabismus.

A. It is recommended that patients be re-examined 7-14 days after each injection to assess the effect of that dose.

B. Patients experiencing adequate paralysis of the target muscle that require subsequent injections should receive a dose comparable to the initial dose.

C. Subsequent doses for patients experiencing incomplete paralysis of the target muscle may be increased up to two-fold compared to the previously administered dose.

D. Subsequent injections should not be administered until the effects of the previous dose have dissipated as evidenced by substantial function in the injected and adjacent muscles.

E. The maximum recommended dose as a single injection for any one muscle is 25 U.

The initial listed doses of the reconstituted BOTOX® (see previous Dilution Table) typically create paralysis of injected muscles beginning one to two days after injection and increasing in intensity during the first week. The paralysis lasts for 2 to 6 weeks and gradually resolves over a similar time period. Over-corrections lasting over six months have been rare. About one-half of patients will require subsequent doses because of inadequate paralytic response of the muscle to the initial dose, or because of mechanical factors such as large deviations or restrictions, or because of the lack of binocular motor fusion to stabilize the alignment.

Spasmodic torticollis (cervical dystonia):

Dosing must be tailored to the individual patient based on the patient's head and neck position, localization of pain, muscle hypertrophy, patient's bodyweight, and patient response. A 25, 27 or 30 gauge needle may be used for superficial muscles, and a 22 gauge needle may be used for deeper musculature. For cervical dystonia, localization of the involved muscles with electromyographic guidance may be useful.

In initial controlled clinical trials to establish safety and efficacy for cervical dystonia, doses of reconstituted BOTOX® ranged from 140 to 280 U. In more recent studies, the doses have ranged from 95 to 360 U (with an approximate mean of 240 U). As with any drug treatment, initial dosing in a naïve patient should begin at the lowest effective dose. The treatment of cervical dystonia typically may include, but is not limited to, injection of BOTOX® into the sternocleidomastoid, levator scapulae, scalene, splenius capitis, and/or the trapezius muscle(s). In general, a total dose of 6 U/kg every two months should not be exceeded for treatment of cervical dystonia.

Diluted BOTOX® is injected using an appropriately sized needle (usually 25, 27 or 30 gauge). The table below is intended to give dosing guidelines for injection of BOTOX® in the treatment of cervical dystonia:

Torticollis Classification	Muscle Groupings	Total Dosage; Number of Sites
Type I Head rotated toward side of shoulder elevation	Sternocleidomastoid Levator scapulae Scalene Splenius capitis Trapezius	50 - 100 U; at least 2 sites 50 U; 1 - 2 sites 25 - 50 U; 1- site 25 - 75 U; 1 - 3 sites 25 - 100 U; 1 - 8 sites
Type II Head rotation only	Sternocleidomastoid	25 - 100 U; at least 2 sites if > 25 U given
Type III Head tilted towards side of shoulder elevation	Sternocleidomastoid Levator scapulae Scalene Trapezius	25 - 100 U at posterior border; at least 2 sites if > 25 U given 25 - 100 U; at least 2 sites 25 - 75 U; at least 2 sites 25 - 100 U; 1 - 8 sites
Type IV Bilateral posterior cervical muscle spasm with elevation of the face	Splenius capitis and cervicis	50 - 200 U; 2 - 8 sites, treat bilaterally

This information is provided as guidance for the initial injection. The extent of muscle hypertrophy and the muscle groups involved in the dystonic posture may change with time necessitating alterations in the dose of toxin and muscles to be injected. The exact dosage and sites injected must be individualised for each patient.

In case of any difficulty in isolating the individual muscles, injections should be made under electromyographic assistance. No more than 50 U should be given at any one site. Limiting the dose injected into the sternocleidomastoid muscle to less than 100 U may decrease the occurrence of dysphagia. (See Precautions.) To minimise the incidence of dysphagia, the sternocleidomastoid should not be injected bilaterally. The concentrations of reconstituted material needed are 5 U/ 0.1 mL and 10 U/ 0.1 mL to allow reasonable injection volumes.

The table below shows the median dose of BOTOX® injected per muscle in a clinical study in which dose was determined by the practitioner based on the presentation of the individual cervical dystonia patient.

Muscles	% Patients treated in this muscle (n= 88)	Dosage reported in 25 - 75% of patients per Unilateral Muscle (Units)
Splenius capitis/ cervicis	94	60 - 100
Sternocleidomastoid	88	40 - 70
Levator scapulae	59	25 - 60
Trapezius	56	35 - 100

Scalene	17	15 - 55

Multiple injection sites allow BOTOX® to have more uniform contact with the innervation areas of the dystonic muscle and are especially useful in larger muscles. The optimal number of injection sites is dependent upon the size of the muscle to be chemically denervated.

Clinical improvement generally occurs within the first two weeks after injection. The maximum clinical benefit generally occurs approximately six weeks post-injection. Repeat doses should be administered when the clinical effect of a previous injection diminishes. The duration of therapeutic effect reported in the clinical trials showed substantial variation (from 2 to 32 weeks), with a typical duration of approximately 12 to 16 weeks, depending on the patient's individual disease and response. "Booster" injections are not recommended. Dosing intervals should not be more often than every two months.

Paediatric cerebral palsy:

For the treatment of equinus due to spasticity in paediatric cerebral palsy, diluted BOTOX® is injected using a sterile 23-26 gauge needle. In clinical trials, doses of 4 U/kg were administered by injecting BOTOX® into each of two sites in the medial and lateral heads of the gastrocnemius muscle of the affected lower limb(s).

Following initial injection to the gastrocnemius muscle, further involvement of the anterior or posterior tibialis may need to be considered for additional improvement in the foot position at heel strike and during standing.

Clinical gait improvement generally begins within the first two weeks after injection, with further improvement over the next several weeks. Repeat doses should be administered when the clinical effect of a previous injection diminishes but not more frequently than every two months. The average duration of the therapeutic effect reported in an open-label clinical trial of 207 patients was 3.1 to 3.6 months. In this study, the dose was 4 U/kg, up to a maximum of 200 U at any single treatment session.

Focal Spasticity in Adults:

The exact dosage and number of injection sites should be tailored to the individual based on the size, number and location of muscles involved, the severity of spasticity, presence of local muscle weakness, and the patient response to previous treatment.

The recommended dilution is 200 Units/4 mL or 100 Units/2 mL with preservative-free 0.9% Sodium Chloride Injection (see Dilution Tables). A 25, 27 or 30 gauge sterile needle may be used for superficial muscles, and a 22-gauge needle may be used for deeper musculature. For focal spasticity, localization of the involved muscles with electromyographic guidance or nerve stimulation techniques may be useful.

Multiple injection sites allow BOTOX® to have more uniform contact with the innervation areas of the muscle and are especially useful in larger muscles.

If it is deemed appropriate by the treating physician, repeat BOTOX® 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 BOTOX® and muscles to be injected.

Upper Limb Spasticity

In clinical trials, the doses did not exceed 360 U divided among selected muscles (typically in the flexor muscles of the elbow, wrist and fingers) at any treatment session. Clinical improvement in muscle tone generally occurs within two weeks following treatment with the peak effect seen four to six weeks following treatment. In clinical studies, patients were reinjected at 12 to 16 week intervals.

The table below is intended to give dosing guidelines for injection of BOTOX® in the treatment of upper limb spasticity associated with stroke.

Muscle	Total Dosage; Number of Sites
Biceps brachii	100 - 200 U; up to 4 sites
Flexor digitorum profundus	15 - 50 U; 1-2 sites
Flexor digitorum sublimis	15 - 50 U; 1-2 sites
Flexor carpi radialis	15 - 60 U; 1-2 sites
Flexor carpi ulnaris Adductor Pollicis Flexor Pollicis Longus	10 - 50 U; 1-2 sites 20 U; 1-2 sites 20 U; 1-2 sites

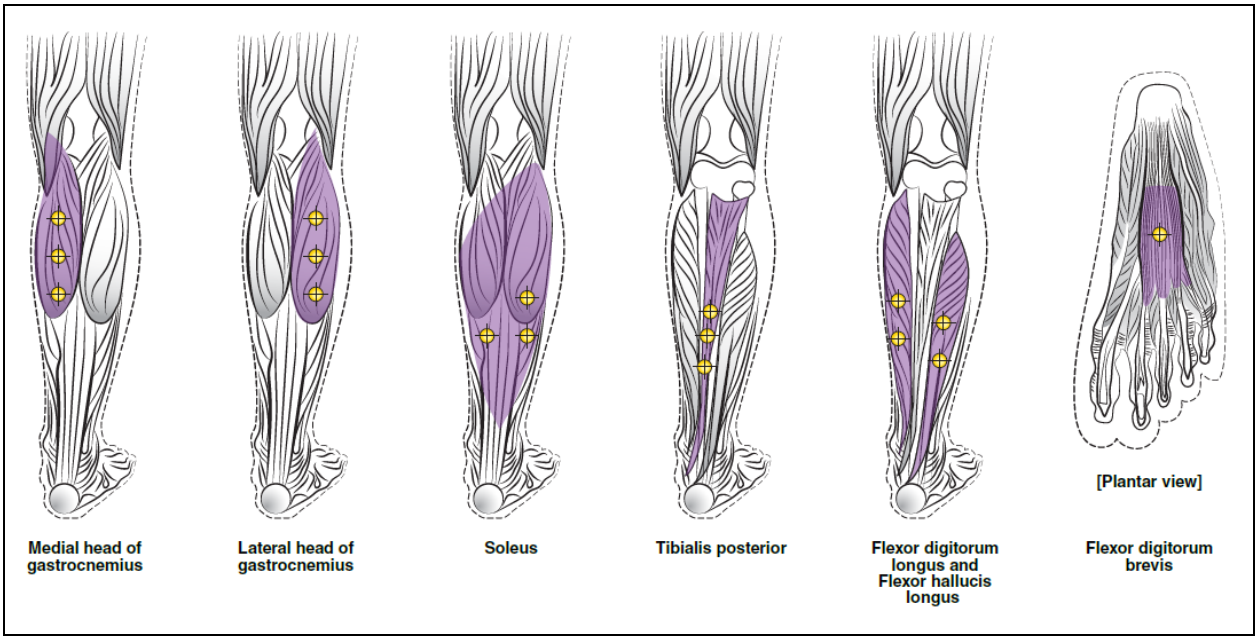
Lower Limb Spasticity

The recommended dose for treating lower limb spasticity is 300 Units to 400 Units divided among affected muscles (see table and figure below).

BOTOX® Dosing by Muscle for Lower Limb Spasticity

Muscle	Recommended Dose Total Dosage (Number of Sites)
Gastrocnemius medial head	75 Units divided in 3 sites
Gastrocnemius lateral head	75 Units divided in 3 sites
Soleus	75 Units divided in 3 sites
Tibialis Posterior	75 Units divided in 3 sites
Flexor hallucis longus	50 Units divided in 2 sites
Flexor digitorum longus	50 Units divided in 2 sites
Flexor digitorum brevis	25 Units divided in 1 site

Injection Sites for Lower Limb Spasticity



Hyperhidrosis of the Axillae:

The hyperhidrotic area to be injected may be defined using standard staining techniques, e.g. Minor's iodine-starch test. BOTOX® is reconstituted with 0.9% non-preserved sterile saline (100 U/4.0 mL). The recommended dose is 50U per axillae. Using a 30 gauge needle, 50 U (2.0 mL) is injected intradermally, in 0.1 to 0.2 mL aliquots to each axillae evenly distributed in multiple sites (10 to 15) approximately 1-2 cm apart.

At week 1 BOTOX® treated patients demonstrated 95% treatment responder rate based on gravimetric assessment. At 16 weeks 82% of BOTOX® treated patients were responding to treatment. When patients received at least 2 consecutive treatments with BOTOX® the mean time to re-treatment following their first treatment was 33 weeks (range 15 to 51 weeks). Repeat injections for axillary hyperhidrosis should be administered when effects from previous injections subside but usually not more frequently than every four months.

Upper Facial Lines (Glabellar Lines, Crow's Feet Lines, Forehead Lines):

As optimum dose levels and number of injection sites per muscle may vary among patients, individual dosing regimen should be drawn up. The recommended injection volume per injection site is 0.1 mL.

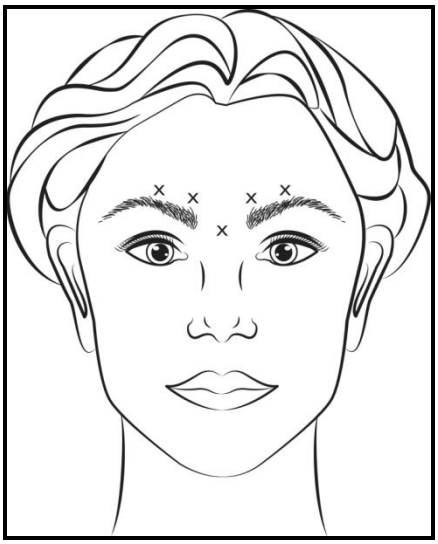
Dilution Instructions for BOTOX® Upper Facial Lines (100 Units and 50 Units)

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	1.25 mL	4 Units

*Preservative-free 0.9% Sodium Chloride Injection

Glabellar Lines:

BOTOX® is reconstituted with 0.9% sterile non-preserved saline (100 units in 2.5 mL or injected as 4 U/0.1 mL) and 0.1 mL is administered using a 30 gauge needle in each of 5 sites (see figure below), 2 in each corrugator muscle and 1 in the procerus muscle for a total dose of 20 U (see dilution table under *Upper Facial Lines (Glabellar Lines, Crow's Feet, Forehead Lines)*).



In order to reduce the complication of ptosis, avoid injection near the levator palpebrae superioris, particularly in patients with larger brow-depressor complexes. Medial corrugator injections should be placed at least 1 cm above the bony supraorbital ridge.

In controlled clinical trials, improvement of severity of glabellar lines generally occurred within one week after treatment and the effect was demonstrated for up to 4 months. Typically the initial doses of reconstituted BOTOX® induce chemical denervation of the injected muscles one to two days after injection, increasing in intensity during the first week.

Injection intervals should be no more frequent than every 3 months and should be performed using the lowest effective dose.

Treatment with BOTOX® for cosmetic purposes may result in the formation of antibodies that may reduce the effectiveness of subsequent treatments with BOTOX® for glabellar lines or for other indications.

Crow's Feet Lines:

BOTOX® should be injected bilaterally at 3 sites in the lateral aspect of the orbicularis oculi (i.e. total of 6 injections), where most lines are seen when a smile is forced. In general, 2-6 U is recommended per injection site at a 2-3 mm depth, for a total dose of 6-18 U per side. (see dilution table under *Upper Facial Lines (Glabellar Lines, Crow's Feet, Forehead Lines)*).

Injections should be at least 1 cm outside the bony orbit, not medial to the vertical line through the lateral canthus and not close to the inferior margin of the zygoma.

Forehead Lines:

Inject 4 Units (0.1mL) of reconstituted BOTOX® into 5 sites in the frontalis muscle, for a total of 20 Units (0.5mL).

Treat forehead lines in conjunction with glabellar lines (see Glabellar Lines Administration) to minimize the potential for brow ptosis. The recommended total dose for treatment of forehead lines (20 Units [0.5mL]) in conjunction with glabellar lines (20 Units [0.5mL]) is 40 Units (1mL).

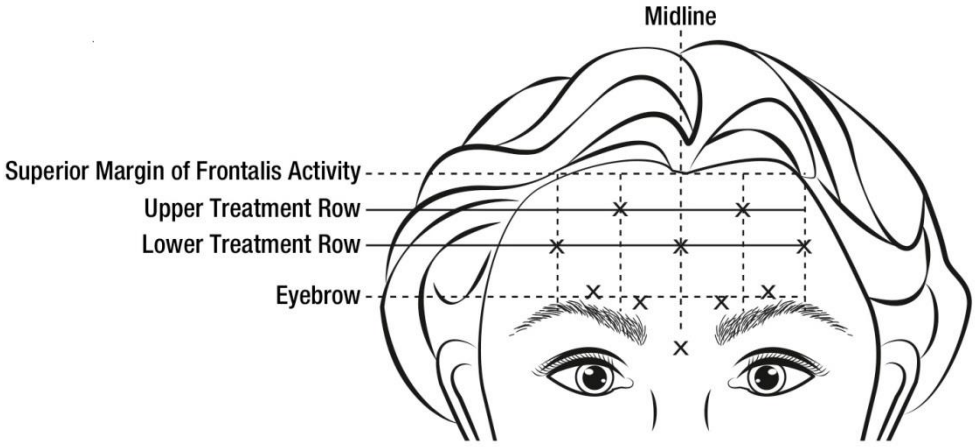
When identifying the location of the appropriate injection sites in the frontalis muscle, assess the overall relationship between the size of the patient's forehead, and the distribution of frontalis muscle activity.

Locate the following horizontal treatment rows by light palpation of the forehead at rest and maximum eyebrow elevation:

- Superior Margin of Frontalis Activity: approximately 1 cm above the most superior forehead crease
- Lower Treatment Row: midway between the superior margin of frontalis activity and the eyebrow, at least 2

cm above the eyebrow
- Upper Treatment Row: midway between the superior margin of frontalis activity and lower treatment row

Place the 5 injections at the intersection of the horizontal treatment rows with the following vertical landmarks (see Figure below):
- On the lower treatment row at the midline of the face, and 0.5 – 1.5 cm medial to the palpated temporal fusion line (temporal crest); repeat for the other side.
- On the upper treatment row, midway between the lateral and medial sites on the lower treatment row; repeat for the other side.



For simultaneous treatment with Crows' Feet lines, the total dose is 64 Units, comprised of 20 Units for forehead lines, 20 Units for glabellar lines, and 24 Units for Crows' Feet lines (see Crows' Feet Lines Administration).

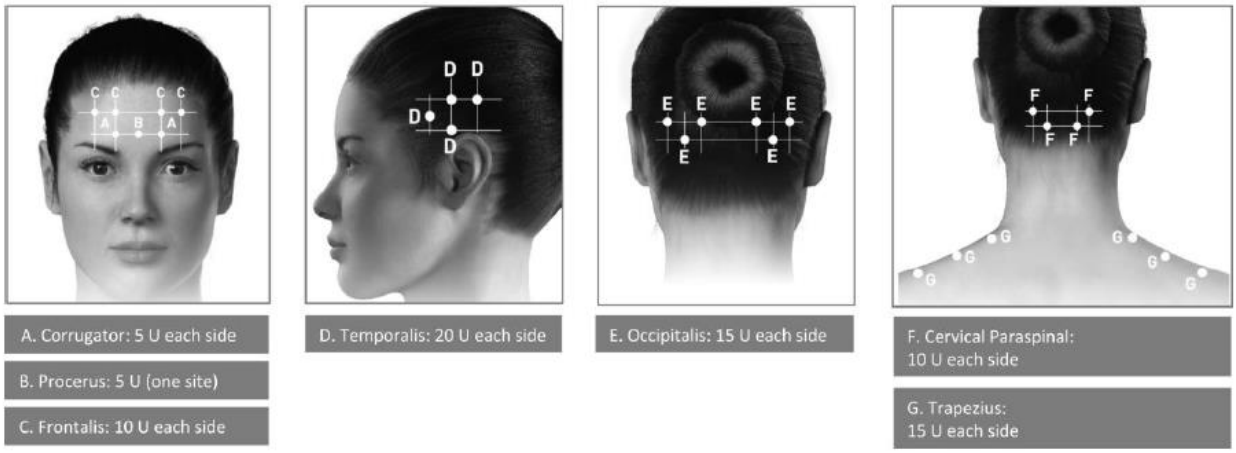
Improvement in the severity of forehead lines seen at maximum eyebrow elevation occurred within one week of treatment.

The time to retreatment of BOTOX® for forehead lines is approximately 4 months. The safety and effectiveness of dosing with BOTOX® more frequently than every 3 months have not been clinically evaluated.

Chronic Migraine:

The recommended dilution is 100 Units/2mL, with a final concentration of 5 Units per 0.1mL. The recommended dose for treating chronic migraine is 155 U to 195 U administered intramuscularly (IM) using a sterile 30-gauge, 0.5 inch needle as 0.1 ml (5 U) injections per each site. Injections should be divided across 7 specific head/neck muscle areas as specified in the diagrams and table below. A 1 inch needle may be needed in the neck region for patients with thick neck muscles. With the exception of the procerus muscle, which should be injected at 1 site (midline), all muscles should be injected bilaterally with the minimum dose per muscle as indicated below, with half the number of injection sites administered to the left, and half to the right side of the head and neck. The recommended re-treatment schedule is every 12 weeks. If there is a predominant pain location(s), additional injections to one or both sides may be administered in up to 3 specific muscle groups (occipitalis, temporalis, and trapezius), up to the maximum dose per muscle as indicated in the table below.

The following diagrams indicate the **injection sites:**



BOTOX® Dosing By Muscle for Chronic Migraine

	Recommended Dose
Head/Neck Area	**Total Number of Units (U) (number of IM injection sites[a])**
Frontalis[b]	20 U (4 sites)
Corrugator[b]	10 U (2 sites)
Procerus	5 U (1 site)
Occipitalis[b]	30 U (6 sites) up to 40 U (up to 8 sites)
Temporalis[b]	40 U (8 sites) up to 50 U (up to 10 sites)
Trapezius[b]	30 U (6 sites) up to 50 U (up to 10 sites)
Cervical Paraspinal Muscle Group[b]	20 U (4 sites)
Total Dose Range:	**155 U to 195 U**

[a] Each IM injection site = 0.1 mL = 5 U BOTOX®

[b] Dose distributed bilaterally for the minimum dose

Bladder Dysfunction (Overactive Bladder and Neurogenic Detrusor Overactivity):

Patients should not have a urinary tract infection prior to treatment. Prophylactic antibiotics (except aminoglycosides, see DRUG INTERACTIONS) should be administered 1-3 days pre-treatment, on the treatment day, and 1-3 days post-treatment.

It is generally recommended that patients discontinue anti-platelet therapy at least three days before the injection procedure. Patients on anti-coagulant therapy need to be managed appropriately to decrease the risk of bleeding.

Overactive Bladder

An intravesical instillation of diluted local anesthetic with or without sedation may be used prior to injection, per local site practice. If a local anesthetic instillation is performed, the bladder should be drained and irrigated with sterile saline before injection.

The recommended dose is 100 Units of BOTOX®. The recommended dilution is 100 Units/10 mL with 0.9% non-preserved saline solution (see dilution table). Dispose of any unused saline.

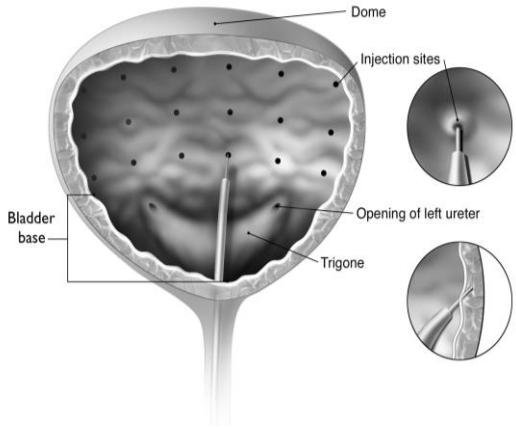
Reconstituted BOTOX® (100 Units/10 mL) is injected into the detrusor muscle via a flexible or rigid cystoscope, avoiding the trigone. The bladder should be instilled with enough saline to achieve adequate visualization for the injections, but over-distension should be avoided.

The injection needle should be filled (primed) with approximately 1 mL of reconstituted BOTOX® prior to the start of injections (depending on the needle length) to remove any air.

The needle should be inserted approximately 2 mm into the detrusor, and 20 injections of 0.5 mL each (total volume of 10 mL) should be spaced approximately 1 cm apart (see figure below). For the final injection, approximately 1 mL of sterile normal saline should be injected so the full dose is delivered. After the injections are given, the saline used for bladder wall visualization should not be drained so that patients can demonstrate their ability to void prior to leaving the clinic. The patient should be observed for at least 30 minutes post-injection and until a spontaneous void has occurred.

Clinical improvement may occur within 2 weeks. Patients should be considered for reinjection when the clinical effect of the previous injection has diminished (median duration in phase 3 clinical studies was 166 days [~24 weeks]), but no sooner than 3 months from the prior bladder injection. Based on patients who received treatments with only BOTOX® 100 Units from the pivotal studies through the open label extension study (N=438), the overall median duration of response was ~212 days (~30 weeks).[195]

Injection Pattern for Overactive Bladder and Neurogenic Detrusor Overactivity



Neurogenic Detrusor Overactivity

An intravesical instillation of diluted local anesthetic with or without sedation, or general anesthesia may be used prior to injection, per local site practice. If a local anesthetic instillation is performed, the bladder should be drained and irrigated with sterile saline before injection.

The recommended dose is 200 Units of BOTOX®.

Reconstitution of 200 Unit Vial

Reconstitute a 200 Unit vial of BOTOX® with 6 mL of 0.9% non-preserved saline solution and mix the vial gently. Draw 2 mL from the vial into each of three 10 mL syringes. Complete the reconstitution by adding 8 mL of 0.9% non-preserved saline solution into each of the 10 mL syringes, and mix gently. This will result in three 10 mL syringes each containing 10 mL (~67 Units in each), for a total of 200 Units of reconstituted BOTOX®. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

Reconstitution of 100 Unit Vial

Reconstitute two 100 Unit vials of BOTOX®, each with 6 mL of 0.9% non-preserved saline solution and mix the vials gently. Draw 4 mL from each vial into each of two 10 mL syringes. Draw the remaining 2 mL from each vial into a third 10 mL syringe. Complete the reconstitution by adding 6 mL of 0.9% non-preserved saline solution into each of the 10 mL syringes, and mix gently. This will result in three 10 mL syringes each containing 10 mL (~67 Units in

each), for a total of 200 Units of reconstituted BOTOX®. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

Reconstitution of 50 Unit Vial

It is recommended that a 200 Unit vial or two 100 Unit vials are used for convenience of reconstitution.

Reconstitute four 50 Unit vials of BOTOX®, each with 3 mL of 0.9% non-preserved saline solution and mix the vials gently. Draw 3 mL from the first vial and 1 ml from the second vial into one 10 ml syringe. Draw 3 ml from the third vial and 1 ml from the fourth vial into a second 10 ml syringe. Draw the remaining 2 ml from the second and fourth vials into a third 10 ml syringe. Complete the reconstitution by adding 6 mL of 0.9% non-preserved saline solution into each of the three 10 mL syringes, and mix gently. This will result in three 10 mL syringes containing a total of 200 Units of reconstituted BOTOX®. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

Administration

Reconstituted BOTOX® (200 Units/30 mL) is injected into the detrusor muscle via a flexible or rigid cystoscope, avoiding the trigone. The bladder should be instilled with enough saline to achieve adequate visualization for the injections, but over-distension should be avoided.

The injection needle should be filled (primed) with approximately 1 mL prior to the start of injections (depending on the needle length) to remove any air.

The needle should be inserted approximately 2 mm into the detrusor, and 30 injections of 1mL each (total volume of 30 mL) should be spaced approximately 1 cm apart (see Figure above). For the final injection, approximately 1 mL of sterile normal saline should be injected so the full dose is delivered. After the injections are given, the saline used for bladder wall visualization should be drained. The patient should be observed for at least 30 minutes post-injection.

Clinical improvement may occur within 2 weeks. Patients should be considered for reinjection when the clinical effect of the previous injection diminished (median duration in phase 3 clinical studies was 256-295 days (36-42 weeks) for BOTOX® 200 Units), but no sooner than 3 months from the prior bladder injection. Based on patients who received treatments with only BOTOX® 200 Units from the pivotal studies through the open label extension study (N=174), the overall median duration of response was 253 days (~36 weeks). The safety and efficacy data beyond two intradetrusor treatments are limited.

4. CONTRA-INDICATIONS, WARNINGS AND PRECAUTIONS

General Warnings and Precautions

• The term "unit" upon which dosing is based, is a specific measurement of toxin activity that is unique to Allergan's formulation of botulinum toxin type A. Therefore, the "unit" used to describe BOTOX® activity are different from those used to describe that of other botulinum toxin preparations and the units representing BOTOX® activity are not interchangeable with other products.

• BOTOX® 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 BOTOX® and injection into vulnerable anatomic structures must be avoided.

Contra-indications:

BOTOX® is contra-indicated, a) in individuals with a known hypersensitivity to botulinum toxin type A or any constituent of the formulation;b) in patients with myasthenia gravis or Lambert-Eaton Syndrome. BOTOX® is contraindicated in the presence of infection at the proposed injection site(s). The recommended dosages and frequencies of administration of BOTOX® should not be exceeded.

BOTOX® for treatment of bladder dysfunction is also contraindicated:

- in patients who have a urinary tract infection

- in patients with acute urinary retention who are not routinely performing clean intermittent self-catheterization (CIC).

Warnings and Precautions

General:

Use BOTOX® only as directed.

Do not use dosage recommendations and potency Units applied to other botulinum toxin products when using BOTOX®.

The safe and effective use of BOTOX® (Botulinum Toxin type A) depends upon proper storage of the product, selection of the correct dose, and proper reconstitution and administration techniques.

The relevant anatomy, and any alterations to the anatomy due to prior surgical procedures, must be understood prior to administering BOTOX® and 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 BOTOX® injected directly into salivary glands, the oro-lingual-pharyngeal region, esophagus and stomach. Some patients had pre-existing dysphagia or significant debility. Pneumothorax associated with injection procedure has been reported following the administration of BOTOX® near the thorax. Caution is warranted when injecting in proximity to the lung, particularly the apices. An understanding of standard electromyographic techniques is also required for treatment of strabismus, and may be useful for the treatment of cervical dystonia, and focal spasticity associated with paediatric cerebral palsy and spasticity.

Caution should be exercised when BOTOX® is used in the presence of inflammation at the proposed injection site(s) or when excessive weakness or atrophy is present in the target muscle. Muscle weakness remote to the site of injection and other serious adverse effects (e.g. dysphagia, aspiration pneumonia) have been rarely reported in both paediatric and adult patients, in some cases associated with a fatal outcome.

Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders arise.

Patients with a history of underlying neurological disorders, dysphagia and/or aspiration should be treated with extreme caution. The botulinum toxin product should be used under specialist supervision in these patients and should only be used if the benefit of treatment is considered to outweigh the risk.

Injection specific dosage and administration recommendations should be followed. In treating adult patients, including when combining indications, the maximum cumulative dose should generally not exceed 400 U, up to a maximum of 6 U/kg, in a 3 month interval. In treating paediatric patients, the maximum cumulative dose should generally not exceed 4 U/kg, up to a maximum of 200 U, in a 3 month interval.

One unit (U) of BOTOX® corresponds to the calculated median intraperitoneal lethal dose (LD_{50}) in mice. The method utilized for performing the assay is specific to Allergan's product, BOTOX®. Due to specific details of this assay such as the vehicle, dilution scheme and laboratory protocols for the various mouse LD_{50} assays, Units of biological activity of BOTOX® cannot be compared to nor converted into Units of any other botulinum toxin or any toxin assessed with any other specific assay method. Therefore, differences in species sensitivities to different botulinum neurotoxin serotypes precludes extrapolation of animal-dose activity relationships to human dose estimates. The specific activity of BOTOX® is approximately 20U/nanogram of neurotoxin protein complex.

As is expected for any injection procedure, localized pain, inflammation, paresthesia, hypoaesthesia, tenderness, swelling/edema, erythema, localized infection, bleeding and/or bruising have been associated with the injection. Needle-related pain and/or anxiety have resulted in vasovagal responses, including transient symptomatic hypotension and syncope.

Human Albumin:

This product contains human serum albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

Dynamic equinus foot deformity due to spasticity in paediatric cerebral palsy - BOTOX® is a treatment of spasticity that has only been studied in association with usual standard of care regimens, and is not intended as a replacement for these modalities. BOTOX® is not likely to be effective in improving range of motion at a joint affected by a fixed contracture.

Cardiovascular System:

There have been reports following administration of botulinum toxin of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including pre-existing cardiovascular disease. The exact relationship of these events to BOTOX® is unknown.

Immunogenicity:

Formation of neutralizing antibodies to botulinum toxin type A may reduce the effectiveness of BOTOX® treatment by inactivating the biological activity of the toxin. The critical factors for neutralizing antibody formation have not been well characterized. The results from some studies suggest that BOTOX® injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation. When appropriate, the potential for antibody formation may be minimized by injecting with the lowest effective dose given at the longest feasible intervals between injections.

As with all biologic products, an anaphylactic reaction may occur. Necessary precautions should be taken and epinephrine should be available.

Hypersensitivity Reactions:

Serious and/or immediate hypersensitivity reactions such as anaphylactic and serum sickness have been rarely reported, as well as other manifestations of hypersensitivity including urticaria, soft tissue edema, and dyspnea. Some of these reactions have been reported following the use of BOTOX® either alone or in conjunction with other products associated with similar reactions. One fatal case of anaphylaxis has been reported in which lidocaine was used as the diluent for BOTOX® and consequently the causal agent cannot be reliably determined. If such a reaction occurs, further injection should be discontinued and appropriate medical therapy immediately instituted.

Pre-Existing Neurologic Disorders:

Extreme caution should be exercised when administering BOTOX® to individuals with peripheral motor neuropathic (e.g. amyotrophic lateral sclerosis, or motor neuropathy) or neuromuscular junction disorders (e.g. myasthenia gravis or Lambert-Eaton syndrome). Patients with neuromuscular junction disorders may be at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of BOTOX®. There have been rare cases of administration of botulinum toxin to patients with known or unrecognized neuromuscular junction 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 gastric feeding tube.

When exposed to very high doses, patients with neurologic disorders, e.g. paediatric cerebral palsy or adult spasticity, may also be at increased risk of clinically significant systemic effects.

Seizures:

New onset or recurrent seizures have been reported, typically in patients who are predisposed to experiencing these events. The reports in children were reports predominantly from cerebral palsy patients treated for spasticity. The exact relationship of these events to the botulinum toxin injection has not been established.

Bladder Dysfunction:

Appropriate medical caution should be exercised for performing a cystoscopy.

In patients who are not catheterizing, post-void residual urine volume should be assessed within 2 weeks post-treatment and periodically as medically appropriate up to 12 weeks. Patients should be instructed to contact their physician if they experience difficulties in voiding as catheterization may be required.

Due to the risk of urinary retention, only patients who are willing and/or able to initiate catheterization post-treatment, if required, should be considered for treatment.

For the management of urinary incontinence, BOTOX® should be administered by physicians who are experienced in the assessment and treatment of bladder dysfunction (eg, urologists and urogynaecologists).

Overactive Bladder

Urinary Retention

In double-blind, placebo-controlled trials in patients with OAB, the proportion of subjects who initiated clean intermittent catheterisation (CIC) for urinary retention following treatment with BOTOX® or placebo is shown in the Table below. The duration of post-injection catheterisation for those who developed urinary retention is also shown.

Proportion of Patients Catheterising for Urinary Retention and Duration of Catheterisation following an injection in double-blind, placebo-controlled clinical trials in OAB

Timepoint	**BOTOX® 100 Units (N=552)**	**Placebo (N=542)**
Proportion of Patients Catheterising for Urinary Retention		
At any time during complete treatment cycle	6.5% (n=36)	0.4% (n=2)
Duration of Catheterisation for Urinary Retention (Days)		
Median	63	11
Min, Max	1, 214	3, 18

Patients with diabetes mellitus treated with BOTOX® were more likely to develop urinary retention than those without diabetes, as shown in the Table below.

Proportion of Patients Experiencing Urinary Retention following an injection in double-blind, placebo-controlled clinical trials in OAB according to history of Diabetes Mellitus

	Patients with Diabetes		**Patients without Diabetes**	
	BOTOX® 100 Units (N=81)	Placebo (N=69)	BOTOX® 100 Units (N=526)	Placebo (N=516)
Urinary retention	12.3% (n=10)	0	6.3% (n=33)	0.6% (n=3)

Urinary Tract Infection

BOTOX® increases the incidence of urinary tract infection (see Adverse Effects). Clinical trials for overactive bladder excluded patients with more than 2 UTIs in the past 6 months and those taking antibiotics chronically due to recurrent UTIs. Use of BOTOX® for the treatment of overactive bladder in such patients and in patients with multiple recurrent UTIs during treatment should only be considered when the benefit is likely to outweigh the potential risk.

Use in Males

The pivotal studies in overactive bladder were not powered for a subgroup analysis based on gender, however a statistically significant treatment-by-gender interaction was demonstrated. No statistically significant benefit was demonstrated in males for incontinence frequency or on the Treatment Benefit Scale (see Clinical Trials). In men, 12.2% of the overall study population, mean incontinence was decreased by 0.42 episodes per day (by LS mean difference) relative to placebo (p=0.612) from a baseline of 5.6 episodes per day, whereas in women it was reduced by 2.0 episodes (p<0.001). The proportion of men who felt that treatment had led to improvement on the Treatment Benefit Scale was ~40% (p=0.060), with the attributable proportion being 15% (after subtracting the placebo response of 25%). Approximately 60% of men given BOTOX® for overactive bladder felt that their condition was unchanged or worsened after treatment. Men considering BOTOX® for overactive bladder should be made aware of the gender specific results, including potential risk of urinary tract infections (BOTOX® 9.5% vs placebo 2.6%) and urinary retention (BOTOX® 7.9% vs placebo 1.3%).

Neurogenic Detrusor Overactivity

In these patients, autonomic dysreflexia associated with the procedure could occur, which may require prompt medical therapy.

Patients with spinal cord injury above T1 were excluded from BOTOX® clinical trials.

Other Warnings:

Blepharospasm/Hemifacial Spasm - Reduced blinking following BOTOX® injection into 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.

Because of the anticholinergic activity of botulinum toxin, caution should be exercised when treating patients at risk for angle closure glaucoma, including patients with anatomically narrow angles. Acute angle closure glaucoma has been reported very rarely following periorbital injections of botulinum toxin.

Strabismus – BOTOX® is ineffective in chronic paralytic strabismus except to reduce antagonist contracture in conjunction with surgical repair. The efficacy of BOTOX® in deviations over 50 prism diopters, in restrictive strabismus, in Duane's syndrome with lateral rectus weakness, and in secondary strabismus caused by prior surgical over-recession of the antagonist is doubtful. In order to enhance efficacy, multiple injections over time may be required.

During the administration of BOTOX® for the treatment of strabismus, retrobulbar hemorrhages sufficient to compromise retinal circulation have occurred from needle penetrations into the orbit. It is recommended that appropriate instruments to decompress the orbit be accessible. Ocular (globe) penetrations by needles have also occurred. An ophthalmoscope to diagnose this condition should be available.

Inducing paralysis in one or more extraocular muscles may produce spatial disorientation, double vision, or past-pointing. Covering the affected eye may alleviate these symptoms.

Cervical Dystonia – Dysphagia is a commonly reported adverse event following treatment of cervical dystonia patients with all types of botulinum toxins. Patients with cervical dystonia should be informed of the possibility of experiencing dysphagia which may be mild, but could be severe. Consequent to the dysphagia there is the potential for aspiration, dyspnea and occasionally the need for tube feeding. In rare cases, dysphagia followed by aspiration pneumonia and death has been reported.

Injections into the levator scapulae may be associated with an increased risk of upper respiratory infection and dysphagia.

Dysphagia has contributed to decreased food and water intake resulting in weight loss and dehydration. Patients with subclinical dysphagia may be at increased risk of experiencing more severe dysphagia following a BOTOX® injection.

Limiting the dose injected into both sternocleidomastoid muscles to less than 100 units may decrease the occurrence of dysphagia. Patients with smaller neck muscle mass, or patients who receive bilateral injections into the sternocleidomastoid muscle, have been reported to be at greater risk of dysphagia. Dysphagia is attributable to the localized diffusion of the toxin to the oesophageal musculature.

Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders arise.

Focal Spasticity associated with Pediatric Cerebral Palsy and Focal Spasticity associated with Stroke in Adults – BOTOX® is a treatment of focal spasticity that has only been studied in association with usual standard of care regimens, and is not intended as a replacement for these treatment modalities. BOTOX® is not likely to be effective in improving range of motion at a joint affected by a fixed contracture.

BOTOX® should not be used for the treatment of focal lower limb spasticity in adult post-stroke patients if muscle tone reduction is not expected to result in improved function (e.g., improvement in gait), or improved symptoms (e.g. reduction in pain), or to facilitate care.

Caution should be exercised when treating adult patients with post-stroke spasticity who may be at increased risk of fall.

BOTOX® should be used with caution for the treatment of focal lower limb spasticity in elderly post-stroke patients with significant co-morbidity and treatment should only be initiated if the benefit of treatment is considered to

outweigh the potential risk.

There have been rare spontaneous reports of death sometimes associated with aspiration pneumonia in children with severe cerebral palsy after treatment with botulinum toxin. Caution should be exercised when treating pediatric patients who have significant neurologic debility, dysphagia, or have a recent history of aspiration pneumonia or lung disease.

Primary hyperhidrosis of the axillae – Medical history and physical examination, along with specific additional investigations as required, should be performed to exclude potential causes of secondary hyperhidrosis (e.g. hyperthyroidism or phaeochromocytoma). This will avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of underlying disease.

Upper Facial Lines – Reduced blinking from BOTOX® injection of the orbicularis oculi muscle can lead to corneal exposure, persistent epithelial defects and corneal ulceration, especially in patients with cranial nerve VII disorders. Caution should be used when BOTOX® treatment is used in patients who have an inflammation at the injection site, marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, thick sebaceous skin or the inability to substantially lessen glabellar lines by physically spreading them apart.

In order to reduce the complications of ptosis, avoid injection near the levator palpebrae superioris, particularly in patients with larger brow-depressor complexes. Medial corrugator injections should be placed at least 1 cm above the bony supraorbital ridge. To reduce the occurrence of diplopia, injections of the lateral canthal lines should be outside the bony orbit, not medial to the vertical line through the lateral canthus. To reduce the occurrence of lip ptosis, injections should be above the insertion of the zygomaticus muscles.

Chronic Migraine – Refer to Warnings and Precautions for head and neck injections, due to similar injection sites.

Carcinogenesis and Mutagenesis:

Studies in animals have not been performed to evaluate the carcinogenic potential of BOTOX®. BOTOX® was not mutagenic in *in vitro* and *in vivo* mutagenicity studies.

5. ADVERSE REACTIONS

Adverse Drug Reaction Overview

In general, adverse reactions occur within the first few days following injection and while generally transient may have duration of several months or, in rare cases, longer.

Local muscle weakness represents the expected pharmacological action of botulinum toxin in muscle tissue. However, weakness of adjacent muscles associated with local diffusion and/or injection technique has been reported. Muscle weakness remote to the site of injection and other serious adverse effects (e.g. dysphagia, aspiration pneumonia) have been rarely reported in both pediatric and adult patients, some associated with a fatal outcome.

As is expected for any injection procedure, localized pain, inflammation, paresthesia, hypoaesthesia, tenderness, swelling/oedema, erythema, localized infection, bleeding and/or bruising have been associated with the injection. Needle-related pain and/or anxiety have resulted in vasovagal responses, including transient symptomatic hypotension and syncope.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

For each indication the frequency of adverse reactions documented during clinical trials is given. The frequency is defined as follows: Very Common (≥1/10); Common (≥1/100, <1/10); Uncommon (≥1/1,000; <1/100); Rare (≥1/10,000; <1/1,000); Very Rare (<1/10,000).

Blepharospasm / Hemifacial Spasm

Safety data compiled from controlled clinical trials and open label studies involving 1732 patients treated with BOTOX®, the following adverse reactions were reported.

Nervous system disorders	
Uncommon:	Dizziness, facial palsy
Eye disorders	
Very Common	Eyelid ptosis.
Common	Punctate keratitis, lagophthalmos, dry eye, photophobia, eye irritation, lacrimation increase
Uncommon:	Keratitis, ectropion, diplopia, entropion, vision blurred
Rare:	Eyelid edema
Very rare:	Ulcerative keratitis, corneal epithelium defect, corneal perforation
Skin and subcutaneous tissue disorder	
Common	Ecchymosis
Uncommon:	Rash
General disorders and administration site conditions	
Uncommon:	Fatigue

Strabismus

Safety data compiled from clinical trials involving approximately 2058 patients treated with BOTOX®. The following adverse reactions were reported.

Eye disorders	
Very Common	Eyelid ptosis, eye movement disorder
Uncommon:	Ocular retrobulbar hemorrhages, eye penetration, Holmes-Adie pupil
Rare:	Vitreous hemorrhage

Cervical Dystonia

Safety data compiled from placebo controlled, double-blind trial involving 231 patients treated with BOTOX®. The following adverse reactions were reported.

Infections and infestations	
Common:	Rhinitis, upper respiratory tract infection.
Nervous system disorders	
Common:	Dizziness, hypertonia, hypoaesthesia, somnolence, headache
Eye disorder	
Uncommon:	Diplopia, eyelid ptosis
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Dyspnea
Gastrointestinal disorders	
Very common:	Dysphagia
Common:	Dry mouth, nausea

Musculoskeletal and connective tissue disorders	
Very common:	Muscular weakness
Common:	Musculoskeletal stiffness
General disorders and administration site condition	
Very common:	Pain
Common:	Asthenia, malaise, influenza like illness
Uncommon:	Pyrexia

Pediatric Cerebral Palsy

Safety data were compiled from two double-blind, randomized, placebo controlled and an open-label extension studies involving approximately 304 patients treated with BOTOX®. The following adverse reactions were reported.

Infections and infestations	
Very common:	Viral infection, ear infection
Nervous system disorders	
Common:	Somnolence, gait disturbance, paresthesia
Skin and subcutaneous tissue disorders	
Common:	Rash
Musculoskeletal and connective tissue disorders	
Common:	Myalgia, muscular weakness, pain in extremity
Renal and urinary disorders	
Common:	Urinary incontinence
Injury, poisoning and procedural complications	
Common:	Fall
General disorders and administration site conditions	
Common:	Malaise, injection site pain, asthenia

Upper Limb Spasticity in Adults

Safety data compiled from double-blind and open label studies involving 339 patients treated with BOTOX®. The following adverse reactions were reported.

Nervous system disorders	
Common:	Hypertonia
Uncommon:	Hypoesthesia, headache, paresthesia
Vascular disorders	
Uncommon:	Orthostatic hypotension
Gastrointestinal disorders	
Uncommon:	Nausea
Skin and subcutaneous tissue disorders	
Common:	Ecchymosis
Uncommon:	Dermatitis, pruritus, rash
Musculoskeletal and connective tissue disorders	

Common:	Muscular weakness, pain in extremity
Uncommon:	Arthralgia, bursitis
General disorders and administration site conditions	
Common:	Injection site pain, pyrexia, influenza like illness
Uncommon:	Asthenia, pain, injection site hypersensitivity, malaise

Lower limb spasticity in Adults

Safety data were compiled from double-blind, placebo-controlled, clinical studies involving 538 adult lower limb spasticity patients treated with BOTOX®. The most frequently reported adverse reactions reported by ≥1% of BOTOX® treated patients and more frequent than in placebo-treated are listed below. No change was observed in the overall safety profile with repeat dosing.

Musculoskeletal and connective tissue disorders	
Common:	Arthralgia
General disorders and administration site conditions	
Common:	Peripheral edema

Primary Hyperhidrosis of the Axillae

Safety data compiled from double-blind and open- label studies involving 397 patients treated with BOTOX®. The following adverse reactions were reported.

Nervous system disorders	
Common:	Headache, paresthesia
Vascular disorders	
Common:	Hot flush
Gastrointestinal disorders	
Common:	Nausea
Skin and subcutaneous tissue disorders	
Common:	Hyperhidrosis, skin odor abnormal, pruritus, subcutaneous nodule, alopecia
Musculoskeletal and connective tissue disorders	
Common:	Pain in extremity
General disorders and administration site conditions	
Very common:	Injection site pain
Common:	Pain, injection site edema, injection site hemorrhage, injection site hypersensitivity, injection site irritation, asthenia

Note: increase in non-axillary sweating was reported in 4.5% of patients within one month after injection and showed no pattern with respect to anatomical sites affected. Resolution was seen in approximately 30% of the patients within four months.

Upper Facial Lines (Glabellar Lines, Crow's Feet, Forehead Lines):

Glabellar Lines

Safety data were compiled from two double-blind, placebo-controlled, multicenter studies involving 405 patients treated with BOTOX®. The following adverse events were reported.

Musculoskeletal and connective tissue disorders	
Common:	Muscular weakness
Eye Disorders	
Common:	Eyelid ptosis
Nervous System Disorders	
Common:	Headache, paresthesia
General disorders and administration site conditions	
Common:	Facial pain, injection site edema, ecchymosis, injection site pain, injection site irritation
Gastrointestinal disorders	
Common:	Nausea
Skin and subcutaneous tissue disorders	
Common:	Erythema, skin tightness

Crows' Feet Lines

Safety data compiled from clinical studies treated with BOTOX®. The following adverse reactions were reported.

Eye Disorders	
Common:	Eyelid ptosis
Rare:	Diplopia
Nervous System Disorders	
Common:	Headache
Musculoskeletal and connective tissue disorders	
Rare:	Muscular weakness
General disorders and administration site conditions	
Very Common:	Injection site bruising
Common:	Facial pain

Rare cases of adverse events of asymmetric smile due to injection of zygomaticus major have been reported.

Forehead Lines

The table below presents the most frequently reported adverse reactions in double-blind, placebo-controlled clinical studies following injection of BOTOX® for forehead lines with glabellar lines.

Adverse Reactions Reported by ≥1% of BOTOX® treated Patients and More Frequent than in Placebo-treated Patients in Double-blind, Placebo-controlled Clinical Studies

Eye Disorders	
Very Common:	Eyelid edema
Common:	Eyelid ptosis
Nervous System Disorders	
Common:	Headache
Skin and Subcutaneous Tissue Disorders	
Common:	Brow ptosis, Skin tightness (including Mephisto sign)
General disorders and administration site conditions	
Very Common:	Injection site bruising, injection site pruritus, facial pain

There were no additional adverse drug reactions reported with the simultaneous treatment of Facial Lines (inclusive of forehead lines, glabellar lines, and crow's feet lines).

Chronic Migraine:

Safety data compiled from two double-blind, placebo controlled studies involving 687 patients treated with 155 U – 195 U of BOTOX®. The following adverse reactions were reported.

Nervous system disorders	
Common:	Headache, migraine, facial paresis
Eye disorders	
Common:	Eyelid ptosis
Gastrointestinal disorders	
Uncommon:	Dysphagia
General disorders and administration site conditions	
Common:	Injection site pain
Skin and subcutaneous tissue disorders	
Common:	Pruritus, rash
Uncommon:	Pain of skin
Infections & Infestations	
Common:	Sinusitis, bronchitis
Musculoskeletal and connective tissue disorders	
Common:	Neck pain, musculoskeletal stiffness, muscular weakness, myalgia, musculoskeletal pain, muscle spasms, muscle tightness
Uncommon:	Pain in jaw

Migraine, including worsening migraine, was reported in 3.8% of BOTOX® and 2.6% of placebo patients, typically occurring within the first month after treatment. These reactions did not consistently reoccur with subsequent treatment cycles, and the overall incidence decreased with repeated treatments.

The discontinuation rate due to adverse events in these phase 3 trials was 3.8% for BOTOX® vs. 1.2% for placebo. The most frequently reported adverse events leading to discontinuation in the BOTOX® group were neck pain (0.6%), muscular weakness (0.4%), headache (0.4%), and migraine (0.4%).

Overactive Bladder:

The table below presents the most frequently reported adverse reactions in double-blind, placebo-controlled, pivotal

Phase 3 studies within 12 weeks of injection for overactive bladder.

Table 1: Adverse Reactions Reported by ≥1% of BOTOX treated Patients and More Frequent than in Placebo-treated Patients in Adult Lower Limb Spasticity Double-blind, Placebo-controlled Clinical Trials

Adverse Reactions by System Organ Class	BOTOX® 100 Unit (N=552)	Placebo (N=542)
Infections and infestations		
Urinary tract infection	99 (17.9%)	30 (5.5%)
Bacteriuria	24 (4.3%)	11 (2.0%)
Renal and urinary disorders		
Dysuria	50 (9.1%)	36 (6.6%)
Urinary retention	31 (5.6%)	2 (0.4%)
Investigations		
Residual urine volume*	17 (3.1%)	1 (0.2%)

*Elevated PVR not requiring catheterization

During the complete treatment cycle, the following adverse reactions with BOTOX® 100 Units were reported: urinary tract infections (26%), dysuria (11%), bacteriuria (8%), urinary retention (6%), residual urine volume (3%), and pollakiuria (2%).

Events considered to be procedure-related by the investigator reported at any time following initial injection were dysuria (6%) and hematuria (2%).

Catheterization was initiated in 6.5% following treatment with BOTOX® 100 Units versus 0.4% in the placebo group.

No change was observed in the overall safety profile with repeat dosing.

Neurogenic Detrusor Overactivity:

The table below presents the most frequently reported adverse reactions in double-blind, placebo-controlled studies within 12 weeks of injection for detrusor overactivity associated with a neurologic condition.

Adverse Reactions Reported by ≥1% of BOTOX® treated Patients and More Frequent than in Placebo-treated Patients Within the First 12 Weeks after Intradetrusor Injection in Double-blind, Placebo-controlled Clinical Trials

Adverse Reactions by System Organ Class	BOTOX® 200 Unit (N=262)	Placebo (N=272)
Infections and infestations		
Urinary tract infection	24.4%	17.3%
Renal and urinary disorders		
Urinary retention	17.2%	2.9%
General disorders and administration site conditions		
Fatigue	3.8%	1.1%
Psychiatric disorders		
Insomnia	1.5%	0%

The following adverse event rates with BOTOX® 200 U were reported at any time following initial injection and prior to re-injection or study exit (median duration of 44 weeks of exposure): urinary tract infections (49%), urinary retention (17%), fatigue (6%), haematuria* (5%), constipation (4%), muscular weakness (4%), dysuria* (4%), fall (3%), gait disturbance (3%), insomnia (3%), muscle spasm (2%), autonomic dysreflexia* (2%), and bladder diverticulum (1%). No change was observed in the overall safety profile with repeat dosing.

*procedure-related events

In the multiple sclerosis (MS) patients enrolled in the pivotal studies, the MS exacerbation annualized rate (i.e., number of MS exacerbation events per patient-year) was 0.23 for BOTOX® and 0.20 for placebo.

Among patients who were not catheterizing at baseline prior to treatment, catheterization was initiated in 38.9% following treatment with BOTOX® 200 U versus 17.3% on placebo. Catheterization rates by etiology (multiple sclerosis [MS] and spinal cord injury [SCI]) are further presented in the table below.

Proportion of Patients by Etiology (MS and SCI) not Using CIC at Baseline and then Initiating Catheterization following Injection at Any Time During the Complete Treatment Cycle of the two Phase 3 Double-blind, Placebo-controlled Clinical Trials (Study 1 and 2)

	MS		SCI	
	BOTOX® 200 Unit (N=86)	Placebo (N=88)	BOTOX® 200 Unit (N=22)	Placebo (N=16)
CIC initiated for any reason	34 (40%)	15 (17%)	8 (36%)	3 (19%)
CIC initiated for urinary retention	27 (31%)	4 (5%)	6 (27%)	3 (19%)

In the clinical trials, no change in the type of adverse reactions was observed following two treatments.

Abnormal Hematologic and Clinical Chemistry Findings

No specific trends in abnormal hematologic or clinical chemistry findings have been reported.

Post-Market Adverse Drug Reactions

There have been rare spontaneous reports of death, sometimes associated with anaphylaxis, dysphagia, respiratory compromise, pneumonia, and/or other significant debility, after treatment with BOTOX®.

Serious and/or immediate hypersensitivity reactions such as anaphylaxis and serum sickness have been rarely reported, as well as other manifestations of hypersensitivity including urticaria, soft tissue edema, and dyspnea. Some of these reactions have been reported following the use of BOTOX® either alone or in conjunction with other products associated with similar reactions. One fatal case of anaphylaxis has been reported in which the patient died after being injected with BOTOX® inappropriately diluted with 5 ml of 1% lidocaine. The causal role of BOTOX®, lidocaine, or both cannot be reliably determined.

There have also been reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including cardiovascular disease. New onset or recurrent seizures have also been reported, typically in patients who are predisposed to experiencing these events.

Angle closure glaucoma has been reported very rarely following BOTOX® treatment for blepharospasm.

Lagophthalmos has been reported following BOTOX® injection into the glabellar lines or crow's feet lines.

Eyelid edema has been reported following periocular BOTOX® injection.

These reactions are reported voluntarily from a population of uncertain size. The exact relationship of these events to the botulinum toxin injection has not been established.

Mephisto sign has been reported for chronic migraine and for glabellar lines indications following BOTOX® injection into or near the frontalis muscle.

The following list includes adverse drug reactions or other medically relevant adverse events that have been reported since the drug has been marketed, regardless of indication, and may be in addition to those cited in WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS: denervation/muscle atrophy; respiratory depression and/or respiratory failure; dyspnea; aspiration pneumonia; dysarthria; dysphonia; dry mouth; strabismus; peripheral neuropathy; abdominal pain; diarrhea; nausea; vomiting; pyrexia; anorexia; vision blurred; visual disturbance, hypoacusis; tinnitus;

vertigo; facial palsy, facial paresis; brachial plexopathy; radiculopathy; syncope; hypoesthesia; malaise; myalgia; myasthenia gravis; paresthesia; rash, erythema multiforme; pruritus; dermatitis psoriasiform; hyperhidrosis; alopecia, including madarosis, dry eye, and localized muscle twitching/involuntary muscle contractions.

6. DRUG INTERACTIONS

Overview

No specific tests have been carried out to establish the possibility of clinical interaction with other medicinal products. No drug interactions of clinical significance have been reported.

Drug-Drug Interactions

Table 1: Established or Potential Drug-Drug Interactions

Proper name of drug	Ref	Effect	Clinical comment
aminoglycoside antibiotics or spectinomycin, or other medicinal products that interfere with neuromuscular transmission (e.g. neuromuscular blocking agents, both depolarizing (succinylcholine) and non-depolarizing (tubocurarine derivatives), lincosamides, polymyxins, quinidine, magnesium sulfate, and anticholinesterases).	T	Theoretically, the effect of botulinum toxin type A may be potentiated	The effect of botulinum toxin may be potentiated by aminoglycoside antibiotics or spectinomycin, or other drugs that interfere with neuromuscular transmission (e.g. tubocuraine-type muscle relaxants). Caution should be exercised when BOTOX® is used with aminoglycosides (e.g. streptomycin, tobramycin, neomycin, gentamycin, netilmicin, kanamycin, amikacin), spectinomycin, polymyxins, tetracyclines, lincomycin or any other drugs that interfere with neuromuscular transmission.
Different botulinum neurotoxin serotypes	T	Unknown	The effect of administering different botulinum neurotoxin serotypes at the same time or within several months of each other is unknown. Excessive weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Use In Pregnancy and Lactation:

There are no adequate data from postmarketing surveillance on the developmental risk associated with use of BOTOX® administration in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. BOTOX® should not be used during pregnancy unless clearly necessary. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risks, including abortion or fetal malformations, which have been observed in rabbits.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BOTOX® is administered to a nursing woman.

Pediatrics Use (2-18 years of age):

There have been rare spontaneous reports of death sometimes associated with aspiration pneumonia in children with severe cerebral palsy after treatment with botulinum toxin. A causal association to BOTOX® has not been established in these cases. Post-marketing reports of possible distant effects from the site of injection of toxin have been very rarely reported in pediatric patients with co-morbidities, predominantly with cerebral palsy, who received > 8 U/kg. Extreme caution should be exercised when treating pediatric patients who have significant neurologic debility, dysphagia, or have a recent history of aspiration pneumonia or lung disease.

The safety and effectiveness of BOTOX® in the prophylaxis of headaches in chronic migraine has not been investigated in children and adolescents under 18 years of age.

The safety and effectiveness of BOTOX® in the treatment of blepharospasm or strabismus have not been investigated in children under 12 years of age.

The safety and effectiveness of BOTOX® in the treatment of cervical dystonia has not been investigated in children under 16 years of age.

The safety and effectiveness of BOTOX® in the management of focal spasticity, of the upper limbs associated with stroke and severe, primary hyperhidrosis of the axillae, has not been investigated in children and adolescents under 18 years of age.

The safety and effectiveness of BOTOX® in the treatment of dynamic equinus foot deformity due to spasticity in pediatric cerebral palsy patients has not been investigated in children under two years of age.

The safety and effectiveness of BOTOX® in the treatment of overactive bladder, and urinary incontinence due to neurogenic detrusor overactivity have not been established in children and adolescents under 18 years of age.

Geriatrics (> 65 years of age):

The reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range. The safety and effectiveness of BOTOX® in the prophylaxis of headaches in chronic migraine has not been investigated in subjects over 65 years of age.

Overactive Bladder

Of 1242 patients in placebo-controlled clinical studies of BOTOX®, 41.4% (n=514) were 65 years of age or older, and 14.7% (n=l82) were 75 years of age or older. No overall difference in the safety profile following BOTOX® treatment was observed between patients aged 65 years and older compared to younger patients in these studies, with the exception of urinary tract infection. In the placebo group, the incidence of urinary tract infection was higher in patients 65 years of age or older compared to younger patients (15.2% vs. 6.6%, respectively). The incidence was also higher in patients 65 years and older who were given BOTOX® compared to younger patients (33.1% vs. 21.2 %, respectively). No overall difference in effectiveness was observed between these age groups in placebo-controlled pivotal clinical studies.

Incidence of Urinary Tract Infection and Urinary Retention according to Age Group during First Placebo-controlled Treatment, Placebo-controlled Clinical Trials in Patients with OAB

	< 65 Years	**65 to 74 Years**	**≥ 75 Years**

Adverse Reactions	BOTOX® 100 Units (N=344)	Placebo (N=348)	BOTOX® 100 Units (N=169)	Placebo (N=151)	BOTOX® 100 Units (N=94)	Placebo (N=86)
Urinary tract infection	73 (21%)	23 (7%)	51 (30%)	20 (13%)	36 (38%)	16 (19%)
Urinary retention	21 (6%)	2 (0.6%)	14 (8%)	0 (0%)	8 (9%)	1 (1%)

Effects on the Ability to Drive and Use Machines:

Asthenia, muscle weakness, dizziness and visual disturbance have been reported after treatment of BOTOX® and could make driving or using machines dangerous.

7. OVERDOSAGE

Overdose of BOTOX® is a relative term and depends upon dose, site of injection, and underlying tissue properties. Signs and symptoms of overdose are likely not to be apparent immediately post-injection. Excessive doses may produce local, or distant, generalized and profound neuromuscular paralysis. Should accidental injection or oral ingestion occur, or overdose be suspected, the person should be medically monitored for up to several weeks for progressive signs or symptoms of systemic muscular weakness which could be local, or distant from the site of injection which may include ptosis, diplopia, dysphagia, dysarthria, generalized weakness or respiratory failure. These patients should be considered for further medical evaluation and appropriate medical therapy immediately instituted, which may include hospitalization.

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 ventilation, in addition to other general supportive care.

Also see DOSAGE AND ADMINISTRATION.

8. ACTION AND CLINICAL PHARMACOLOGY

8.1 MECHANISM OF ACTION

BOTOX® is a sterile, vacuum-dried form of purified botulinum neurotoxin type A complex, produced from a culture of the Hall strain of *Clostridium botulinum* grown in a medium containing N-Z amine, glucose and yeast extract. It is purified to a crystalline complex consisting of the neurotoxin, a non-toxic protein and four major hemagglutinin proteins.

BOTOX® blocks neuromuscular conduction by binding to receptor sites on motor nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. In sensory neurons, BOTOX® inhibits the release of sensory neurotransmitters (e.g., Substance P, CGRP) and downregulates the expression of cell surface receptors (e.g., TRPV1). BOTOX® also prevents and reverses sensitization in nociceptive sensory neurons. When injected intramuscularly at therapeutic doses, BOTOX® produces partial chemical denervation of the muscle resulting in localized muscle paralysis. When chemically denervated, the muscle may atrophy, axonal sprouting may occur, and extrajunctional acetylcholine receptors may develop. There is evidence that reinnervation of the muscle may occur, thus reversing muscle weakness produced by localized injection of BOTOX®.

Following intradetrusor injections, BOTOX® affects the efferent pathways of detrusor activity via inhibition of acetylcholine release. In addition, BOTOX® inhibits afferent neurotransmitters and sensory pathways.

The primary release procedure for BOTOX® uses a cell-based potency assay to determine the potency relative to a reference standard. The assay is specific to Allergan's product BOTOX®. One Allergan Unit (U) of BOTOX® corresponds to the calculated median intraperitoneal lethal dose (LD_{50}) in mice. Due to specific method details such as the vehicle, dilution scheme and laboratory protocols, Units of biological activity of BOTOX® can not be compared

to or converted into units of any other botulinum toxin activity. The specific activity of BOTOX® is approximately 20 U/nanogram of neurotoxin protein complex.

8.2 PHARMACODYNAMICS

When injected into neck muscles, BOTOX® reduces both objective signs and subjective symptoms of cervical dystonia (spasmodic torticollis). These improvements include reduced angle of head turning, reduced shoulder elevation, decreased size and strength of hypertrophic muscles, and decreased pain. Based on the results of well-controlled studies, 40-58% of patients with cervical dystonia would be expected to have a significant improvement in their symptoms.

The paralytic effect on muscles injected with BOTOX® reduces the excessive, abnormal contractions of blepharospasm associated with dystonia.

When used for the treatment of strabismus, it has been postulated that the administration of BOTOX® affects muscle pairs by inducing an atrophic lengthening of the injected muscle and a corresponding shortening of the antagonist muscle.

Following injection of BOTOX® some distant muscles have shown increased electrophysiologic neuromuscular jitter. This effect is not associated with other types of electrophysiologic abnormalities, or with clinical signs of weakness or symptoms regarding either safety or efficacy.

In the treatment of pediatric cerebral palsy patients with dynamic equinus foot deformity due to spasticity, BOTOX® injections into the gastrocnemius produce an improvement in ankle position (reduction in equinus) and an improvement in gait pattern due to increased heel-to-floor contact.

In the treatment of hyperhidrosis of the axillae (N=320), BOTOX®-treated patients demonstrated a responder rate based on gravimetric assessment of 95% at week 1 and 82% at week 16. The mean percentage reduction in sweat production in the BOTOX®-treated patients ranged from 83% at week 1 to 69% at week 16. Treatment response has been reported to persist for 4 to 7 months (average of 5.2 months) in patients (N=12) treated with 50 U per axillae. Repeat injections should be administered when effects from previous injections subside.

When used for the treatment of focal spasticity BOTOX® injected into upper limb muscles reduces the objective signs and subjective symptoms of spasticity. Improvements include reduction of muscle tone, increase in range of motion, and in some patients reduction of spasticity-related disability.

When used for the prophylaxis of headaches in adults with chronic migraine BOTOX® may act as an inhibitor of neurotransmitters associated with the genesis of pain. The presumed mechanism for headache prophylaxis is by blocking peripheral signals to the central nervous system, which inhibits central sensitization, as suggested by pre-clinical studies.

Clinical Studies:

Blepharospasm

In one study, injection of botulinum toxin was evaluated in 27 patients with essential blepharospasm. Twenty-six (26) of the patients had previously undergone drug treatment utilizing benztropine mesylate, clonazepam and/or baclofen without adequate clinical results. Three of these patients then underwent muscle stripping surgery, again without an adequate outcome. One patient of the 27 was previously untreated. Twenty-five (25) of the 27 patients reported improvement within 48 hours following injection of botulinum toxin. Blepharospasm in one of the other patients was later controlled with a higher dosage of botulinum toxin. The remaining patient reported only mild improvement but remained functionally impaired.

In a double-blind, placebo-controlled study, 12 patients with blepharospasm were evaluated; 8 patients received botulinum toxin and 4 received placebo. All patients who received botulinum toxin improved compared to none in the placebo group. Among the botulinum toxin-treated patients, the mean dystonia score improved by 72%, the self-assessment score rating improved by 61%, and a videotape evaluation rating improved by 39%. The mean duration of treatment effects was 12.5 weeks.

In an open trial, 1684 patients with blepharospasm showed clinical improvement after treatment with BOTOX® lasting an average of 12.5 weeks prior to the need for re-treatment.

Strabismus

In an open trial, 677 patients with strabismus were treated with one or more injections of BOTOX®. Fifty-five percent (55%) of these patients were improved to an alignment of 10 prism diopters or less when evaluated six months or more following injection. These results are consistent with results from additional open label trials which were conducted for this indication.

Cervical dystonia (spasmodic torticollis)

In a double-blind, vehicle-controlled parallel study, 51 patients with idiopathic cervical dystonia (spasmodic torticollis) were evaluated. Patients treated with BOTOX® experienced an average of 8 to 12 degrees decrease in head rotation at rest, corresponding to a mean decrease of 13% to 20%, respectively. There was also a significant decrease in strength and size of the contralateral sternocleidomastoid and trapezii (i.e., muscles involved in head rotation). Vehicle-treated patients showed a mean decrease of only 0 to 4 degrees (0% to 6%) of head rotation at rest, and had no change in muscle strength or size. The difference in head rotation between treatment groups was statistically significant. Among BOTOX® treated patients, improvement was reported by 42%, 58% and 57% of the patients at 2, 6 and 12 weeks after injection, respectively. Improvement was reported by 8%, 8% and 17% of vehicle-treated subjects at the same time points, respectively.

In a double-blind, vehicle-controlled crossover study, there was a significant decrease in the size of the sternocleidomastoid muscle contralateral to head turning following BOTOX® compared to placebo injection. By crossover analysis, 41% of patients reported a positive global assessment of response after BOTOX® injection (which includes measures of head rotation, head tilt, anterocollis, retrocollis, duration of sustained movements, shoulder elevation and tremor duration and severity), compared to 14% after vehicle injection.

Two additional double-blind, vehicle-controlled crossover studies evaluated the efficacy of BOTOX® in patients with cervical dystonia. There was a significant decrease in discomfort in the patients treated with BOTOX® in one study. In the other study, patients treated with BOTOX® had a mean decrease in head rotation of 18% (crossover analysis) and 30% (parallel analysis) compared with a mean decrease in head rotation of 3% (crossover) and 16% (parallel) in patients treated with placebo. In both of these studies, the global assessment of cervical dystonia showed trends of improvement for patients treated with BOTOX® relative to those treated with vehicle.

Pediatric Cerebral Palsy

In a three-month, double-blind, placebo-controlled, parallel study, 145 ambulatory children with cerebral palsy, 2 to 16 years of age, were evaluated. Patients exhibited muscle spasticity of the lower extremity(ies) associated with an equinovalgus foot position during gait. A significantly greater number of patients treated with BOTOX® vs. placebo demonstrated improvement based on a physician's rating of dynamic gait which was composed of assessments of gait pattern, ankle position, hindfoot position during foot strike, knee position during gait, degree of crouch and speed of gait. Improvement was reported by 53%, 50%, 60% and 54% of BOTOX®-treated patients vs. 25%, 27%, 25% and 32% of placebo-treated patients at Weeks 2, 4, 8 and 12, respectively. Of the individual assessments which were included in the physician's rating of dynamic gait, a significantly greater number of BOTOX®-treated vs. placebo-treated subjects had improvements in gait pattern (Weeks 2, 8, and 12) and ankle position (Weeks 2, 4, 8 and 12).

Electromyography confirmed that BOTOX® produces a partial denervation of the gastrocnemius muscle. No significant changes in electromyography were seen in the placebo-treated patients.

In a long-term, open-label study, 207 patients were evaluated for up to three years. The percent of patients who showed an improvement based on the physician's rating of dynamic gait ranged from 41% to 67% over the three-year period. Of the individual assessments which were included in the physician's rating of dynamic gait, significant improvements in gait pattern were seen at every visit over the three-year period.

Focal Spasticity in Adults

Upper Limb Spasticity

The efficacy of BOTOX® used for the treatment of upper limb spasticity associated with stroke was evaluated in double-blind and open label studies in 387 unique patients who received 531 treatment exposures.

In a three month, double-blind, placebo controlled study, 126 patients with upper limb spasticity post-stroke were treated with 200 U to 240 U of BOTOX® into the wrist, finger, and thumb flexor muscles. A clinically significant greater reduction in muscle tone was observed in BOTOX® treated patients compared to placebo as measured on the Ashworth scale 1 to 12 weeks post-treatment. The Physician Global Assessment showed parallel statistically significant improvements. Furthermore, patients treated with BOTOX® had significant improvement for a pre-determined, targeted disability item associated with upper limb spasticity at 4 to 12 weeks post-treatment.

In three- and four-month, double-blind, placebo-controlled, dose-ranging studies involving a total of 130 patients with upper limb spasticity post-stroke, patients were treated with a total dose of up to 300 U or 360 U of BOTOX®. Improvements in wrist, elbow and finger flexor muscle tone were reported at the highest dose in each study at various timepoints. The Physician Global Assessment also showed significant benefit at doses ranging from 75 to 360 U at various timepoints.

Lower Limb Spasticity

The efficacy and safety of BOTOX® for the treatment of lower limb spasticity was evaluated in a randomized, multi-center, double-blind, placebo-controlled study. This study included 468 post-stroke patients (233 BOTOX® and 235 placebo) with lower limb spasticity (Modified Ashworth Scale [MAS] ankle score of at least 3) who were at least 3 months post-stroke. Patients with previous surgical intervention, phenol block, ethanol block, or muscle afferent bloc to treat lower limb spasticity were excluded from the study.

BOTOX® 300 to 400 Units or placebo were injected intramuscularly into the study mandatory muscles gastrocnemius, soleus, and tibialis posterior and optional muscles including flexor hallucis longus, flexor digitorum longus, flexor digitorum brevis, extensor hallucis, and rectus femoris (see table below). The use of electromyographic guidance, nerve stimulation, or ultrasound was required to assist in proper muscle localization for injections. Patients were followed for 12 weeks.

Study Medication Dose and Injection Sites

Muscles Injected	BOTOX® (Units)	Number of Injection Sites
Mandatory Ankle Muscles		
Gastrocnemius (medial head)	75	3
Gastrocnemius (lateral head)	75	3
Soleus	75	3
Tibialis Posterior	75	3
Optional Muscles		
Flexor Hallucis Longus	50	2
Flexor Digitorum Longus	50	2
Flexor Digitorum Brevis	25	1
Extensor Hallucis	25	1
Rectus Femoris	100	4

The primary endpoint was the average change from baseline of weeks 4 and 6 MAS ankle score and a key secondary endpoint was the average CGI (Physician Global Assessment of Response) at weeks 4 and 6. The MAS uses a similar scoring system as the Ashworth Scale. The CGI evaluated the response to treatment in terms of how

the patient was doing in his/her life using a 9-point scale from -4=very marked worsening to +4=very marked improvement.

Statistically and clinically significant between-group differences for BOTOX over placebo were demonstrated for the primary efficacy measures of MAS and key secondary measure of CGI and are presented in Table 2 below.

Table 2: Primary and Key Secondary Efficacy Endpoints

	BOTOX® 300 to 400 Units (ITT) (N=233)	**Placebo (N=235)**
Mean Changes from Baseline in Ankle Plantar Flexors in MAS Score		
Week 4 and 6 Average	-0.8*	-0.6
Mean Clinical Global Impression Score by Investigator		
Week 4 and 6 Average	0.9*	0.7
Mean Change in Toe Flexors in MAS Score		
FHL Week 4 and 6 Average	-1.0*	-0.6
FDL + FDB Week 4 and 6 Average	-0.9	- 0.8

*Significantly different from placebo ($p<0.05$)

FHL = flexor hallucis longus; FDL = flexor digitorum longus; FDB = flexor digitorum brevis

Statistically significant improvements in MAS change from baseline (Figure 1) and CGI by Physician (Figure 2) for BOTOX® were observed at weeks 2,4, and 6, compared to placebo.

Figure 1: Modified Ashworth Scale Ankle Score for Study 2 – Mean Change from Baseline by Visit

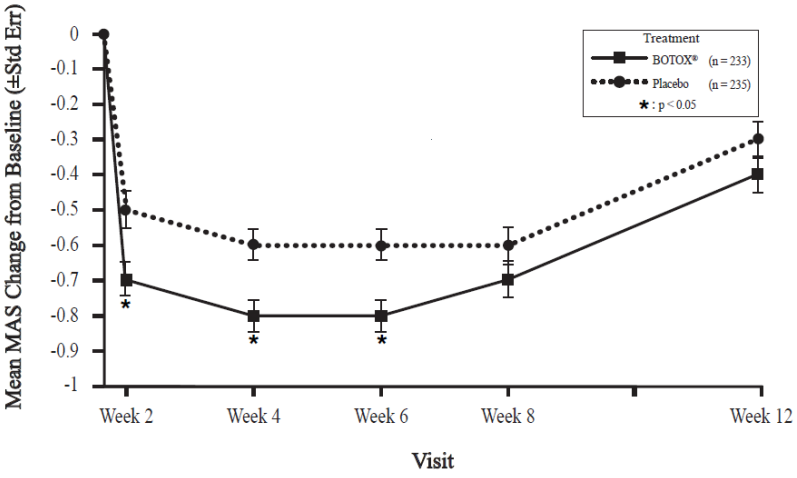
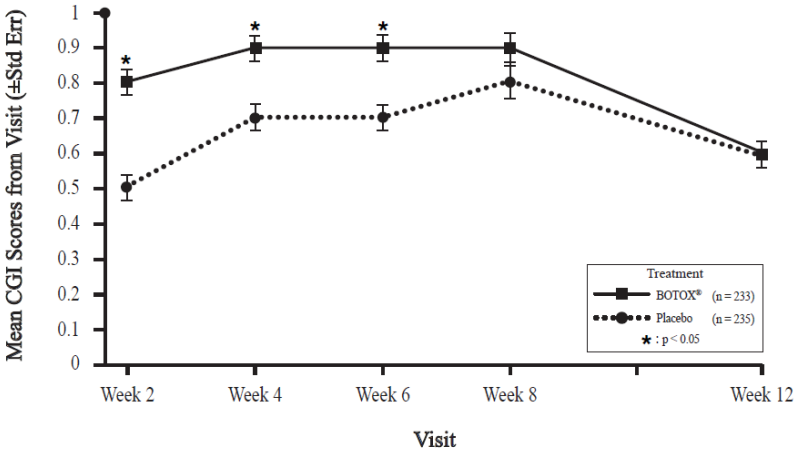


Figure 2: Clinical Global Impression by Physician for Study 2 – Mean Scores by Visit



Hyperhidrosis of the Axillae

When injected intradermally, BOTOX® produces temporary chemical denervation of the sweat gland resulting in local reduction in sweating. The efficacy and safety of BOTOX® for the treatment of primary axillary hyperhidrosis were evaluated in a randomized, multi-center, double-blind, placebo-controlled study.

In the study, 320 adults with bilateral axillary primary hyperhidrosis were randomized to receive either 50 U of BOTOX® (n=242) or placebo (n=78). Treatment responders were defined as subjects showing at least a 50% reduction from baseline in axillary sweating measured by gravimetric measurement at 4 weeks. At week 4 post-injection, the percentages of responders were 91% (219/242) in the BOTOX® group and 36% (28/78) in the placebo group, $p < 0.001$.

The difference in percentage of responders between BOTOX® and placebo was 55% (95% CI = 43.3, 65.9).

Upper Facial Lines (Glabellar Lines, Crow's Feet, Forehead Lines)

In a clinical study, the safety and efficacy of BOTOX® was compared with placebo for the treatment of glabellar lines. BOTOX®–was administered to 203 subjects as a single treatment of intramuscular injections at 5 sites, 2 in each corrugator muscle and 1 in the procerus muscle. Each injection was 0.1 mL (4 U), for a total of 0.5 mL (20 U). The following was concluded:

- >80% of subjects responded to treatment as rated by investigators and >90% by self-assessment.
- For both primary efficacy variables, the investigator's rating of glabellar line severity at maximum frown and the subject's global assessment of change of appearance of glabellar lines, there was a statistically and clinically significant higher responder rate with BOTOX® than with placebo at all timepoints from day 7 through day 120 ($p<0.001$).
- For the investigator's rating of glabellar line severity at rest, there was a significantly higher responder rate with BOTOX®than with placebo at all timepoints.
- Subgroup analyses of the primary efficacy variables by age group (≤50 years and ≥51 years) and by investigator gave results similar to those for the overall study population.
- Subjects rated their impression of improvement even more highly than did the investigators, particularly later in the study. By day 120, 44.1% of subjects rated their appearance as at least moderately improved.
- BOTOX® was shown in this study to be well-tolerated, with no treatment-related serious adverse events.

The safety and efficacy of BOTOX® for the treatment of horizontal forehead lines has been described in published investigator clinical studies. BOTOX® was administered to 59 subjects as a single treatment of intramuscular injections at injection doses into the frontalis of 8, 16 and 24 U. The following was concluded:

- Approximately 90% of subjects responded to treatment as rated by investigators and up to 75- 80% by self-assessment.
- There was a reduction in horizontal rhytide severity in all three BOTOX® treatment groups at both contraction and repose.

- There was a significant dose-response trend for rate of improvement at maximum brow elevation: 53% in the 24 U group versus 15% in the 8 U group at 16 weeks, by a trained observer.
- There was a significant dose-response trend for rate of relapse to baseline: 35% in the 24 U group versus 75% in the 8 U group at 16 weeks, by a trained observer.
- BOTOX® was shown in this study to be well-tolerated, with no treatment-related serious adverse events. The most common treatment-related adverse events were headache, local pain and swelling resulting from injection.

In another published investigator clinical study, the safety and efficacy of BOTOX® was compared with placebo for the treatment of lateral canthal lines (crow's feet). BOTOX® was administered to 60 subjects in orbicularis oculi muscle as a single injection treatment at one of 3 doses (6, 12 and 18 U total) on one side, and placebo contralaterally. In a second study of lateral canthal lines, BOTOX® (5-15 U) was injected on each side in 80 subjects. The following was concluded:

- BOTOX® was associated with significantly higher success rates than placebo at all dose levels, as determined by both trained observers and patients.
- At four weeks post-injection, 89-95% patients on the BOTOX®-treated side were considered by investigators as treatment responders, and 60-80% of patients felt they had treatment success, compared to approximately 5-15% and 15-45%, respectively on the placebo-treated side.
- No clear dose-response relationship was observed.
- Benefits of the second injection lasted longer than the first. The success rate of a second injection reached 100% for the 12 and 18 U groups, and approximately 80% of patients were considered treatment successes at 16 weeks, for all groups.
- Patient surveys revealed high satisfaction with BOTOX® treatments; 89% described themselves as satisfied or very satisfied; 93% indicated they would undergo treatment again.

BOTOX® was well tolerated. No serious or severe adverse events were reported. The most common adverse event related to treatment was bruising; the incidence was similar on the placebo-treated side.

Two multicenter, randomized, double-blind, placebo-controlled studies evaluated BOTOX® (N=921, randomized to receive any BOTOX® treatment or N=257, randomized to receive placebo) for the temporary improvement in the appearance of moderate to severe forehead lines (FHL).

Study 1 assessed BOTOX® treatment of FHL with glabellar lines (GL); Study 2 also assessed simultaneous treatment of FHL, GL, and lateral canthal lines [LCL]. Both studies enrolled healthy adults with moderate to severe FHL at maximum eyebrow elevation at baseline and moderate to severe GL at maximum frown at baseline; Study 2 also required subjects to have moderate to severe LCL at maximum smile at baseline.

In the 12-month Study 1, subjects were randomized to receive BOTOX® 20 Units to the frontalis muscle with 20 Units to the glabellar region (for a total of 40 Units) or placebo in both areas.

In the 12-month Study 2, subjects were randomized to receive BOTOX® 20 Units to the frontalis muscle, 20 Units to the glabellar region, and 0 Units to the LCL region (for a total of 40 units) or BOTOX® 20 Units to the frontalis muscle, 20 Units to the glabellar region, and 24 Units to the LCL region (for a total of 64 Units) or placebo in all three areas.

The primary efficacy measure was the assessment of FHL severity at maximum eyebrow elevation using the 4-point Facial Wrinkle Scale with Photonumeric Guide (FWS; 0=none, 1= mild, 2=moderate, 3=severe). The FWS assessment was performed independently by both investigators and subjects. The primary timepoint was Day 30 following the first treatment.

The primary efficacy response definition was a composite ≥2-grade improvement from baseline in FHL severity at maximum eyebrow elevation, assessed by both investigator and subject on a per-subject basis. For Studies 1 and 2, the proportion of responders was greater in the BOTOX Cosmetic arms compared to placebo at Day 30 ($p<0.0001$ for Studies 1 and 2).

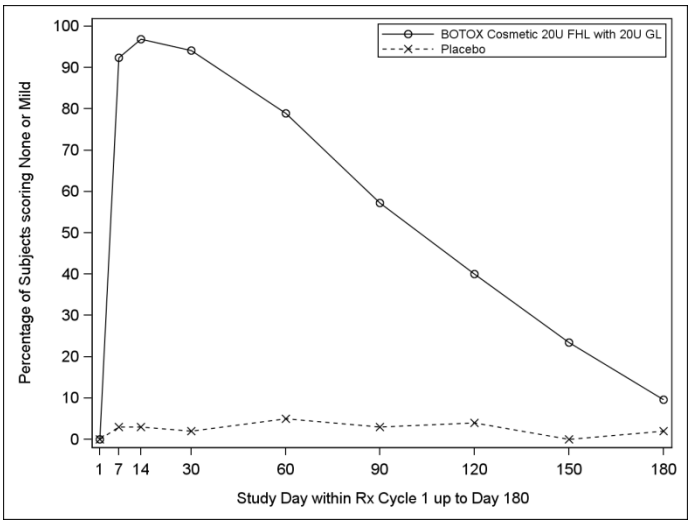
Studies 1 and 2: Composite Investigator and Subject Assessment of FHL Severity at Maximum Eyebrow Elevation at Day 30 – Responder Rates (% and Number of Subjects Achieving ≥2-Grade Improvement from Baseline)

Study	BOTOX® Cosmetic (20 Units FHL with 20 Units GL)	BOTOX® Cosmetic (20 Units FHL, 20 Units GL, and 24 Units LCL)	Placebo
Study 1	N=290 61%	-	N=101 0%
Study 2	N=318 46%	N=313 53%	N=156 1%

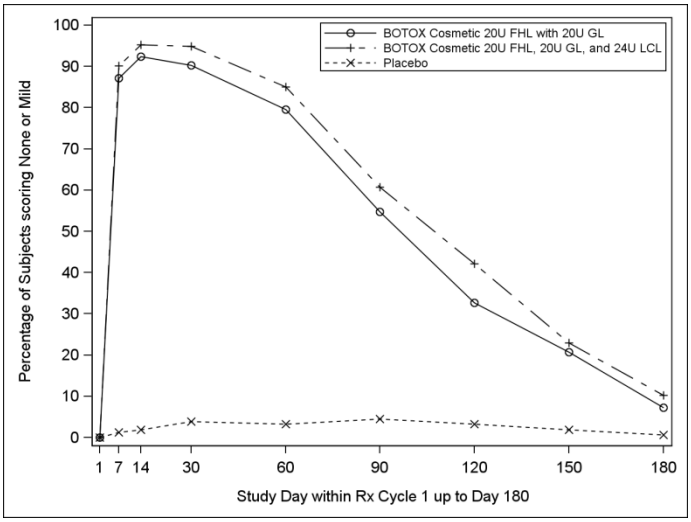
A total of 165 and 197 subjects received 3 cycles over 1 year of BOTOX® Cosmetic 40 Units (20 Units FHL with 20 Units GL) and 64 Units (20 Units FHL, 20 Units GL, and 24 Units LCL), respectively. The response rate for FHL was similar across all treatment cycles.

The results for a key secondary endpoint of responders achieving a grade of none or mild on investigator ratings at maximum eyebrow elevation of FHL severity are presented below for Studies 1 and 2.

Percentage of Subjects with Treatment Success (Achieving None or Mild FHL from Baseline at Maximum Eyebrow Elevation) by Visit (Study 1)



Percentage of Subjects with Treatment Success (Achieving None or Mild FHL from Baseline at Maximum Eyebrow Elevation) by Visit (Study 2)



The results of the Facial Line Satisfaction Questionnaire are presented below.

Facial Lines Satisfaction Questionnaire Response Frequency at Day 60 (Percentage of Subjects)

	Study 1		Study 2	
	BOTOX® Cosmetic (20 Units FHL with 20 Units GL) N=289	**Placebo N=99**	**BOTOX® Cosmetic (20 Units FHL with 20 Units GL) N=317**	**Placebo N=155**
"Very satisfied"	57%	1%	35%	0%
"Mostly satisfied"	33%	0%	47%	3%
"Neither dissatisfied nor satisfied"	4%	22%	9%	23%
"Mostly dissatisfied"	4%	21%	7%	20%
"Very dissatisfied"	2%	56%	2%	54%

Chronic Migraine

BOTOX® was evaluated in two multi-national, multi-center 56 week studies that included a 24 week, 2 injection cycle, double-blind phase comparing BOTOX® to placebo that was followed by a 32-week, 3 injection cycle, open-label phase. A total of 1,384 chronic migraine adults who had either never received or were not using any concurrent headache prophylaxis, had > 15 headache days, with 50% being migraine/probable migraine, and > 4 headache episodes during a 28-day baseline phase were studied in 2 phase 3 clinical trials. These patients were randomized to placebo or to 155 U - 195 U BOTOX® injections every 12 weeks, maximum 5 injection cycles. Patients were allowed to use acute headache treatments (65.5% overused acute treatments during the baseline period). The number (percentage) of patients who received BOTOX® injections at 31 sites and at 39 sites at Week 12 were N=345/627 (55.0%) and N=44/627 (7.0%), respectively.

Phase 3 Study 1*: Least Square (LS) Mean Change from Baseline, Between-Group Differences and 99% Confidence Intervals for Primary and Secondary Efficacy Variables at Week 24 Primary Timepoint

Efficacy per 28 days[c]	**BOTOX® (N=341)**		**Placebo (N=338)**	**Between-Group Difference (99% CI)**[a]	**P-Value** [a,b]
Frequency of headache days	-7.8		-6.4	-1.4 (-2.72, -0.09)	0.006
Frequency of migraine/probable migraine episodes	-5.0		-4.5	-0.5 (-1.45, 0.50)	0.206
Frequency of migraine/probable migraine days	-7.6		-6.0	-1.6 (-2.91, -0.27)	0.002
Frequency of headache episodes[d]	-5.4		-5.0	-0.4 (-1.36, 0.63)	0.344
Frequency of acute headache pain medication intakes	-10.1		-9.8	-0.3 (-3.82, 3.12)	0.795

* Allergan study 191622-079

[a] To control the type-1 error rate at 0.05, p-values were examined relative to 0.01 under a Bonferroni multiple-comparison adjustment for the 5 variables that were protocol-specified as primary or secondary. Accordingly, for the least-squares means' difference between treatment groups, 99% confidence intervals are displayed rather than 95% confidence intervals.

[b] P-values for between-treatment comparisons are from covariate analysis of variance (ANCOVA), with baseline values as covariate. The main effects in the ANCOVA included treatment and medication-overuse strata, where the type III sum of squares was used.

[c] Missing values were estimated using modified last observation carried forward, with the patient's most-recent previous score multiplied by the change rate across non-missing observations for all other patients, applied iteratively across sequential time periods.

[d] Primary endpoint

Phase 3 Study 2*: LS Mean Change from Baseline, Between-Group Differences and 95% Confidence Intervals for Primary and Secondary Efficacy Variables at Week 24 Primary Timepoint

Efficacy per 28 days[c]	**BOTOX® (N=347)**	**Placebo (N=358)**	**Between-Group Difference (95% CI)**	**P-Value** [a,b]
Frequency of headache days[e]	-9.2	-6.9	-2.3 (-3.25, -1.31)	<0.001
Frequency of migraine/probable migraine days	-8.8	-6.5	-2.3 (-3.31, -1.36)	<0.001
Number of moderate/severe headache days	-8.4	-6.0	-2.4 (-3.37, -1.48)	<0.001
Total cumulative hours of	-134.15	-94.54	-39.6	<0.001

headache on headache days			(-58.23, -21.05)	
Proportion of patients with severe (≥60) Headache Impact Test (HIT)-6 score[d]	66.3%	76.5%	-10.3% (-16.9, -3.6)	0.003
Frequency of headache episodes	-5.6	-4.6	-1.0 (-1.65, -0.33)	0.003

***** Allergan study 191622-080

[a] To control the type 1 error rate for multiple secondary endpoints, a gatekeeping approach was used for the five secondary variables at the primary visit (week 24). Each secondary variable could only indicate significance if the primary variable and each secondary variable ranked ahead of it indicated statistical significance.

[b] P-values for between-treatment comparisons are from covariate analysis of variance (ANCOVA), with baseline values as covariate. The main effects in the ANCOVA included treatment and medication-overuse strata, where the type III sum of squares was used.

[c] Missing values were estimated using modified last observation carried forward, with the patient's most-recent previous score multiplied by the change rate across non-missing observations for all other patients, applied iteratively across sequential time periods.

[d] P-values from statistical comparisons are for raw values, not for changes from baseline.

[e] Primary endpoint

In Study 1, at the Week 24 primary timepoint, the mean changes from baseline in total cumulative hours of headache on headache days were -106.7 hours in the BOTOX® group and -70.4 hours in the placebo group. At the Week 24 primary timepoint, the mean changes from baseline for total HIT-6 score were -4.7 in the BOTOX® group and -2.4 in the placebo group in Study 1, and -4.9 in the BOTOX® group and -2.4 in the placebo group in Study 2.

The treatment effect appeared smaller in the subgroup of male patients (N=188) than in the whole study population. BOTOX® for chronic migraine has not been evaluated in clinical trials beyond 5 injection cycles.

Overactive Bladder

Two double-blind, placebo-controlled, randomised, multi-center, 24-week Phase 3 clinical studies were conducted in patients with OAB with symptoms of urinary incontinence, urgency, and frequency. A total of 1105 patients, whose symptoms had not been adequately managed with anticholinergic therapy (inadequate response or intolerable side effects), were randomised to receive either 100 Units of BOTOX® (n=557), or placebo (n=548). Patients had to have at least 3 urinary urgency incontinence episodes and at least 24 micturitions in 3 days, a negative urine dipstick at randomisation and to be willing to use Clean Intermittent Catheterisation (CIC) if deemed necessary by the investigator. Patients were excluded if they had other urological conditions that could confound the studies such as: OAB secondary to any known neurological reason, a predominance of stress incontinence, anticholinergic treatment or any other therapies for OAB within the 7 days prior to baseline , already using CIC or an in-dwelling catheter, previous botulinum toxin therapy within the previous 12 weeks or immunisation for any botulinum toxin serotype, significant pelvic or urological abnormalities other than OAB or post-void residual (PVR) urine volume > 100 ml at screening among others.

Baseline characteristics were similar between the treatment groups in both studies: pooled mean age 60 years, 87.8% female, 90.9% Caucasian, 13.7% diabetic patients, mean 5.4 daily episodes of urinary incontinence, mean 11.7 daily episodes of micturition and mean 8.6 daily average urgency episodes.

In both studies, significant improvements compared to placebo in the change from baseline in daily frequency of urinary incontinence episodes were observed for BOTOX® (100 U) at the primary time point of week 12, including the proportion of dry patients. Using the Treatment Benefit Scale, the proportion of patients reporting a positive treatment response (their condition has been 'greatly improved' or 'improved') was significantly greater in the BOTOX® group compared to the placebo group in both studies. Significant improvements compared to placebo were also observed

for the daily frequency of micturition, urgency, and nocturia episodes. Volume voided per micturition was also significantly higher. Significant improvements were observed in all OAB symptoms from week 2.

BOTOX® treatment was associated with significant improvements over placebo in health-related quality of life as measured by the Incontinence Quality of Life (I-QOL) questionnaire (including avoidance and limiting behavior, psychosocial impact, and social embarrassment) and the King's Health Questionnaire (KHQ) (including incontinence impact, role limitations, social limitations, physical limitations, personal relationships, emotions, sleep/energy, and severity/coping measures).

Results from the pivotal studies are presented below:

Primary and Secondary Efficacy Variables at Baseline and Change from Baseline in Study 1 (191622-095) and Study 2 (191622-520):

	Study 1 (191622-095)			**Study 2 (191622-520)**		
Endpoint Timepoint	**BOTOX® 100 Units (N=280)**	**Placebo (N=277)**	**P-value; Absolute difference from placebo (95% CI)**	**BOTOX® 100 Units (N=277)**	**Placebo (N=271)**	**P-value; Absolute difference from placebo (95% CI)**
Daily Frequency of Urinary Incontinence Episodes*						
Mean Baseline	5.47	5.09		5.52	5.70	
Mean Change at Week 2	-2.85	-1.09		-2.85	-1.34	
Mean Change at Week 6	-3.05	-1.07		-3.18	-1.37	
Mean Change at Week 12[a]**	**-2.65**	**-0.87**	**< 0.01; -1.65 (-2.13, -1.17)**	**-2.95**	**-1.03**	**< 0.01; -1.91 (-2.43, -1.39)**
Proportion of Positive Treatment Response using Treatment Benefit Scale (%)						
Week 2	64.5	32.6		64.2	36.8	
Week 6	66.9	34.7		69.3	30.9	
Week 12*[a]	**60.8**	**29.2**	**< 0.001; 31.8 (23.9, 39.7)**	**62.8**	**26.8**	**< 0.001; 36.0 (28.2, 43.8)**
Daily Frequency of Micturition Episodes						
Mean Baseline	11.98	11.20		12.01	11.77	
Mean Change at Week 2	-1.58	-0.79		-1.48	-0.77	
Mean Change at Week 6	-1.96	-0.98		-2.40	-0.97	
Mean Change† at Week 12[b]	**-2.15**	**-0.91**	**< 0.001 -1.04 (-1.48, -0.59)**	**-2.56**	**-0.83**	**< 0.001; -1.72 (-2.19, -1.26)**
Daily Frequency of Urgency Episodes						
Mean Baseline	8.54	7.85		9.11	8.78	
Mean Change at Week 2	-2.83	-1.34		-2.95	-1.36	
Mean Change at Week 6	-3.21	-1.45		-3.91	-1.35	
Mean Change† at Week 12[b]	**-2.93**	**-1.21**	**< 0.001; -1.51 (-2.15, -0.87)**	**-3.67**	**-1.24**	**< 0.001; -2.44 (-3.09, -1.79)**
Incontinence Quality of Life						

	Study 1 (191622-095)			Study 2 (191622-520)		
Endpoint Timepoint	**BOTOX® 100 Units (N=280)**	**Placebo (N=277)**	**P-value; Absolute difference from placebo (95% CI)**	**BOTOX® 100 Units (N=277)**	**Placebo (N=271)**	**P-value; Absolute difference from placebo (95% CI)**
Total Score						
Mean Baseline	36.5	37.3		31.7	32.1	
Mean Change† at Week 12[bc]	**+21.9**	**+6.8**	**< 0.001; 14.9 (11.1, 18,7)**	**+23.1**	**+6.3**	**< 0.001; 16.9 (13.2, 20.6)**
King's Health Questionnaire: Role Limitation						
Mean Baseline	61.2	56.2		69.6	66.4	
Mean Change† at Week 12[bc]	**-24.3**	**-2.4**	**< 0.001; -20.6 (-25.6, -15.7)**	**-26.5**	**-5.0**	**< 0.001; -19.8 (-24.8, -14.7)**
King's Health Questionnaire: Social Limitation						
Mean Baseline	40.5	39.4		49.1	45.4	
Mean Change† at Week 12[bc]	**-17.3**	**-3.8**	**< 0.001 -13.9 (-18.1, -9.7)**	**-16.2**	**-1.3**	**< 0.001; -13.2 (-17.8, -8.6)**

* Percentage of patients who were dry (without incontinence) at week 12 was 22.9% for the BOTOX® group and 6.5% for placebo group in Study 1 and 31.4% for the BOTOX® group and 10.3% for placebo group in Study 2. The proportions achieving at least a 75% and 50% reduction from baseline in urinary incontinence episodes were 44.6% and 57.5% in the BOTOX® group compared to 15.2% and 28.9% in the placebo group in Study 1 and 47.3% and 63.5% in the BOTOX® group compared to 20.3% and 33.2% in the placebo group in Study 2.

** P-value, absolute difference in Least Squares Mean (LS Mean) and its 95% CI for daily frequency of urinary incontinence episodes at Week 12 are based on an ANCOVA model using a LOCF method with baseline value as covariate and treatment group and site as factors.

*** P-value, absolute difference from placebo and its 95% CI for proportion of positive treatment response using TBS at Week 12 are based on Cochran-Mantel-Haenszel (CMH) test using a LOCF method with urinary urgency incontinence ≤9 or >9 episodes at baseline as a stratification factor.

† P-values, absolute differences from placebo in LS Mean and its 95% CI for the secondary efficacy endpoints are based on an ANCOVA model with baseline value as covariate and stratification factor, treatment group and site as factors.

[a] Co-primary endpoints

[b] Secondary endpoints

[c] Pre-defined minimally important change from baseline was +10 points for I-QOL and -5 points for KHQ

A total of 834 patients were evaluated in a long term extension study. For all efficacy endpoints, patients experienced consistent response with re-treatments. In the subset of 345 patients, who had reached week 12 of treatment cycle 3, the mean reductions in daily frequency of urinary incontinence were -3.07, -3.49, and -3.49 episodes at week 12 after the first, second, and third BOTOX® 100 Unit treatments, respectively. The corresponding proportions of patients with a positive treatment response on the Treatment Benefit Scale (TBS) were 63.6%, 76.9%, and 77.3% respectively.

In the pivotal studies, none of the 615 (0%) patients with analyzed specimens developed the presence of serum neutralizing antibodies to BOTOX®.[36] In patients with analyzed specimens from the pivotal phase 3 and the open-label extension studies, neutralizing antibodies developed in 0 of 954 patients (0.0%) while receiving BOTOX® 100 Unit doses and 3 of 260 patients (1.2%) after subsequently receiving at least one 150 Unit dose. One of these three patients continued to experience clinical benefit.

Only a limited number of males (n=135, 12.2%) were studied in the two phase 3 clinical studies and the results were not statistically significant for patients administered BOTOX® compared to placebo. Results for the co-primary endpoints in males are presented below and further details are located in Precautions, Overactive Bladder, Use in Males:

Co-primary Efficacy Endpoints at Baseline and Change from Baseline in Male Patients (Pooled Pivotal Studies, Placebo-controlled ITT Population)

	BOTOX® 100 Units (N=61)	Placebo (N=74)	P-value	Absolute difference from placebo (95% CI)
Daily Frequency of Urinary Incontinence Episodes				
Mean Baseline	5.61	4.33		
Mean Change at Week 12	-1.86	-1.23	0.612	-0.42 (-2.08, 1.23)
Proportion with Positive Treatment Response using Treatment Benefit Scale (%)				
Week 12	40.7	25.4	0.060	15.2 (-0.8, 31.3)

The median duration of response in patients who continued into the open label extension study and received treatments with only BOTOX® 100 Units (N=438) was 212 days (~30 weeks).[195] To qualify for retreatment, at least 12 weeks must have passed since the prior treatment, post-void residual urine volume must have been less than 200 mL, and patients must have reported at least 2 urinary incontinence episodes over 3 days.

Neurogenic Detrusor Overactivity

Two double-blind, placebo-controlled, randomized, multi-center Phase 3 clinical studies were conducted in patients with urinary incontinence due to neurogenic detrusor overactivity who were either spontaneously voiding or using catheterization. A total of 691 spinal cord injury or multiple sclerosis patients, not adequately managed with at least one anticholinergic agent, were enrolled. These patients were randomized to receive either 200 U of BOTOX® (n=227), 300 U of BOTOX® (n=223), or placebo (n=241).

In both phase 3 studies, significant improvements compared to placebo in the primary efficacy variable of change from baseline in weekly frequency of incontinence episodes were observed for BOTOX® (200 U and 300 U) at the primary efficacy time point at week 6. Significant improvements in urodynamic parameters including increase in maximum cystometric capacity and decreases in peak detrusor pressure during the first involuntary detrusor contraction were observed. These primary and secondary endpoints are shown in the tables and figures below.

No additional benefit of BOTOX® 300 U over 200 U was demonstrated.

Primary and Secondary Endpoints at Baseline and Change from Baseline in Study 1 (ITT population with LOCF Imputation)

	BOTOX® 200 U (N=135)	Placebo (N=149)	Treatment difference*	p-values
Weekly Frequency of Urinary Incontinence*				
N	135	149		
Mean Baseline	32.3	28.3		

Mean Change at Week 2	-15.3	-10.0	-5.3	
Mean Change at Week 6[a]	**-19.9**	**-10.6**	**-9.3** (-13.2, -5.4)	**p<0.001**
Mean Change at Week 12	-19.8	-8.8	-11.0	
Maximum Cystometric Capacity (mL)				
N	123	129		
Mean Baseline	253.8	259.1		
Mean Change at Week 6[b]	**+135.9**	**+12.1**	**123.9** (89.1, 158.7)	**p<0.001**
Maximum Detrusor Pressure during 1st Involuntary Detrusor Contraction (cmH_20)				
N	41	103		
Mean Baseline	63.1	57.4		
Mean Change at Week 6[b]	**-28.1**	**-3.7**	**-24.4**	

* Mean change, treatment difference and p-value are based on a LOCF analysis using an ANCOVA model with baseline weekly endpoint as covariate and treatment group, etiology at study entry (spinal cord injury or multiple sclerosis), concurrent anticholinergic therapy at screening, and investigator as factors.

[a] Primary endpoint

[b] Key secondary endpoints

Study 1 = *Study* 191622-515
Study 2 = *Study* 191622-516

Primary and Secondary Endpoints at Baseline and Change from Baseline in Study 2 (ITT population with LOCF Imputation)

	BOTOX® 200 U (N=92)	**Placebo (N=92)**	**Treatment difference***	**p-values**
Weekly Frequency of Urinary Incontinence*				
N	92	92		
Mean Baseline	32.5	36.7		
Mean Change at Week 2	-18.1	-7.9	-10.3	
Mean Change at Week 6[a]	**-19.8**	**-10.8**	**-9.0** (-14.8, -3.3)	**p=0.002**
Mean Change at Week 12	-19.6	-10.7	-8.9	

Maximum Cystometric Capacity (mL) N **Mean Baseline** **Mean Change at Week 6[b]**	 88 239.6 **+150.8**	 85 253.8 **+2.8**	 **148.0** (101.8, 194.3)	 **p<0.001**
Maximum Detrusor Pressure during 1st Involuntary Detrusor Contraction (cmH_20) N Mean Baseline **Mean Change at Week 6[b]**	 29 65.6 **-28.7**	 68 43.7 **+2.1**	 **-30.7**	

* Mean change, treatment difference and p-value are based on a LOCF analysis using an ANCOVA model with baseline weekly endpoint as covariate and treatment group, etiology at study entry (spinal cord injury or multiple sclerosis), concurrent anticholinergic therapy at screening, and investigator as factors.

[a] Primary endpoint

[b] Key secondary endpoints

Study 1 = Study 191622-515
Study 2 = Study 191622-516

Mean Change from Baseline in Weekly Frequency of Urinary Incontinence Episodes During Treatment Cycle 1 in Study 1

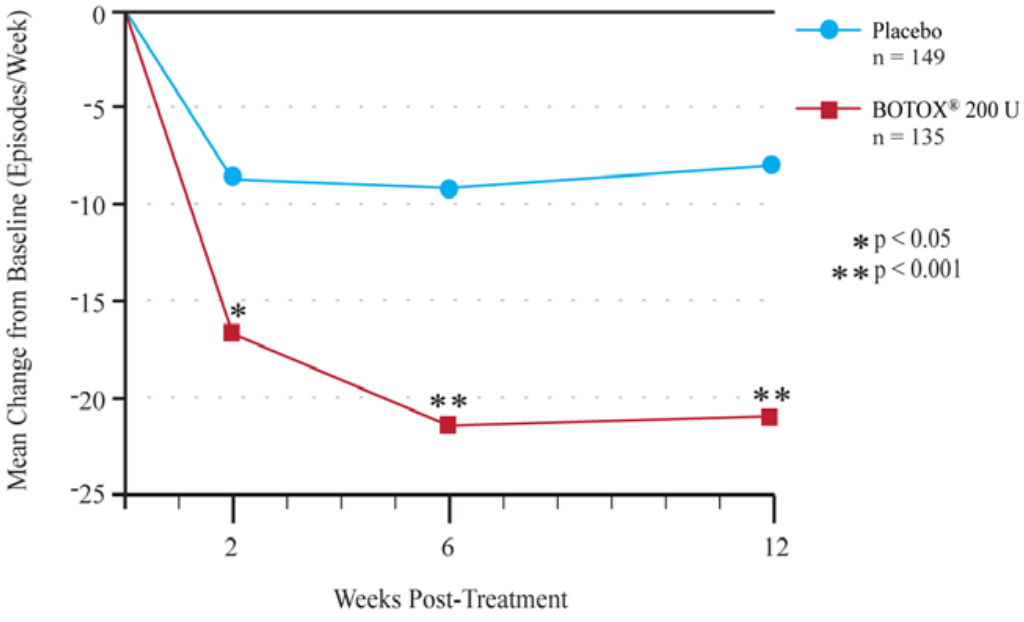
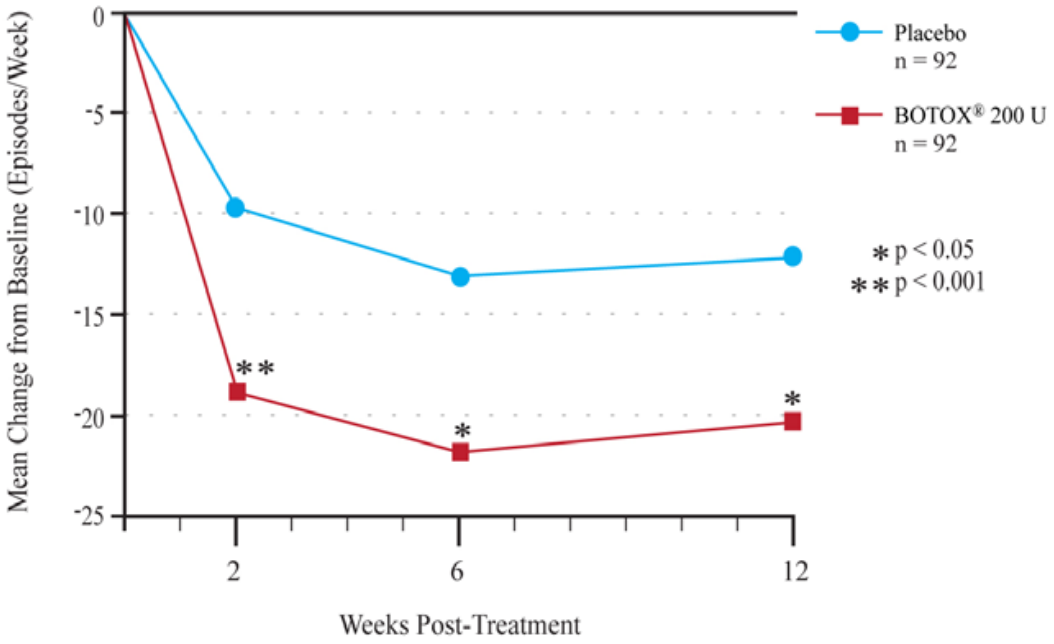


Figure 2: Mean Change from Baseline in Weekly Frequency of Urinary Incontinence Episodes During Treatment Cycle 1 in Study 2



The median duration of response in the two pivotal studies, based on patient request for retreatment, was 256-295 days (36-42 weeks) for the 200 Unit dose group compared to 92 days (13 weeks) with placebo. The median duration of response in patients who continued into the open label extension study and received treatments with only BOTOX® 200 Units (N=174) was 253 days (~36 weeks).[196] Retreatment criteria were: patient request, at least 12 weeks since previous treatment, and < 50% reduction (Study 1) or < 30% reduction (Study 2) from baseline in urinary incontinence episodes.

In the pivotal studies, none of the 475 neurogenic detrusor overactivity patients with analyzed specimens developed the presence of neutralizing antibodies. In patients with analyzed specimens in the drug development program (including the open-label extension study), neutralizing antibodies developed in 3 of 300 patients (1.0%) after receiving only BOTOX® 200 Unit doses and 5 of 258 patients (1.9%) after receiving at least one 300 Unit dose. Four of these eight patients continued to experience clinical benefit.

8.3 PHARMACOKINETICS

It is believed that little systemic distribution of therapeutic doses of BOTOX® occurs. BOTOX® is not expected to be presented in the peripheral blood at measurable levels following IM or intradermal injection at the recommended doses. The recommended quantities of neurotoxin administered at each treatment session are not expected to result in systemic, overt distant clinical effects, i.e. muscle weakness, in patients without other neuromuscular dysfunction. However, clinical studies using single fiber electromyographic techniques have shown subtle electrophysiologic findings consistent with neuromuscular inhibition (i.e. “jitter”) in muscles distant to the injection site, but these were unaccompanied by any clinical signs or symptoms of neuromuscular inhibition from the effects of botulinum toxin.

9. INCOMPATIBILITIES

In the absence of incompatibility studies, this medicinal product should not be mixed with other medicinal products.

10. INFORMATION FOR PATIENTS

As with any treatment with the potential to allow previously sedentary patients to resume activities, the sedentary patient should be cautioned to resume activity gradually following the administration of BOTOX®. Patients should also be advised of the potential for experiencing malaise lasting up to six weeks after injection.

After bladder injections for urinary incontinence, patients should be instructed to contact their physician if they experience difficulties in voiding.

11. PHARMACEUTICAL PRECAUTIONS

Unopened vials should be stored in a refrigerator (2 to 8°C). Do not use after the expiration date on the vial. After reconstitution BOTOX® may be stored in a refrigerator (2 - 8°C) for up to 24 hours prior to use.

For safe disposal, unused vials should be reconstituted with a small amount of water then autoclaved. Any unused vials, syringes and spillages, etc., should be autoclaved, or the residual BOTOX® inactivated using dilute hypochlorite solution (0.5%) for 5 minutes.

12. LEGAL CATEGORY

Prescription-only medicine (POM).

13. PACKAGE QUANTITIES

BOTOX® 50 Units is supplied in a clear glass vial of 5 mL nominal capacity with rubber stopper and tamper-proof aluminum seal.

BOTOX® 100 Units and 200 Units is supplied in a clear glass vial of 10 mL nominal capacity with rubber stopper and tamper-proof aluminum seal.

Manufactured by:

Allergan Pharmaceuticals Ireland, Westport, Co. Mayo, Ireland.

Date of Revision: DD MMM YYYY (CCDS v22)