BOTOX® (Botulinum Toxin Type A)

Purified Neurotoxin Complex

PRESENTATION
A sterile white vacuum dried powder in a clear glass vial, for use in a single patient. One unit corresponds to the median lethal dose (LD_{50}) when reconstituted BOTOX® is injected intraperitoneally into mice under defined conditions).

Each vial of BOTOX® 50 Units contains 50 Units of *Clostridium botulinum* type A neurotoxin complex 900 kD, 0.25 mg of human albumin and 0.45 mg of sodium chloride in a sterile, vacuum-dried form without a preservative.

Each vial of BOTOX® 100 Units contains 100 Units of *Clostridium botulinum* type A neurotoxin complex 900 kD, 0.5 mg of human albumin and 0.9 mg of sodium chloride in a sterile, vacuum-dried form without a preservative.

Each vial of BOTOX® 200 Units contains 200 Units of *Clostridium botulinum* type A neurotoxin complex 900 kD, 1.0 mg of human albumin and 1.8 mg of sodium chloride in a sterile, vacuum-dried form without a preservative.

INDICATIONS
BOTOX® (botulinum toxin type A) purified neurotoxin complex is indicated for the following <u>therapeutic indications</u>:

- BOTOX® is indicated for the treatment of blepharospasm associated with dystonia, including benign essential blepharospasm, hemifacial spasm and 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 and older.
- BOTOX® is indicated in the management of focal spasticity:
    - upper and lower limb spasticity in adults
- BOTOX® is indicated for the management of severe hyperhidrosis of the axillae which does not respond to topical treatment with antiperspirant or antihidrotics.
- 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 urinary incontinence due to neurogenic detrusor overactivity (NDO) associated with Multiple Sclerosis or Spinal Cord Injury in adults who had an inadequate response to or are intolerant of an anticholinergic medication.
- BOTOX® is indicated for the treatment of overactive bladder with symptoms of urinary incontinence, urgency, and frequency, in adult patients who have an inadequate response to or are intolerant of an anticholinergic medication.

BOTOX® (botulinum toxin type A) purified neurotoxin complex is indicated for the following <u>cosmetic indications</u>:

- BOTOX® is indicated for the temporary improvement in the appearance of upper facial rhytides (glabellar lines, crow's feet and forehead lines) in adults.

- BOTOX® is indicated for the temporary treatment of glabellar lines associated with corrugator and/or procerus muscle activity in adult patients below 65 years of age.

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.

BOTOX® should only be given by physicians or healthcare providers 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.

Route of Administration:
Intramuscular injection. May be subcutaneous injection for blepharospasm. Intradermal for primary hyperhidrosis of axillae. Intradetrusor use for bladder dysfunction only.

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. 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.

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.

Dilution Table for 50 Unit, 100 Unit, and 200 Unit Vials:

Diluent Added (0.9% Sodium Chloride Injection)	**50 Unit Vial** Resulting dose in U per 0.1 mL	**100 Unit Vial** Resulting dose in U per 0.1 mL	**200 Unit Vial** Resulting dose in U per 0.1 mL
0.5 mL	10.00 U	20.00 U	40.00 U
1.0 mL	5.00 U	10.00 U	20.00 U
2.0 mL	2.50 U	5.00 U	10.00 U

4.0 mL	1.25 U	2.50 U	5.00 U
8.0 mL	NA	1.25 U	2.50 U
10.0 mL	NA	1.00 U	2.00 U

Note: These dilutions are calculated for an injection volume of 0.1 mL. A decrease or increase in the BOTOX® dose is also possible by administering a smaller or larger injection volume - from 0.05 mL (50% decrease in dose) to 0.15 mL (50% increase in dose).

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.

Lack of Response:

There are several potential explanations for a diminished or absent response to an individual treatment with BOTOX®. These may include:

- inadequate dose selection,
- selection of inappropriate muscles for injection,
- muscles inaccessible to injection,
- underlying structural abnormalities, such as muscle contractures or bone disorders,
- change in pattern of muscle involvement,
- patient perception of benefit compared with initial results,
- inappropriate storage or reconstitution,
- neutralising antibodies to botulinum toxin.

A neutralising antibody is defined as an antibody that inactivates the biological activity of the toxin. In general, the proportion of patients who lose their response to botulinum toxin therapy and have demonstrable levels of neutralising antibodies is less than 5%, though in a long-term juvenile cerebral palsy study, of 117 patients treated with BOTOX®, antibodies were detected in 33/117 (28%) at either 27 or 39 months. Thirty-one of these 33 had been responders, 19/31 (6%) continued to respond, with 7/31 (2%) becoming non-responders, and no data available for 5/31.

The critical factors for neutralising antibody production are the frequency and dose of injection. Tolerance may be observed in some patients treated more frequently than every three months. The potential for neutralising antibody formation may be minimised by injecting with the lowest effective dose given at the longest feasible intervals between injections (injection intervals should typically be no more frequent than three months). When patients do not respond to BOTOX® injections a suggested course of action is: (1) wait the usual treatment interval; (2) consider reasons for lack of response listed above; (3) test the patient's serum for neutralising antibody presence. More than one ineffective treatment course should occur before classification of a patient as a non-responder, because there are patients who continue to respond to therapy despite the presence of neutralising antibodies.

Injection intervals of BOTOX® should generally be no more frequent than every three months. Indication-specific dosage and administration recommendations should be followed. Although data are not available from controlled clinical trials for concurrent treatment of multiple indications, as a practical consideration, in treating adult patients, including when treating for multiple indications, the maximum cumulative dose should generally not exceed 400 Units, in a 3 month interval. In treating paediatric patients, including when treating for multiple indications, the maximum cumulative dose in a 3-month interval should

generally not exceed 10 Units/kg body weight or 340 Units, whichever is lower (refer to indication-specific maximum dosing recommendations). Clinical outcomes, including risks, at higher dosages across all age groups are not fully established.

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 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 medial 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 anaesthetic 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 stabilise 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, localisation 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 rotated toward 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 by an experienced physician or healthcare provider. 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/ 0.1mL and 10 U/ 0.1mL 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 Focal Lower Limb Spasticity

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 needle may be used for superficial muscles, and a 22-gauge needle may be used for deeper musculature. Localisation of the involved muscles with electromyographic guidance, nerve stimulation, or muscle ultrasound 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 or healthcare provider, 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 reinjection may necessitate alterations in the dose of BOTOX® and muscles to be injected.

Focal Upper Limb Spasticity in Adults

The recommended dose for treating upper limb spasticity in adults is up to 400 Units divided among the affected muscles (see Table and Figure below).

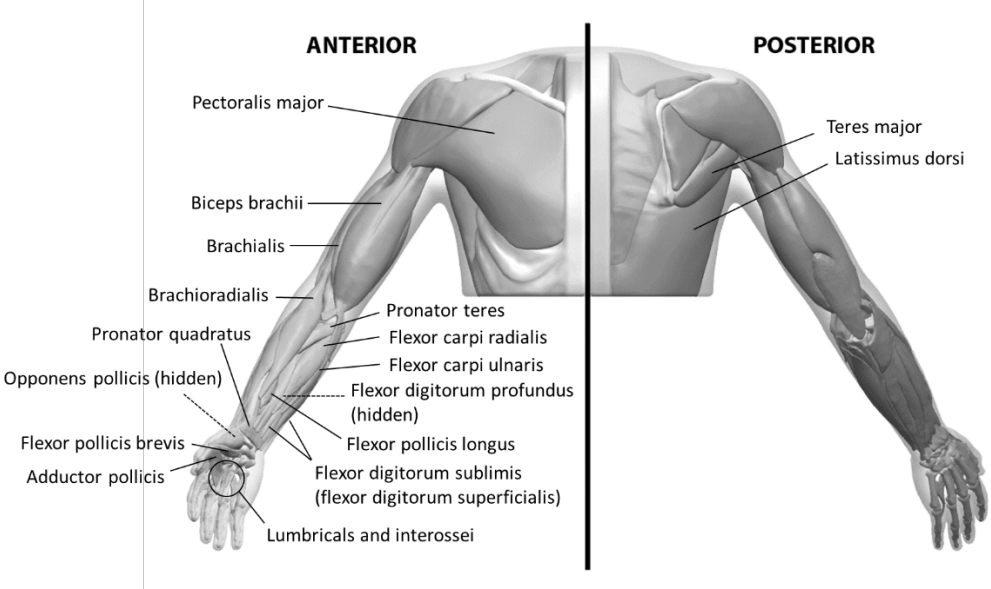
Table **BOTOX® Dosing by Muscle for Adult Upper Limb Spasticity**

Muscle	**Recommended Dose; Number of Sites**
Shoulder*	
Pectoralis major	75 – 125 Units; 3 sites
Teres major	30 – 50 Units; 2 sites
Latissimus dorsi	45 – 75 Units; 3 sites
Elbow	
Biceps brachii	60 – 200 Units; 2 to 4 sites
Brachioradialis	45 – 75 Units; 1 to 2 sites
Brachialis	30 – 50 Units; 1 to 2 sites
Forearm	
Pronator quadratus	10 – 50 Units; 1 site
Pronator teres	15 – 25 Units; 1 site
Wrist	
Flexor carpi radialis	15 – 60 Units; 1 to 2 sites
Flexor carpi ulnaris	10 – 50 Units; 1 to 2 sites
Fingers/Hand	
Flexor digitorum profundus	15 – 50 Units; 1 to 2 sites
Flexor digitorum sublimis/ superficialis	15 – 50 Units; 1 to 2 sites
Lumbricals**	5 – 10 Units; 1 site
Interossei**	5 – 10 Units; 1 site
Thumb	
Adductor pollicis	20 Units; 1 to 2 sites
Flexor pollicis longus	20 Units; 1 to 2 sites
Flexor pollicis brevis	5 – 25 Units; 1 site
Opponens pollicis	5 – 25 Units; 1 site

*When injecting the shoulder muscles in combination, the recommended maximum dose is 250 U.

** When injecting both lumbricals and/or interossei, the recommended maximum dose is 50 U per hand.

Figure Muscles Injected for Adult Upper Limb Spasticity



The maximum dose at a single treatment session of BOTOX® is 400 Units; re-injections should not occur before 12 weeks. Improvement in muscle tone occurred within two weeks, with the peak effect generally seen within four to six weeks.

If it is deemed appropriate by the treating physician or healthcare provider, repeat doses may be administered, when the effect of the previous injection has diminished.

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. The lowest effective dose should be used.

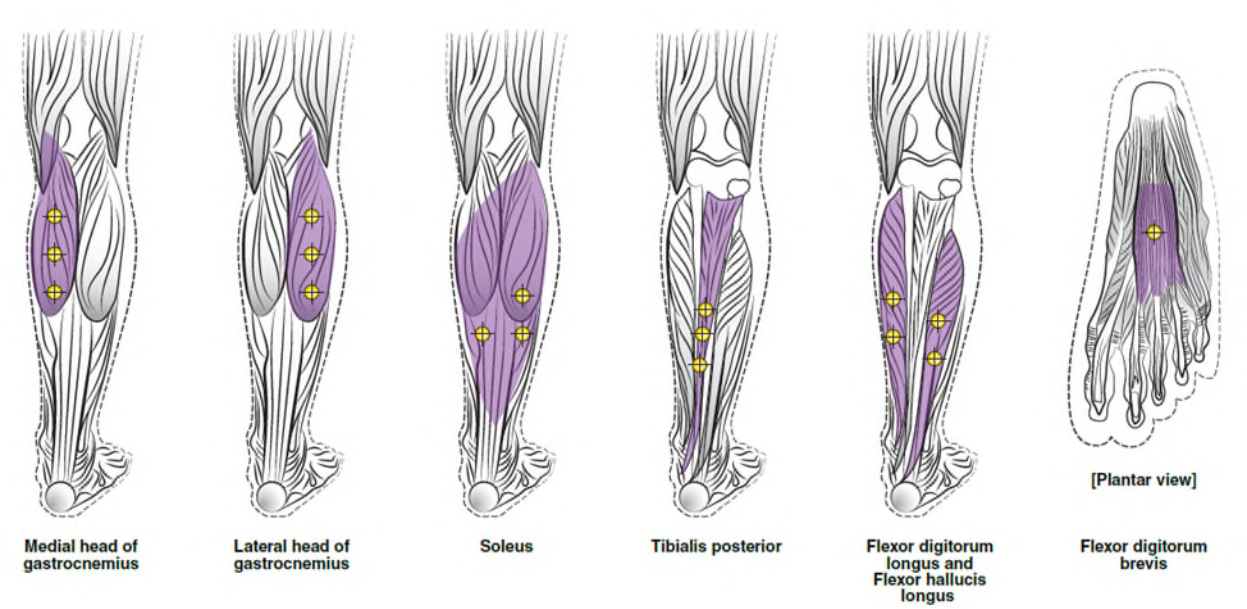
Focal Lower Limb Spasticity in Adults

The recommended dose for treating adult lower limb spasticity involving the ankle and toes is 300 Units to 400 Units divided among affected muscles (gastrocnemius, soleus, tibialis posterior, flexor hallucis longus, flexor digitorum longus and flexor digitorum brevis) (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 in 1 site

Figure Injection Sites for Lower Limb Spasticity



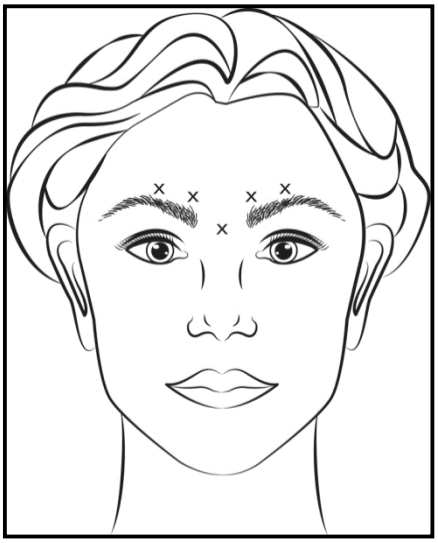
Upper Facial Lines (Glabellar Lines, Crow's Feet and Forehead Lines):

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

Glabellar Lines:

BOTOX® is reconstituted with 0.9% sterile non-preserved saline (100 U 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.

Figure Injection Sites for Glabellar 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:

Injections for Crow's Feet Lines should be given with the needle tip bevel up and oriented away from the eye. Using a 30-33 gauge needle, inject 4 Units/0.1 mL of reconstituted BOTOX® into 3 sites per side (6 total injection points) in the lateral orbicularis oculi muscle for a total of 24 Units/0.6 mL (12 Units per side). The first injection (A) should be made at approximately 1.5-2.0 cm temporal to the lateral canthus and just temporal to the orbital rim. If the lines in the crow's feet region are above and below the lateral canthus, inject per Figure below. Alternatively, if the lines in the crow's feet region are primarily below the lateral canthus, inject per Figure below.

Figure **Injection Sites for Crow's Feet Region Above and Below Lateral Canthus**

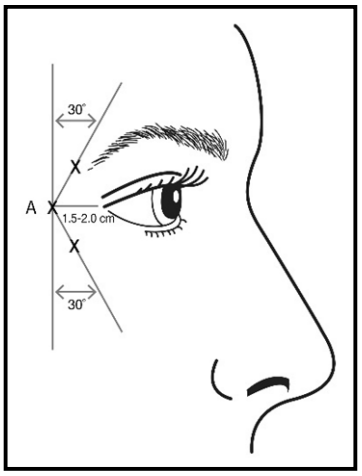
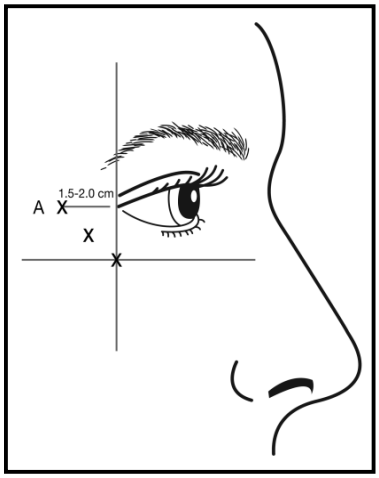


Figure **Injection Sites for Crow's Feet Region Primarily Below Lateral Canthus**



For simultaneous treatment with glabellar lines, the dose is 24 Units for crow's feet lines and 20 Units for glabellar lines (see Glabellar Lines Administration and Figure above), with a total dose of 44 Units.

The median time to onset of crow's feet lines treatment effect is three to four days. The duration of response with BOTOX® for crow's feet lines is up to 5 months. The safety and effectiveness of dosing with BOTOX® more frequently than every 3 months have not been evaluated.

Forehead Lines:

Using a 30 Gauge needle, inject 4 Units/0.1 mL of reconstituted BOTOX® into 5 sites in the frontalis muscle, for a total dose of 20 Units/0.5 mL (see Figure below).

It is recommended to treat forehead lines in conjunction with glabellar lines (see Glabellar Lines Administration and Figure below) to minimize the potential for brow ptosis. The total dose for treatment of forehead lines (20 Units) in conjunction with glabellar lines (20 Units) is 40 Units/1.0 mL.

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.

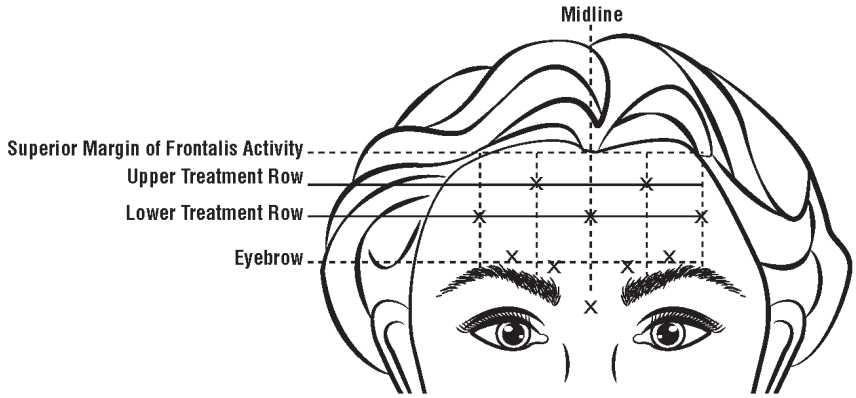
Locate the following horizontal treatment rows by light palpation of the forehead at rest and maximum eyebrow elevation:

- 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:

- 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.

Figure **Injection Sites for Forehead Lines**



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.

For simultaneous treatment with crow's feet lines, the total dose is 64 Units, comprising of 20 Units for forehead lines, 20 Units for glabellar lines, and 24 Units for crow's feet lines (see Crow's Feet Lines Administration).

Hyperhidrosis Of The Axilla:

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). Using a 30 gauge needle, 50 U of BOTOX® (2.0 mL) is injected intradermally, to each axilla evenly distributed in multiple sites approximately 1-2 cm apart.

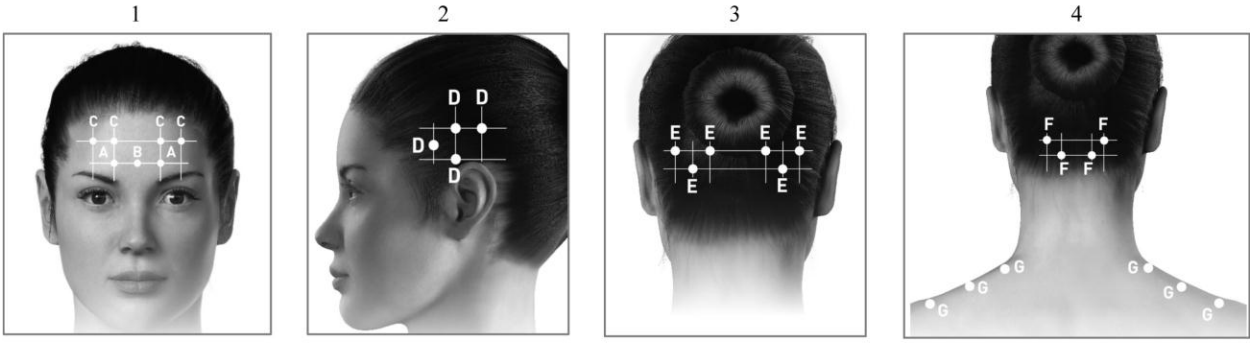
At week 1 BOTOX® treated patients demonstrated 95% treatment responder rate based on gravimetric assessment. At 16 weeks 82% of BOTOX® treated patients were responding to treatment. Approximately 40% of patients received only 1 treatment with BOTOX® and had duration of effect for over 1 year (median time 68 weeks). 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 two months.

Chronic Migraine:

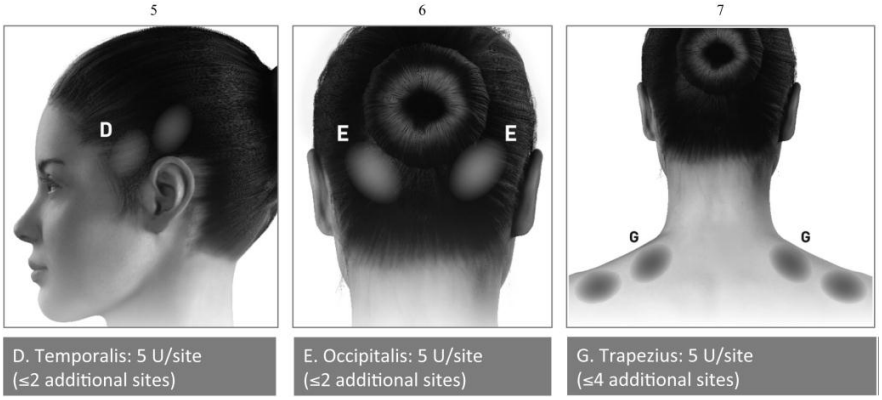
The recommended dilution is 100 U/2 mL, with a final concentration of 5 U per 0.1 mL. The recommended dose for treating chronic migraine is 155 U to 195 U administered intramuscularly (IM) using a sterile 30-gauge, 0.5 inch needle as 0.1 mL (5 U) injections per each site. Injections should be divided 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.

i. Diagrams 1 – 4: Recommended injection sites for minimum 155 U dose for chronic migraine



ii. Diagrams 5-7: Recommended muscle groups for optional additional injections for chronic migraine



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 (31 to 39 sites)**

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

[b] Dose distributed bilaterally for the minimum dose

Bladder Dysfunction (Neurogenic Detrusor Overactivity and Overactive Bladder):

Patients should not have a urinary tract infection prior to treatment. Prophylactic antibiotics 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.

Neurogenic Detrusor Overactivity:

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

The recommended dose is 200 U of BOTOX®.

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

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

Reconstituted BOTOX® (200 U/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.

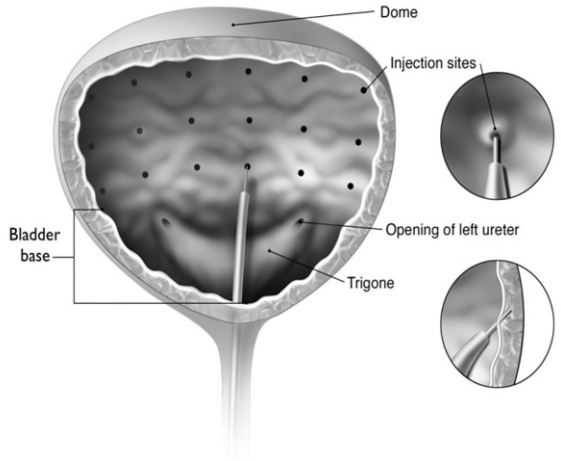
The needle should be inserted approximately 2 mm into the detrusor, and 30 injections of 1mL each (total volume of 30 mL) should be spaced approximately 1 cm apart (see Figure below). For the final injection, approximately 1 mL of sterile normal saline should be injected so the full dose is delivered.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

In the pivotal studies (300 Units and 200 units), none of the 475 neurogenic detrusor overactivity patients with analysed specimens developed the presence of neutralizing antibodies. In patients with analysed 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.

i. Figure : Injection Pattern for Intradetrusor Injections for Treatment of Neurogenic Detrusor Overactivity and Overactive Bladder



<u>Overactive Bladder:</u>

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

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

Reconstituted BOTOX® (100 U/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 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 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).

In the pivotal studies, none of the 615 (0%) patients with analysed specimens developed the presence of serum neutralizing antibodies to Botox®. 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.

CONTRA-INDICATIONS, WARNINGS ETC

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 "units" 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 care should be taken when injecting in or near vulnerable anatomic structures.

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-catheterisation (CIC).
- in patients who are not willing and/or able to initiate catheterisation post-treatment if required.

Warnings and Precautions:

General:

The safe and effective use of BOTOX® 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, oesophagus 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 hemifacial spasm and for the treatment of focal spasticity associated with stroke or paediatric cerebral palsy.

Caution should be used 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(s).

No cases of systemic toxicity have been reported following accidental injection or oral ingestion of BOTOX®. Signs of overdose are not apparent immediately post injection.

As with all biological products, necessary precautions should be taken, adrenaline (epinephrine) and other anaphylactic measures should be available.

There are no known sedative effects of botulinum toxin. Its effects on the neuromuscular junction with consequent effects of muscle activity need to be taken into consideration together with an appraisal of the underlying disease when advising patients on their suitability to drive or to operate machinery.

As is expected for any injection procedure, localized pain, inflammation, paraesthesia, hypoaesthesia, tenderness, swelling/oedema, erythaema, localised 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.

Hypersensitivity Reactions:

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 oedema, and dyspnoea. Some of these reactions have been reported following the use of BOTOX® either alone or in conjunction with other products associated with similar reactions. If such a reaction occurs, further injection should be discontinued and appropriate medical therapy immediately instituted. 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.

Pre-Existing Neurologic Disorders:
Extreme caution should be exercised when administering BOTOX® to individuals with peripheral motor neuropathic diseases (e.g., amyotrophic lateral sclerosis or motor neuropathy) or neuromuscular junctional 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 unrecognised 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 a 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.

Adverse Effects Distant From The Site Of Injection:
Post-marketing 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.

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

Cardiovascular System:
There have been reports of adverse events following administration of BOTOX® 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.

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

Immunogenicity:
Formation of neutralising 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 neutralising antibody formation have not been well characterised. The potential for antibody formation may be minimised by injecting with the lowest effective dose given at the longest feasible intervals between injections.

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.

Blepharospasm:

Reduced blinking following the use of BOTOX® injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defects and corneal ulceration, especially in patients with cranial nerve VII 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 medial 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 closures 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 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 haemorrhages sufficient to compromise retinal circulation have occurred from needle penetrations into the orbit. It is recommended that appropriate instruments to examine and 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:

The most frequently reported severe adverse event associated with the use of botulinum toxin type A in patients with cervical dystonia is dysphagia, with dyspnoea also being reported on occasion. On rare occasions the dysphagia has been severe enough to warrant the insertion of a gastric feeding tube. Patients with cervical dystonia should be informed of the possibility of experiencing dysphagia which may be mild, but could be severe. Dysphagia may persist for two to three weeks after injection, but has been reported to last up to five months post-injection. There have also been at least two reported incidents where subsequent to the finding of dysphagia, patients developed aspiration pneumonia and died.

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 muscle to less than 100 U may decrease the occurrence of dysphagia. Patients with smaller neck muscle mass, or patients who require bilateral injections into the sternocleidomastoid muscle, have been reported to be at greater risk of dysphagia. Dysphagia is attributable to the localised diffusion of the toxin to the esophageal musculature. Patients

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

Paediatric Focal Spasticity and Focal Upper and Lower Limb Spasticity in Adults
BOTOX® is a treatment of focal spasticity that has 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 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 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 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 paediatric patients who have significant neurologic debility, dysphagia, or have a recent history of aspiration pneumonia or lung disease.

Hyperhidrosis:
Patients should be evaluated for potential causes of secondary hyperhidrosis (e.g. hyperthyroidism, pheochromocytoma) to avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of the underlying disease.

Chronic Migraine:
Refer to preceding Warnings and Precautions, including specific information for Cervical Dystonia, Blepharospasm, and Strabismus, due to similar injection sites. Efficacy has not been established for BOTOX® for prophylaxis of episodic migraine (headaches on <15 days per month).

Bladder Dysfunction (Neurogenic Detrusor Overactivity and Overactive Bladder):
Appropriate medical caution should be exercised for performing a cystoscopy.

In patients who are not catheterising, 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 or healthcare provider if they experience difficulties in voiding as catheterisation may be required.

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

Neurogenic Detrusor Overactivity:
In patients with neurogenic detrusor overactivity, autonomic dysreflexia associated with the procedure could occur, which may require prompt medical therapy.

Upper Facial Rhytides (Glabellar Lines, Crow's Feet and Forehead 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. Eyelid oedema has been reported following periocular BOTOX® injection.

Drug Interactions
Theoretically, the effect of botulinum toxin type A may be potentiated by aminoglycoside antibiotics or other medicinal products that interfere with neuromuscular transmission (e.g. neuromuscular blocking agents).

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.

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.

USE IN SPECIFIC POPULATIONS

Pregnancy
There are no adequate data regarding the use of botulinum toxin type A 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 the benefits clearly outweigh the potential risks. If the use of BOTOX® is determined to be warranted during pregnancy, or if the patient becomes pregnant while taking BOTOX®, the patient should be apprised of the potential risks.

Lactation
There is no information on whether BOTOX® is excreted in human milk. The use of BOTOX® during lactation is not recommended.

Paediatric Use:
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 have been very rarely reported in paediatric patients with co-morbidities, predominately with cerebral palsy who received >8 U/kg. Extreme caution should be exercised when treating paediatric patients who have significant neurologic debility, dysphagia, or have a recent history of aspiration pneumonia or lung disease.
The safety and effectiveness of BOTOX® have not been established in children below the age of 2 years for cerebral palsy. In the treatment of blepharospasm, hemifacial spasm, associated focal dystonia and strabismus, in children below 12 years of age have not been demonstrated. The safety and effectiveness

of BOTOX® in the treatment of neurogenic detrusor overactivity and overactive bladder in patients below 18 years of age have not been demonstrated.

Geriatric Use:
Clinical studies of BOTOX® did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently than younger subjects. Other 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.

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=182) 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 where the incidence was higher in patients 65 years of age or older in both the placebo and BOTOX® groups compared to the younger patients. Similarly, no overall difference in effectiveness was observed between these age groups in placebo-controlled pivotal clinical studies.

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.

ADVERSE EVENTS

General:
In general, adverse events occur within the first few days following injection of BOTOX® and, while generally transient, may have a duration of several months, or in rare cases, longer. As is expected for any injection procedure, localised pain, inflammation, paraesthesia, hypoaesthesia, tenderness, swelling/oedema, erythema, localised 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. Local muscle weakness represents the expected pharmacological action of botulinum toxin in muscle tissue. However, weakness of adjacent muscles and/or muscle remote from the site of injection has been reported.

The following events have been reported rarely since the drug has been marketed: skin rash (including erythema multiforme, urticaria and psoriasiform eruption), pruritus and allergic reaction.

There have been rare spontaneous reports of death, sometimes associated with dysphagia, pneumonia and or other significant debility, after treatment with botulinum toxin type A. 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. The exact relationship of these events to BOTOX® is unknown.

Clinical Trials Experience

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 were 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 were 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 were 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 disorder

Common: Dizziness, hypertonia, hypoesthesia, 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

Paediatric Focal Lower Limb Spasticity

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

Focal Upper Limb Spasticity in Adults:

The safety of BOTOX® was evaluated in a total of 1330 patients who received treatment for upper limb spasticity in which 658 patients were from double-blind placebo-control studies. In general, the majority of adverse events reported were mild to moderate in severity and were typically self-limiting.

Gastrointestinal disorders

Common: Nausea

Musculoskeletal and connective tissue disorders

Common: Pain in extremity, muscular weakness

General disorders and administration site conditions

Common: Fatigue, oedema peripheral

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

Focal Lower Limb Spasticity in Adults:

The most frequently reported 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 are listed below.

General disorders and administration site conditions

Common: Peripheral edema

Musculoskeletal and connective tissue disorders

Common: Arthralgia

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

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:

Nervous system disorders

Common: Headache, paresthesia

Eye disorders

Common: Eyelid ptosis

Gastrointestinal disorders

Common: Nausea

Skin and subcutaneous tissue disorders

Common: Erythema, skin tightness

Musculoskeletal and connective tissue disorders

Common: Muscular weakness

General disorders and administration site conditions

Common: Facial pain, injection site edema, ecchymosis, injection site pain, injection site irritation

Crow's Feet:

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

Nervous system disorders

Common: Headache

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

Forehead Lines:

The most frequently reported adverse reactions in double-blind, placebo controlled clinical studies following injections of BOTOX for forehead lines with glabellar lines were reported:

Nervous System Disorders
Common: Headache
Eye Disorders
Common: Eyelid ptosis
Skin and Subcutaneous Tissue Disorders
Common: Brow ptosis, Skin tightness (including Mephisto Sign)

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)

Hyperhidrosis Of The Axilla:

Safety data compiled from double-blind and open-label studies involving 391 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.

Chronic Migraine:

Safety data were 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
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.

Neurogenic Detrusor Overactivity:
The following rates in double-blind studies with BOTOX®200 Units were reported during the complete treatment cycle (median duration of 44 weeks of exposure) of the placebo controlled clinical studies:

Infections and infestations
Very common: Urinary tract infection
Psychiatric disorders
Common: Insomnia
Gastrointestinal disorders
Common: Constipation
Musculoskeletal and connective tissue disorders
Common: Muscular weakness, muscle spasm
Renal and urinary disorders

Very common: Urinary retention
Common: Hematuria*, dysuria*, bladder diverticulum
General disorders and administration site conditions
Common: Fatigue, gait disturbance
Injury, poisoning and procedural complications
Common: Autonomic dysreflexia*, fall
* procedure-related adverse reactions

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

No difference on the MS exacerbation annualized rate (i.e., number of MS exacerbation events per patient-year) was observed (BOTOX®=0.23, placebo=0.20) in the MS patients enrolled in the pivotal studies.

Among patients who were not catheterizing at baseline prior to treatment, catheterization was initiated in 38.9% following treatment with BOTOX®200 Units versus 17.3% on placebo.

Post Approval Study

A placebo-controlled, double-blind post-approval study with BOTOX®100 Units was conducted in Multiple Sclerosis (MS) patients with urinary incontinence due to neurogenic detrusor overactivity. These patients were not adequately managed with at least one anticholinergic agent and not catheterizing at baseline. The lists below presents the most frequently reported adverse reactions during the complete treatment cycle (median duration of 51 weeks of exposure).

Infections and infestations
Very common: Urinary tract infection, bacteriuria
Renal and urinary disorders
Very common: Urinary retention
Common: Dysuria
Investigations
Very common: Residual urine volume*
**elevated PVR not requiring catheterization*
Procedure-related adverse reactions that occurred with a common frequency were dysuria and hematuria.

No difference on the MS exacerbation annualized rate (i.e., number of MS exacerbation events per patient-year) was observed (BOTOX®=0, placebo=0.07).

Catheterization was initiated in 15.2% of patients following treatment with BOTOX®100 Units versus 2.6% on placebo.

Overactive Bladder:

The following rates were reported in double-blind, placebo-controlled, pivotal Phase 3 studies with BOTOX®100 Units during the complete treatment cycle of the clinical trials:

Infections and infestations

Very common: Urinary tract infection
Common: Bacteriuria

Renal and urinary disorders

Very Common: Dysuria
Common: Urinary retention, pollakiuria

Investigations

Common: Residual urine volume*

**elevated PVR not requiring catheterization*

Procedure-related adverse reactions that occurred with a common frequency were dysuria and hematuria.

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.

Post-Marketing Experience:

There have been rare spontaneous reports of death, sometimes associated with dysphagia, 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 oedema, and dyspnoea. 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 following BOTOX® treatment. Some of these patients had risk factors including cardiovascular disease.

New onset or recurrent seizures have also been reported following BOTOX® treatment, 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 oedema has been reported following periocular BOTOX® injection.

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 sections Warnings and Precautions, and Adverse Reactions:
denervation/muscle atrophy; respiratory depression and/or respiratory failure; dyspnoea; aspiration pneumonia; dysarthria; dysphonia; dry mouth; strabismus; peripheral neuropathy, abdominal pain; diarrhoea; nausea; vomiting; pyrexia; anorexia; vision blurred; visual disturbance; hypoacusis; tinnitus; vertigo; facial palsy, facial paresis; brachial plexopathy; radiculopathy; syncope; hypoaesthesia; malaise; myalgia; myasthenia gravis; paraesthesia; rash; erythema multiforme; pruritus; dermatitis psoriasiform; hyperhidrosis; dry eye, localized muscle twitching/involuntary muscle contractions and alopecia, including madarosis.

OVERDOSE

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, generalised and profound neuromuscular paralysis.

Should accidental injection or oral ingestion occur or overdose be suspected, the patients should be medically supervised 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 oesophagus are affected, aspiration may occur which may lead to development of aspiration pneumonia. If the respiratory muscles become paralysed 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.

The entire contents of a vial is below the estimated dose (from primate studies) for toxicity in humans weighing 6kg or greater.

PHARMACOLOGIC PROPERTIES

BOTOX® (botulinum toxin type A) Neurotoxin complex is produced from the fermentation of *Clostridium botulinum* type A (Hall strain) and is purified from the culture solution as an approximately 900 kD molecular weight complex consisting of the neurotoxin and several accessory proteins. The complex is dissolved in sterile sodium chloride solution containing human serum albumin and is sterile filtered (0.2 microns) prior to filling and vacuum-drying.

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 Unit 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®

cannot be compared to or converted into units of any other botulinum toxin activity. The specific activity of BOTOX® is approximately 20 Units/nanogram of neurotoxin protein complex.

Mechanism of Action

Clostridium botulinum type A neurotoxin complex blocks peripheral acetylcholine release at presynaptic cholinergic nerve terminals by cleaving SNAP-25, a protein integral to the successful docking and release of acetylcholine from vesicles situated within the nerve endings.

After injection, there is an initial rapid high-affinity binding of toxin to specific cell surface receptors. This is followed by transfer of the toxin across the plasma membrane by receptor-mediated endocytosis. Finally, the light chain toxin is released into the cytosol where it cleaves SNAP-25. This latter process is accompanied by progressive inhibition of acetylcholine release; clinical signs usually manifest within 2-3 days, with peak effect seen within 5-6 weeks of injection. 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.

Recovery after intramuscular injection takes place normally within 12 weeks as new nerve terminals sprout and allow for reconnection of the neuron with the endplates. However, the sprouts are partially effective and subsequently regress while the primary neuromuscular junction reactivates. After intradermal injection, where the target is the eccrine sweat glands, the effect lasted an average of 6-10 months after the first injection in patients treated with 50 Units per axilla. However, in 27.5% of patients the duration of effect was one year or greater. Recovery of the sympathetic cholinergic nerve endings that innervate sweat glands after intradermal injection with BOTOX® has not been studied.

BOTOX® blocks the release 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 confirmed by pre-clinical and clinical studies.

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

Pharmacokinetics

General characteristics of the active substance:
Distribution studies in rats indicate minimal muscular diffusion of I-botulinum neurotoxin A complex in the gastrocnemius muscle after injection, followed by rapid systemic metabolism and urinary excretion. The amount of radiolabeled material in the muscle declined at a half-life of approximately 10 hours. At the injection site the radioactive material was mainly in the form of large macromolecules, whereas very little of the radioactivity reaching the systemic circulation was TCA-precipitable, suggesting a minimal systemic exposure of toxin following gastrocnemius muscle injection of ^{125}I-botulinum neurotoxin A complex. Within 24 hours of dosing, 60% of the radioactivity was excreted in the urine. The toxin is probably metabolised by proteases and the molecular components cycled through normal metabolic pathways.

Classical absorption, distribution, biotransformation and elimination studies on the active substance have not been performed due to the nature of this product.

Characteristics in patients:
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 fibre 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.

CLINICAL STUDIES

Blepharospasm/Hemifacial Spasm

A randomized, multicenter, double-blind, parallel group clinical study comparing the safety and efficacy of 2 formulations of BOTOX® (active substance derived from different Master Cell Banks, one of which is the current BOTOX® formulation) was conducted in patients with benign essential blepharospasm. The study enrolled patients with previous exposure to BOTOX® and treatment consisted of a single course of injections in the orbicularis oculi muscle of both eyes. The dose (maximum permitted was 100 Units) and injection sites were determined by the investigator based on the patients' response to previous BOTOX® exposure. Patients were observed for a period of 12 weeks after treatment.

There were 98 patients enrolled in the study (48 in the current BOTOX® formulation group). The treatment success rate was measured using a five point rating scale from 0 to 4 where 0 was equal to "none" and 4 equal to "severe" incapacitating spasm of eyelids and possibly other facial muscles. A drop to a score of ≤ 2 in both eyes was considered a treatment success. The primary time point was at week 4. The average dose received by the patients was 33 Units per eye, injected at 3 to 15 sites. Comparable with the earlier BOTOX® formulation, the treatment success rate with the current BOTOX® formulation was approximately 90% at week 4.

In an open study, 56 patients with hemifacial spasm were injected with an initial dose of 10 to 50 Units followed by 22 weeks of observation. Patients who did not show any improvement at Week 4 were re-injected (5 to 50 Units). Subjects were observed at week 2, 4 (if re-treatment required), 6, 14 and 22. The clinical effects were assessed for the various upper and lower facial muscles at each visit.

All 56 patients showed improvement, and 62.5% (35/56) showed marked improvement. When the upper facial muscles were evaluated, improvement was observed in all patients. When the lower facial muscles were evaluated all but 2 patients were considered responders.

Strabismus

Six hundred and seventy-seven adult patients with strabismus treated with one or more injections of BOTOX® were evaluated in a large retrospective case review. Fifty-five percent of these patients improved to an alignment of 10 prism diopters or less when evaluated six months or more following injection.

Cervical Dystonia

A randomized, double blind, placebo-controlled, multicenter study was conducted in patients with cervical dystonia (CD). This study enrolled adult patients with CD and a history of a positive response to BOTOX® treatment. The study was divided into 2 treatment periods, an open label period during which all patients received BOTOX® treatment, with dosage and injection sites determined on an individual basis by the investigator, and a double blind period during which patients considered to be treatment responders in the open label period received either BOTOX® or placebo in a double blind manner. There was an interval of up to 6 weeks between these 2 periods. Overall, up to 360 Units of BOTOX® was administered to patients.

There were 214 patients evaluated in the open label period, of which 170 were randomized into the double blind portion of the study (88 in the BOTOX® group, 82 in the placebo group). Patients were then followed up at 2 week intervals for up to 10 weeks post-treatment. The primary efficacy variables were a change in head position (as measured by the Cervical Dystonia Severity Scale) and the percentage of patients showing any improvement in their CD status as measured by the Physician Global Assessment Scale at 6 weeks post-treatment. Pain, which is an important symptom of CD, was evaluated by patients with respect to its frequency and intensity. In addition, functional disability was assessed by the physician and the patient.

BOTOX® was both clinically and statistically significantly superior to placebo with regards to both primary efficacy variables at 6 weeks. BOTOX® was also statistically significantly better than placebo at reducing intensity and frequency of pain. Significant improvements in physician and patient assessment of functional disability at week 6 were also observed.

An additional double blind, randomized cross over study evaluated the safety and efficacy of 2 formulations of BOTOX® (active substance derived from different Master Cell Banks, one of which is the current BOTOX® formulation) was conducted in patients with cervical dystonia.

The study enrolled patients who had been previously treated with satisfactory results and study treatment consisted of 2 injections separated by a washout period of 8 to 16 weeks. Patients were followed-up for 8 to 16 weeks after each treatment with the primary timepoint at week 6 after each treatment.

There were 135 patients included in this study. The primary efficacy variable was the total severity score on the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS). The secondary efficacy variables were disability pain score (from modified TWSTRS) and global assessment by the patient and physician of cervical dystonia. The results corroborated that maximal clinical improvement following a BOTOX® injection observed at Week 6. The mean decrease in total TWSTRS score represented a 35% improvement from baseline values and the greatest mean decrease in disability pain score represented a 50% decrease from baseline at this timepoint. Global Assessment by both physicians and patients also demonstrated the positive treatment effect with the current BOTOX® formulation, over 85% and 80% reporting treatment success at week 6.

Pediatric Focal Lower Limb Spasticity

Equinus:

A three-month, double-blind, placebo-controlled parallel study was conducted in cerebral palsy children, aged 2 to 16 years with equinus ankle position. Seventy-two were administered 4 Units/kg body weight of BOTOX® into the medial and lateral heads of the gastrocnemius at baseline (2 Units/kg/muscle), for hemiplegic patients and 1 Unit/kg/muscle for diplegic patients) and again at 4 weeks. The cumulative dose of BOTOX® over 4 weeks was 2-4 Units/kg/muscle and overall 8 Units/kg body weight up to a maximum of 200 Units per visit during a 30 day period. BOTOX® was significantly more effective than placebo as assessed by improvement of 2 Units or more on the composite score of Physician's Rating Scale (PRS) of dynamic gait (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® patients versus 25%, 27%, 25% and 32% of placebo patients at weeks 2, 4, 8 and 12, respectively. Of the individual assessments included on the PRS, a significantly greater number of BOTOX® patients versus placebo patients had improvements in gait pattern (weeks 2, 8 and 12) and ankle position (weeks 2, 4, 8 and 12).

In the 39 month long-term, open-label follow up of these patients, the medial and lateral gastrocnemius muscles were injected at a dose of 2 Units/kg/muscle with a maximum total dose of 200 Units of BOTOX® into the medial and lateral heads of the gastrocnemius, and then as needed thereafter. Of the 207 patients evaluated; 155 patients were followed for 12 months, 100 for 18 months, 42 for 2 years and 7 for up to 3 years. The percent of patients who showed an improvement based on the PRS of dynamic gait pattern ranged from 41% to 67% over the 3-year period. Of the individual assessments which were included in the PRS, significant improvements were seen at every visit over the 3-year period.

Focal Upper Limb Spasticity in Adults

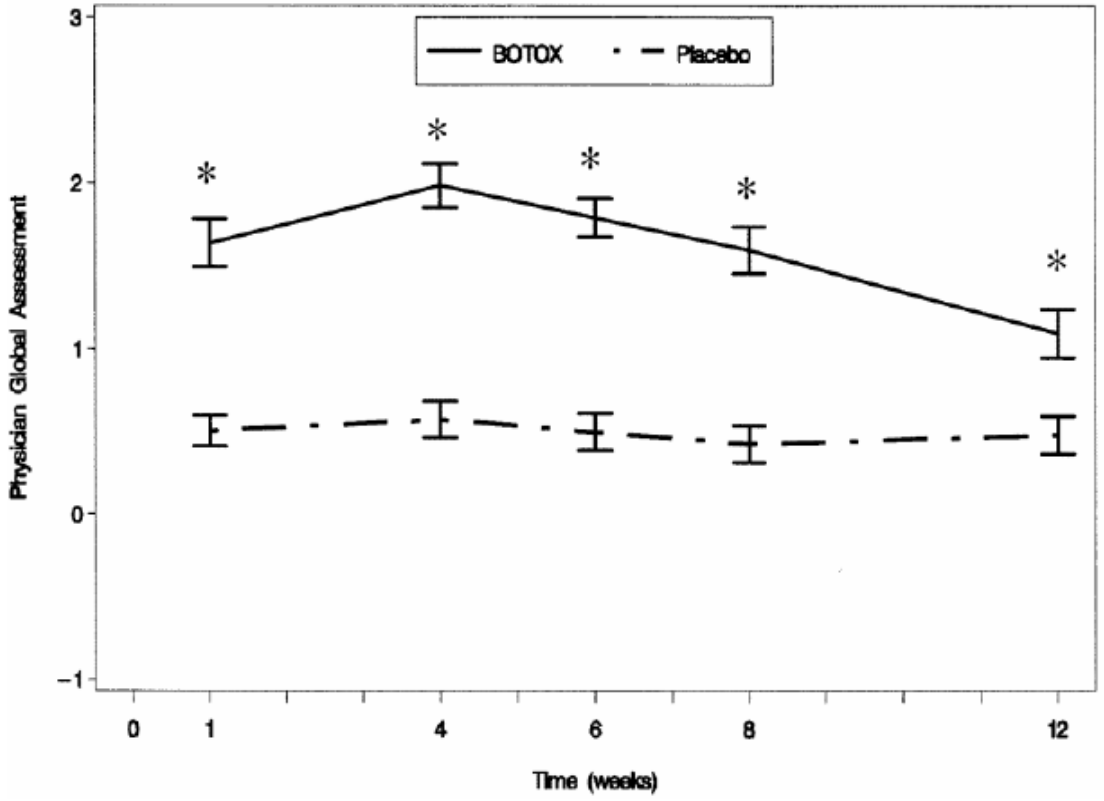
Study 1

Study 1 (study report 191622-008) randomized 126 patients (64 BOTOX® and 62 placebo) with upper limb spasticity (Ashworth score of at least 3 for wrist flexor tone and at least 2 for finger flexor tone) who were at least 6 months post-stroke. BOTOX® (a total dose of 200 to 240 Units) or placebo was injected intramuscularly (IM) into the wrist (flexor carpi radialis, flexor carpi ulnaris), fingers (flexor digitorum profundus, flexor digitorum sublimis) and, if necessary, 1 or both thumb muscles (adductor pollicis and/or flexor pollicis longus).

Patients received 1 treatment and were followed for 12 weeks. The primary efficacy variable was wrist flexor muscle tone at week 6 as measured by the Ashworth score. Statistically and clinically significant differences between BOTOX® and placebo were observed at the first post-treatment visit at week 1 and continuing through weeks 4, 6, 8, and 12 ($p<0.001$). At week 6, the mean change from baseline was -1.66 for BOTOX® treated patients compared with -0.48 in placebo-treated patients ($p<0.001$). There were clinically and statistically significant between-group differences favoring BOTOX® in the mean decrease from baseline for finger flexor muscle tone at all post-treatment visits ($p<0.001$). For patients whose thumbs were treated, there were clinically and statistically significant between-group differences favoring BOTOX® in the mean decrease from baseline at each post-treatment visit ($p=0.017$) except week

6. In this study the Physician Global Assessment evaluated the response to treatment in terms of how the patient was doing in his/her life using a scale from -4=very marked worsening to +4=very marked improvement. At all post-treatment visits, there were statistically significant between-group differences favoring BOTOX® in the mean global assessments of response to treatment (See Figure below). These global assessments correlated well with change from baseline in Ashworth scores, particularly for the wrist and fingers.

Figure



*significant between group difference; p=0.05.

Of the 122 patients that completed the preceding 191622-008 study, 111 enrolled into an open-label extension study (study report 191622-025). These patients received up to 3 additional treatments of 200 Units to 240 Units of BOTOX® injected into wrist, finger and thumb flexor muscles. The mean reduction in wrist flexor muscle tone was sustained over the 4 possible BOTOX® treatment cycles (includes the single treatment in the double-blind study) with mean changes from baseline of –1.4 at Week 6 after the first treatment to – 1.8 at Week 6 after the fourth treatment. The Physician Global Assessment and the Patient/Caregiver Global Assessment of response to treatment showed moderate improvement (~2 points) across the 4 treatment cycles at Week 6. Furthermore, six weeks after each treatment mean improvements in the disability rating for the principal therapeutic intervention target across the 4 treatment cycles were sustained with a mean change from baseline of –0.8 after the first treatment to -1.2 after the fourth treatment.

Study 2:
In a 16 week, randomized, double-blind, placebo-controlled, dose-ranging, parallel-group study, 39 patients with upper limb post-stroke spasticity received 75, 150 or 300 Units of BOTOX® or placebo injected into the elbow and wrist flexor muscles. Patients treated with 300 Units of BOTOX® showed a statistically significant greater reduction in wrist flexor tone compared to placebo ($p \leq 0.044$) as measured on the Ashworth Scale at 2, 4, and 6 weeks post-treatment. Reductions in elbow flexor tone were also significantly greater in the 300 Units BOTOX® group compared to placebo at 2 and 4 weeks post- treatment ($p \leq 0.028$).

Both the Physician and Patient Global Assessments showed a statistically significant improvement in the 75 and 300 Units BOTOX® treatment groups as compared to placebo at 4 and 6 weeks post-treatment ($p \leq 0.035$ and $p \leq 0.044$ respectively) (Study-BTOX-130-8051).

Study 3:
Study 3 (study report BTOX-133/134-8051) compared 3 doses of BOTOX® with placebo and randomized 91 patients (21 BOTOX® 360 Units, 23 BOTOX® 180 Units, 21 BOTOX® 90 Units, and 26 placebo) with upper limb spasticity (expanded Ashworth score of at least 2 for elbow flexor tone and at least 3 for wrist flexor tone) who were at least 6 weeks post-stroke. BOTOX® or placebo was injected IM into the elbow flexors (biceps brachii), wrist flexors (flexor carpi radialis, flexor carpi ulnaris), and finger flexors (flexor digitorum profundus, flexor digitorum sublimis).

Patients were eligible for a second or third treatment at least 12 weeks after the prior treatment if their wrist and/or elbow flexor tone was greater than 2 (expanded Ashworth score). The primary efficacy variable defined a priori was the wrist flexor tone at week 6 as measured by the expanded Ashworth score. All BOTOX® doses produced decreases in wrist flexor tone. At week 6, the mean change from baseline was -1.6, -1.0, -1.2, and -0.7 in the 360 Units, 180 Units, 90 Units, and placebo groups, respectively ($p=0.003$ overall; $p \leq 0.038$ for each BOTOX® group versus placebo pairwise comparison). In addition to week 6, the mean decrease from baseline in wrist flexor tone was statistically significant among groups at the first post-treatment visit at week 1 and at weeks 2, 3, and 9 ($p \leq 0.026$). Pairwise comparisons with the placebo group showed the 360 Units group consistently outperformed all other treatment groups. After the second treatment, BOTOX® treated patients continued to show greater mean decreases in Ashworth scores than placebo-treated patients. Elbow flexor tone reductions from baseline favored all BOTOX® groups over placebo from week 1 through week 12. Finger flexor tone reductions from baseline favored the 180 Units and 360 Units groups over placebo at all visits through week 12. Mean improvement scores for the Physician Global Assessment of response to treatment were significantly greater than placebo for the 360 Units group at Weeks 1 through 9 ($p \leq 0.025$); for the 180 Units group at Weeks 1 through 6 ($p \leq 0.030$); and for the 90 Units group at Week 6 ($p=0.046$).

Study 4:
In a 12-week randomized, double-blind, graduated-dose, parallel-group study, 89 patients with post-stroke upper-limb spasticity received one injection of either 90, 180 or 360 Units of BOTOX® or placebo into the elbow, wrist and finger flexor muscles. Mean decreases in wrist flexor tone as measured by the Ashworth Scale were greater than placebo for all BOTOX® treatment groups through Week 12 except in the 180 Units group, where at Week 12 the results were the same as placebo. Patients treated with 360

Units of BOTOX® showed a statistically significant greater reduction in wrist flexor tone compared to placebo as measured on the Ashworth Scale ($p \leq 0.018$) at 1, 4, and 6 weeks post-treatment. Elbow and finger flexor tone reductions from baseline favored all BOTOX® treatment groups over the placebo group for all visits through Week 12. As compared with the placebo group, mean decreases were significantly greater in the 360 Units BOTOX® group for elbow flexor tone at Weeks 1 and 4 ($p \leq 0.003$) and for finger flexor tone at Weeks 1, 4 and 6 ($p \leq 0.030$) (study report BTOX-418/422-8051).

Results from a 54-week, large, multicenter open-label study evaluating multiple repeated treatments of BOTOX® suggest that the treatment is well tolerated and safe in a population of 279 post-stroke hemiplegic patients with spastic muscles in the upper limb. Up to 5 treatments (of 200 Units to 400 Units of BOTOX® per treatment session) were administered into the elbow, wrist, finger and/or thumb flexor muscles. Only 5.4% (15/279) of patients discontinued the study due to adverse events. There were few treatment-related adverse events, with most of these being mild or moderate in severity and transient in nature. BOTOX® significantly reduced excessive muscle tone in the treated limb. Furthermore, significant improvements from baseline were observed for the Principal Therapeutic Intervention Target, the Physician Global Assessment, and the Patient Global Assessment. Also, the frequency of pain was significantly reduced from baseline with BOTOX® treatment. The response to BOTOX® treatment was sustained over successive treatments without an increase in reports of adverse events. (Study 191622-056)

Study 5:
In a randomized, double-blind, controlled phase 3 study, 124 post-stroke adult patients with upper limb spasticity received either 400 U BOTOX® (240 U in wrist, finger and thumb flexors and 160 U in the elbow flexors; n=61) or 240 U BOTOX® (wrist, finger and thumb flexors and placebo in the elbow flexors; n=63, see Dosing Table below).

EMG, nerve stimulation, or ultrasound techniques were recommended to assist in proper muscle localization for injections. Patients were followed for 12 weeks and then entered the open label phase during which they could receive up to 3 additional treatments of 400 U BOTOX distributed among finger, thumb, wrist, and elbow flexors, forearm pronators, and shoulder adductors/internal rotators. (Study report GSK 207660).

Table BOTOX® Dose and Injection Sites in Study 5

Joint	Muscles	BOTOX® 400 U Dose (Units)	BOTOX® 240 U / Placebo Dose (Units)	Volume (mL)	Number of injection sites (sites/muscle)
Elbow	Biceps brachii	70	Placebo	1.4	2
	Brachialis	45		0.9	1
	Brachioradialis	45		0.9	1
Wrist	Flexor carpi radialis	50	50	1.0	1
	Flexor carpi ulnaris	50	50	1.0	1
Finger	Flexor digitorum profundus	50	50	1.0	1
	Flexor digitorum superficialis	50	50	1.0	1
Thumb	Flexor pollicis longus	20	20	0.4	1

Adductor pollicis	20	20	0.4	1

The responder rate based on the MAS-B score reduction in the elbow flexors at Week 6 after the first treatment (the primary endpoint) was significantly higher in the BOTOX 400 U group (68.9%, 42/61 patients) than in the BOTOX 240 U group (50.8%, 32/63 patients). Significant improvement in the change from baseline in MAS-B elbow score at Week 6 was also observed in the 400 U dose group. During open label, improvements in muscle tone and functional disability were observed.

In addition, in the open-label, 84 patients received BOTOX treatment in the shoulder adductors/internal rotators. The results achieved at Week 6 for the MAS in the shoulder muscles are shown in Table below.

Table Efficacy Results for Shoulder at Week 6 of Open-label Treatment Cycles

	OL Cycle 1 (N=72)	**OL Cycle 2 (N=76)**	**OL Cycle 3 (N=56)**
Mean Baseline Shoulder Muscle Tone on the MAS[a]	3.4	3.3	3.2
Mean Change from Baseline in Shoulder Muscle Tone on the MAS	-0.7	-0.6	-0.5

[a] The MAS is a 6-point scale (0 [no increase in muscle tone], 1, 1+, 2, 3, and 4 [limb rigid in flexion or extension]) which measures the force required to move an extremity around a joint, with a reduction in score representing improvement in spasticity.

Study 6:
Study 6 enrolled 53 post-stroke adult patients with upper limb spasticity. Patients received a single fixed-dose, fixed-muscle treatment of either BOTOX 300 U (150 U elbow; 150 U shoulder), BOTOX 500 U (250 U elbow; 250 U shoulder), or placebo, divided across defined muscles of the elbow and shoulder in a single limb (see Table below). EMG, nerve stimulation, or ultrasound techniques were recommended to assist in proper muscle localization for injections. The duration of follow-up was 12 to 16 weeks (Study report 191622-127).

Table BOTOX® Dose and Injection Sites in Study 6

Joint	**Required Muscle**	**BOTOX 300 U Dose**	**BOTOX 500 U Dose**	**Volume (mL)**	**Number of Injection Sites/Muscle**
Elbow	Biceps brachii	60 U	100 U	2	3
	Brachialis	30 U	50 U	1.5	2
	Brachioradialis	45 U	75 U	1	2
	Pronator teres	15 U	25 U	0.5	1
	Total Elbow	**150 U**	**250 U**		-
Shoulder	Pectoralis major	75 U	125 U	2.5	3
	Teres major	30 U	50 U	1.0	2
	Latissimus dorsi	45 U	75 U	1.5	3
	Total Shoulder	**150 U**	**250 U**		-

Statistically significant improvement in the MAS-B elbow flexor score change from baseline at week 6 (primary endpoint) and at all post-baseline timelines through week 12 were observed for the 500 U BOTOX group compared to placebo. In the 300 U dose group, statistically significant reductions in MAS-B were observed at Weeks 2 and 4, and numerical reduction was observed at all post-baseline timepoints. The proportion of responders (patients with at least a 1-grade improvement) on MAS-B was numerically higher for both BOTOX dose groups at all post baseline visits (Table and Figure below). The CGI score by physician and CGI responder rates were numerically greater in both BOTOX groups compared to placebo indicating overall global improvement.

Table Primary Efficacy Endpoint Results for Elbow Flexors and Shoulder at Week 6 in Study 6 (ITT Population)

	BOTOX 300 U (N=18)	**BOTOX 500 U (N=17)**	**Placebo (N=18)**
Mean Change from Baseline in Elbow Flexor Muscle Tone on the MAS	-1.47	-1.62*	-0.74
MAS Elbow Flexors Responder Rate[a]	72.2%	75.0%	47.1%
Mean Change from Baseline in Shoulder Muscle Tone on the MAS	-1.4	-1.6	-1.4
Mean Shoulder-Specific CGI Score by Physician[b]	1.22	1.21	1.04
Mean CGI score by Physician[c]	1.31	1.21	0.94
CGI by Physician Responder Rate[d]	88.9%	75.0%	64.7%

* Significantly different from placebo ($p \leq 0.05$).

[a] Proportion of patients with MAS score ≥ 1-grade improvement.

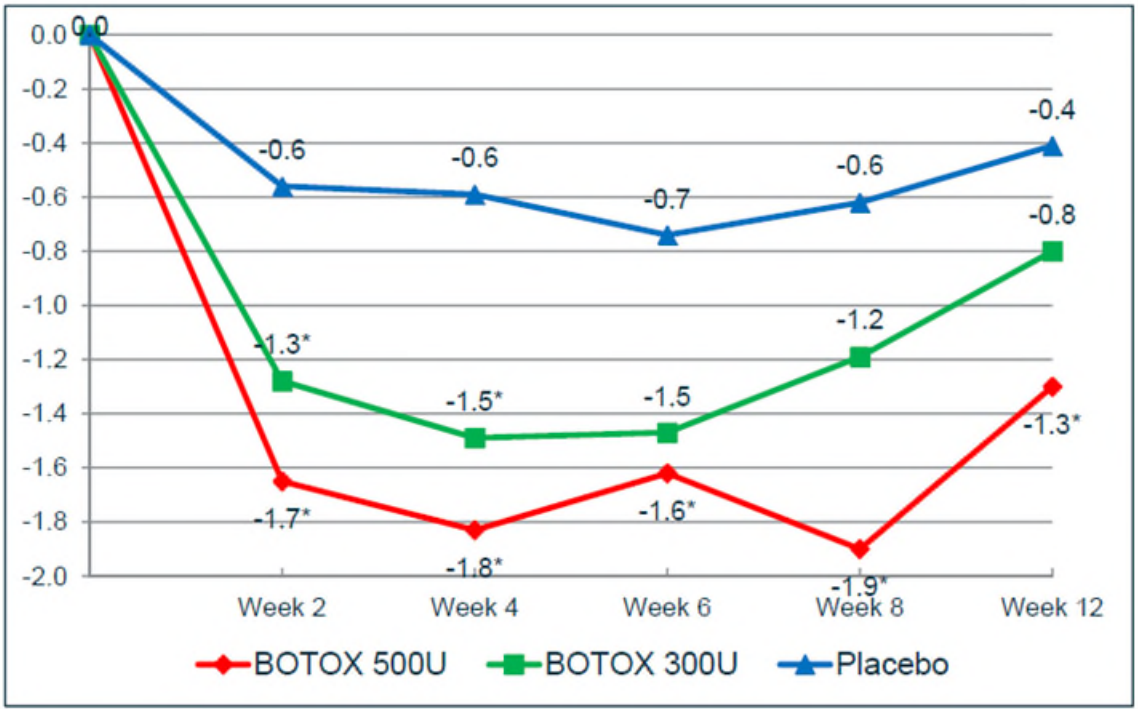
[b] The shoulder-specific Clinical Global Impression of Overall Change by Physician (CGI) evaluates global improvement in the shoulder joint from -4 (very much worsened) to +4 (very much improved).

[c] CGI score evaluates global improvement from -4 (very much worsened) to +4 (very much improved).

[d] Proportion of patients with CGI score ≥ +1.

ITT = intent-to-treat

Figure MAS-B Elbow Score: Mean Change from Baseline by Visit (ITT Population)



ITT = intent-to-treat; MAS-B = Modified Ashworth Scale-Bohannon
*p < 0.05

Study 7:
Study 7 [AGN/HO/SPA/001-191622 (BEST)] included a subgroup of 26 adult post-stroke patients with upper limb spasticity who received up to 2 treatments of BOTOX in up to 3 affected shoulder muscles (pectoralis major with or without teres major and latissimus dorsi). The main results are presented in Table below.

Table Efficacy Results for Shoulder at Week 10 post-2nd injection or Week 24 in Study 10

	BOTOX	**Placebo**
Mean Change from Baseline on REPAS[a]	**(N=20)**	**(N=20)**
Shoulder Muscle Tone	-0.6	-0.2
In Patients with baseline REPAS ≥ 2	-0.7	-0.2
In Patients with baseline REPAS ≥ 3	-1.1	-0.5
Mean GAS score by Physician[b]	**(N=26)**	**(N=23)**
Principal Goal	0.0	-0.8
Secondary Goal	-0.2	-0.9

[a] The REsistance to PAssive movement Scale (REPAS) quantifies resistance to passive movement for passive arm and leg motions and is scored on a scale of 0 (no increase in tone) to 4 (limb rigid in flexion or extension), with a higher score denoting greater resistance to movement. REPAS for shoulder extension is presented here.

[b] Goal Attainment Scale (GAS) is a 6-point scale in which the physician rates goal attainment from -3 (worse than start), -2 (equal to start), -1 (less than expected), 0 (expected goal), +1 (somewhat more than expected) or +2 (much more than expected).

Focal Lower Limb Spasticity in Adults

Study 1

A double-blind, placebo-controlled, randomised, multi-centre Phase 3 clinical study was conducted in adult post-stroke patients with lower limb spasticity affecting the ankle. A total of 120 patients were randomised to receive either BOTOX® (n=58) (total dose of 300 Units) or placebo (n=62).

Significant improvement compared to placebo was observed in the primary endpoint for the overall change from baseline up to week 12 in Modified Ashworth Scale (MAS) ankle score, which was calculated using the area under the curve (AUC) approach. The Modified Ashworth Scale uses a similar scoring system as the Ashworth Scale (see Table below). Significant improvements compared to placebo were also observed for the mean change from baseline in MAS ankle score at individual post-treatment visits at weeks 4, 6 and 8. The proportion of responders (patients with at least a 1 grade improvement) was also significantly higher than in placebo treated patients at these visits. BOTOX® treatment was also associated with significant improvement in the investigator's clinical global impression (CGI) of functional disability compared to placebo. Muscle tone reduction was clinically meaningful, as demonstrated by significant correlations with investigator and patient global assessments.

Table Ashworth Scale and Modified Ashworth Scale (possible scores range from 0 to 4):

Ashworth Scale		**Modified Ashworth Scale (MAS)**	
Score	Definition	Score	Definition
0	No increase in (muscle) tone	0	No increase in muscle tone
1	Slight increase in (muscle) tone, giving a catch (and release) when the limb was moved in flexion or extension	1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion (ROM) when the affected part(s) is (are) moved in flexion or extension
		1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM
2	More marked increase in (muscle) tone but limb easily flexed (or moves easily)	2	More marked increase in muscle tone through most of the ROM, but affected parts easily moved
3	Considerable increase in tone, passive movement difficult	3	Considerable increase in muscle tone, passive movement difficult
4	Limb rigid in flexion or extension	4	Affected part(s) rigid in flexion or extension

Results from the phase 3 study are presented below.

Table Primary and Key Secondary Efficacy Endpoints

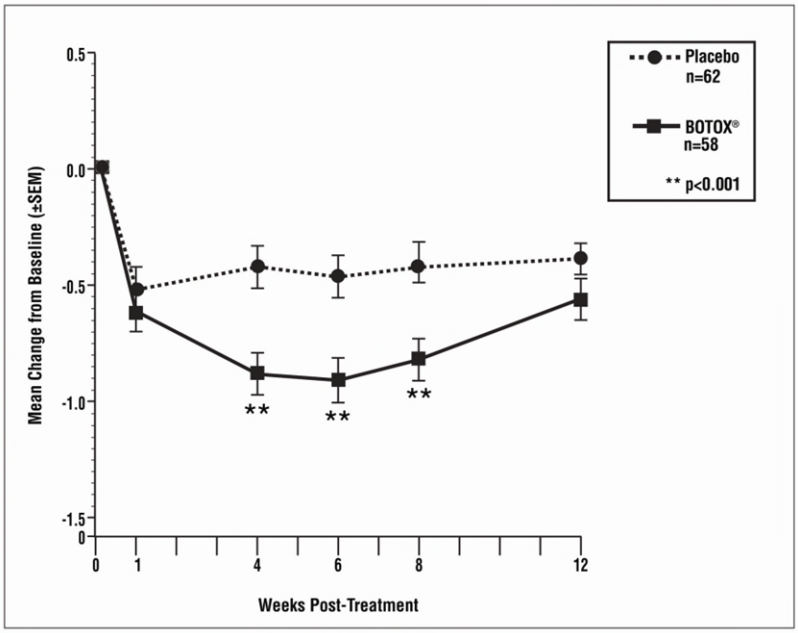
	BOTOX® (N=58)	**Placebo (N=62)**	**P-value**
Mean AUC in MAS Score			
AUC (day 0 to week 12)	-8.5	-5.1	0.006
Mean Change from Baseline in MAS Score			

Baseline	3.28	3.24	
Week 1	-0.61	-0.52	0.222
Week 4	-0.88	-0.43	< 0.001
Week 6	-0.91	-0.47	< 0.001
Week 8	-0.82	-0.43	< 0.001
Week 12	-0.56	-0.40	0.240
Percentage of Responders*			
Week 1	52.6%	38.7%	0.128
Week 4	67.9%	30.6%	< 0.001
Week 6	68.4%	36.1%	< 0.001
Week 8	66.7%	32.8%	< 0.001
Week 12	44.4%	34.4%	0.272

*Patients with at least a 1 grade improvement from baseline in MAS score

A consistent response was observed with re-treatment.

Figure Mean Change from Baseline MAS Ankle Score (±SEM)



Study 2

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 randomized 468 post-stroke patients (233 BOTOX® and 235 placebo) with ankle spasticity (Modified Ashworth Scale [MAS] ankle score of at least 3) who were at least 3 months post-stroke.

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.

Table 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 (see above). 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 below.

Table Primary and Key Secondary Efficacy Endpoints (ITT Population)

	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

ITT = intent-to-treat

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

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

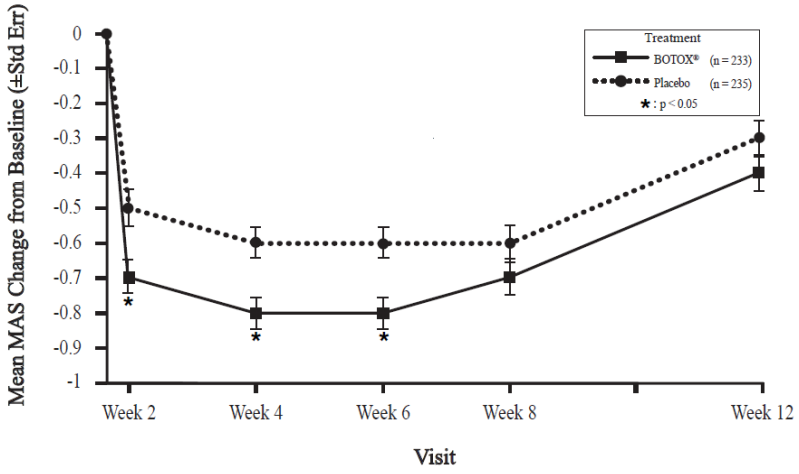
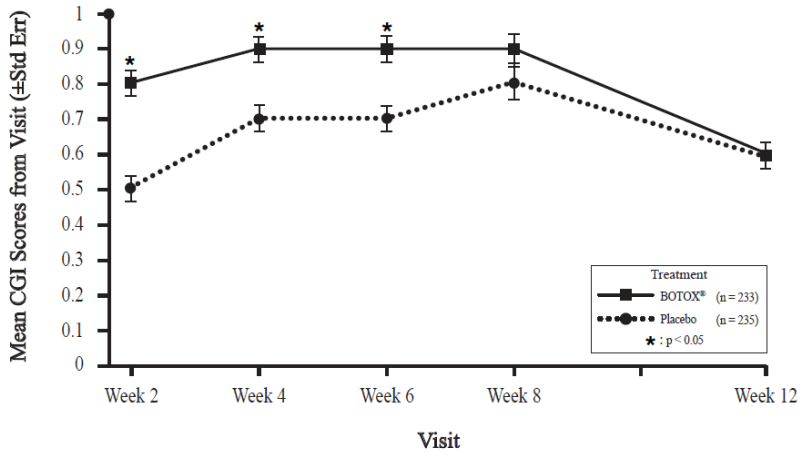


Figure **Clinical Global Impression by Physician for Study 2 – Mean Scores by Visit**



Primary Hyperhidrosis of the Axillae

A double-blind, single-treatment cycle, multicenter clinical study was conducted in patients presenting with persistent bilateral primary axillary hyperhidrosis defined as baseline gravimetric measurement of at least 50 mg spontaneous sweat production in each axilla over 5 minutes at room temperature, at rest. Three hundred and twenty patients were randomized to receive either 50 Units 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. At the primary endpoint, week 4 post-injection, the response rate in the BOTOX® group was 93.8% compared with 35.9% in the placebo group (p<0.001). The incidence of responders among BOTOX® treated patients continued to be significantly higher (p<0.001) than placebo treated patients at all post-treatment time points for up to 16 weeks.

A follow up open-label study enrolled 207 eligible patients who received up to 3 BOTOX® treatments. Overall, 174 patients completed the full 16-month duration of the 2 studies combined (4 month double-blind and 12 month open-label continuation. A high responder rate was seen following each treatment with BOTOX®, with an overall incidence of responders at week 4 post-injection of 91.8% following the

first treatment and 88.2% following the second treatment. The high responder rates seen after the first 2 treatments were maintained at week 16, with an incidence of 86.3% after both the first and second treatments. The mean time to first BOTOX® treatment in this study from the date of BOTOX® treatment in the previous study was 34.5 weeks. A considerable proportion of subjects who received BOTOX® in the preceding study and who also completed this study did not require any further BOTOX® treatments (31.6%). The mean duration of effect, as assessed by calculating the mean time between 2 consecutive treatments, for the first and second treatments is 23.0 weeks.

Another double-blind, placebo-controlled study was conducted in patients with persistent primary axillary hyperhidrosis. Patients could be treated up to 6 times during the study. A total of 322 patients were randomized in a 1:1:1 ratio to treatment in both axillae with 50 Units of BOTOX® (n=104), 75 Units of BOTOX® (n=110), or placebo (n=108). The percentage of responders based on at least a 2 grade decrease from baseline in HDSS or based on a >50% decrease from baseline in axillary sweat production was greater in both 50 Units (54.8%) and 75 Units (49.1%) of BOTOX® groups than in the placebo group (5.6%) ($p< 0.001$), but was not significantly different between the 2 BOTOX® doses.

In an open-label study in an adolescent population between the ages of 12–17 years of age (n=144), the results were comparable to those seen in adult population previously studied (see above).

Overactive Bladder

Two double-blind, placebo-controlled, randomized, 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 randomized to receive either 100 Units of BOTOX® (n=557), or placebo (n=548).

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 Units) 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).

A total of 834 patients were evaluated in a long-term extension study. For all efficacy endpoints, patients experienced consistent response with re-treatments.

The median duration of response following BOTOX® treatment, based on patient request for re-treatment was 166 days (~24 weeks). Qualification for re-treatment required at least 2 urinary incontinence episodes in 3 days. 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).

In the pivotal studies, none of the 615 (0%) patients with analyzed specimens developed the presence of serum neutralizing antibodies to BOTOX®. 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.

Of 1242 patients treated for Overactive Bladder in placebo-controlled registration clinical studies of BOTOX®, 41.4% (n=514) were 65 years of age or older, and 14.7% (n=182) 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 where the incidence was higher in patients 65 years of age or older in both the placebo and BOTOX® groups compared to the younger patients. Similarly, no overall difference in effectiveness was observed between these age groups in placebo-controlled pivotal clinical studies.

Results from the pivotal studies are presented below:

Table **Primary and Secondary Efficacy Endpoints at Baseline and Change from Baseline in the Pooled Pivotal Studies**

Endpoint Timepoint	BOTOX® 100 Units (N=557)	Placebo (N=548)	P-value
Daily Frequency of Urinary Incontinence Episodes*			
Mean Baseline	5.49	5.39	
Mean Change at Week 2	-2.85	-1.21	< 0.001
Mean Change at Week 6	-3.11	-1.22	< 0.001
Mean Change at Week 12[a]	**-2.80**	**-0.95**	**< 0.001**
Proportion with Positive Treatment Response using Treatment Benefit Scale (%)			
Week 2	64.4	34.7	< 0.001
Week 6	68.1	32.8	< 0.001
Week 12[a]	**61.8**	**28.0**	**< 0.001**
Daily Frequency of Micturition Episodes			
Mean Baseline	11.99	11.48	
Mean Change at Week 2	-1.53	-0.78	< 0.001
Mean Change at Week 6	-2.18	-0.97	< 0.001
Mean Change at Week 12[b]	**-2.35**	**-0.87**	**< 0.001**
Daily Frequency of Urgency Episodes			
Mean Baseline	8.82	8.31	
Mean Change at Week 2	-2.89	-1.35	< 0.001
Mean Change at Week 6	-3.56	-1.40	< 0.001
Mean Change at Week 12[b]	**-3.30**	**-1.23**	**< 0.001**
Incontinence Quality of Life Total Score			
Mean Baseline	34.1	34.7	
Mean Change at Week 12[bc]	**+22.5**	**+6.6**	**< 0.001**
King's Health Questionnaire: Role Limitation			
Mean Baseline	65.4	61.2	
Mean Change at Week 12[bc]	**-25.4**	**-3.7**	**< 0.001**
King's Health Questionnaire: Social Limitation			
Mean Baseline	44.8	42.4	
Mean Change at Week 12[bc]	**-16.8**	**-2.5**	**< 0.001**

* Percentage of patients who were dry (without incontinence) at week 12 was 27.1% for the BOTOX® group and 8.4% for placebo group. The proportions achieving at least a 75% and 50% reduction from baseline in urinary incontinence episodes were 46.0% and 60.5% in the BOTOX® group compared to 17.7% and 31.0% in the placebo group, respectively.

[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

Table **Primary and Secondary Efficacy Endpoints at Baseline and Change from Baseline in Study 1**

Endpoint Timepoint	BOTOX® 100 Units (N=280)	Placebo (N=277)	P-value
Daily Frequency of Urinary Incontinence Episodes*			
Mean Baseline	5.47	5.09	
Mean Change at Week 2	-2.85	-1.09	< 0.001
Mean Change at Week 6	-3.05	-1.07	< 0.001
Mean Change at Week 12[a]	**-2.65**	**-0.87**	**< 0.001**
Proportion with Positive Treatment Response using Treatment Benefit Scale (%)			
Week 2	64.5	32.6	< 0.001
Week 6	66.9	34.7	< 0.001
Week 12[a]	**60.8**	**29.2**	**< 0.001**
Daily Frequency of Micturition Episodes			
Mean Baseline	11.98	11.20	
Mean Change at Week 2	-1.58	-0.79	0.041
Mean Change at Week 6	-1.96	-0.98	< 0.001
Mean Change at Week 12[b]	**-2.15**	**-0.91**	**< 0.001**
Daily Frequency of Urgency Episodes			
Mean Baseline	8.54	7.85	
Mean Change at Week 2	-2.83	-1.34	< 0.001
Mean Change at Week 6	-3.21	-1.45	< 0.001
Mean Change at Week 12[b]	**-2.93**	**-1.21**	**< 0.001**
Incontinence Quality of Life Total Score			
Mean Baseline	36.5	37.3	
Mean Change at Week 12[bc]	**+21.9**	**+6.8**	**< 0.001**
King's Health Questionnaire: Role Limitation			
Mean Baseline	61.2	56.2	
Mean Change at Week 12[bc]	**-24.3**	**-2.4**	**< 0.001**
King's Health Questionnaire: Social Limitation			
Mean Baseline	40.5	39.4	
Mean Change at Week 12[bc]	**-17.3**	**-3.8**	**< 0.001**

* Percentage of patients who were dry (without incontinence) at week 12 was 22.9% for the BOTOX® group and 6.5% for placebo group. 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, respectively.

[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

Table **Primary and Secondary Efficacy Endpoints at Baseline and Change from Baseline in Study 2**

Endpoint Timepoint	BOTOX® 100 Units (N=277)	Placebo (N=271)	P-value
Daily Frequency of Urinary Incontinence Episodes*			
Mean Baseline	5.52	5.70	
Mean Change at Week 2	-2.85	-1.34	< 0.001
Mean Change at Week 6	-3.18	-1.37	< 0.001
Mean Change at Week 12[a]	**-2.95**	**-1.03**	**< 0.001**
Proportion with Positive Treatment Response using Treatment Benefit Scale (%)			
Week 2	64.2	36.8	< 0.001
Week 6	69.3	30.9	< 0.001
Week 12[a]	**62.8**	**26.8**	**< 0.001**
Daily Frequency of Micturition Episodes			
Mean Baseline	12.01	11.77	
Mean Change at Week 2	-1.48	-0.77	0.009
Mean Change at Week 6	-2.40	-0.97	< 0.001
Mean Change at Week 12[b]	**-2.56**	**-0.83**	**< 0.001**
Daily Frequency of Urgency Episodes			
Mean Baseline	9.11	8.78	
Mean Change at Week 2	-2.95	-1.36	< 0.001
Mean Change at Week 6	-3.91	-1.35	< 0.001
Mean Change at Week 12[b]	**-3.67**	**-1.24**	**< 0.001**
Incontinence Quality of Life Total Score			
Mean Baseline	31.7	32.1	
Mean Change at Week 12[bc]	**+23.1**	**+6.3**	**< 0.001**
King's Health Questionnaire: Role Limitation			
Mean Baseline	69.6	66.4	
Mean Change at Week 12[bc]	**-26.5**	**-5.0**	**< 0.001**
King's Health Questionnaire: Social Limitation			
Mean Baseline	49.1	45.4	
Mean Change at Week 12[bc]	**-16.2**	**-1.3**	**< 0.001**

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

[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

Figure **Mean Change from Baseline in Daily Frequency of Urinary Incontinence Episodes During Treatment Cycle 1 in Pooled Pivotal Studies**

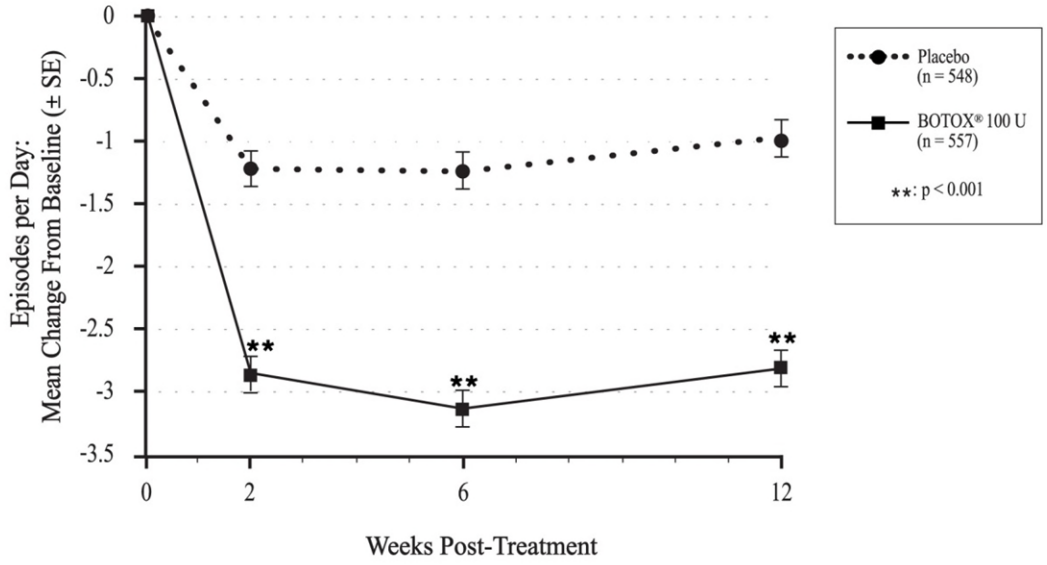


Figure **Mean Change from Baseline in Daily Frequency of Urinary Incontinence Episodes During Treatment Cycle 1 in Study 1**

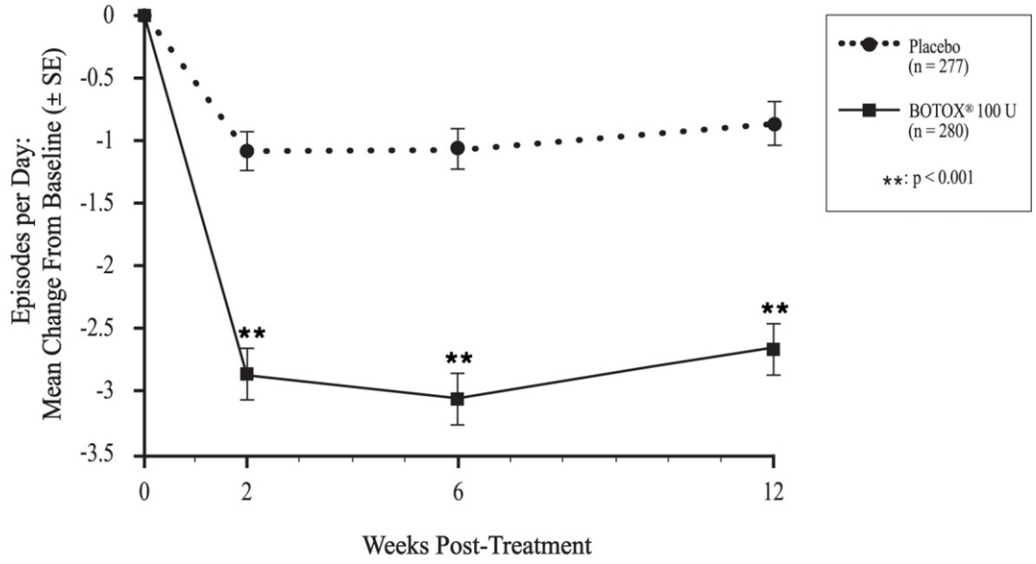
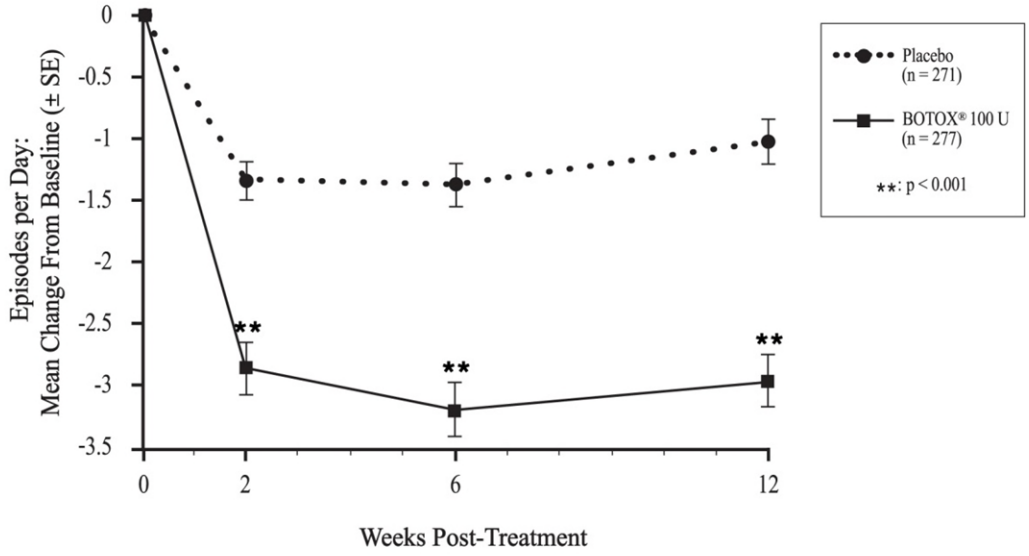


Figure **Mean Change from Baseline in Daily Frequency of Urinary Incontinence Episodes During Treatment Cycle 1 in Study 2**



Adult 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 Units of BOTOX® (n=227), 300 Units 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 Units and 300 Units) at the primary efficacy time point at week 6, including the percentage of dry patients. 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. Significant improvements in patient reported incontinence specific health-related quality of life scores as measured by the Incontinence Quality of Life questionnaire (I-QOL) (including avoidance limiting behavior, psychosocial impact and social embarrassment) were also observed. These primary and secondary endpoints are shown in Tables below and Figure below. No additional benefit of BOTOX® 300 Units over 200 Units was demonstrated.

Table **Primary and Secondary Endpoints at Baseline and Change from Baseline in Study 1**

	BOTOX® 200 Units (N=135)	**Placebo (N=149)**	**p-values**

Weekly Frequency of Urinary Incontinence*			
Mean Baseline	32.3	28.3	
Mean Change at Week 2	-16.9	-8.6	p=0.008
Mean Change at Week 6[a]	**-21.0**	**-8.8**	**p<0.001**
Mean Change at Week 12	-20.8	-8.3	p<0.001
Maximum Cystometric Capacity (mL)			
Mean Baseline	252.3	256.0	
Mean Change at Week 6[b]	**+151.2**	**+15.5**	**p<0.001**
Maximum Detrusor Pressure during 1st Involuntary Detrusor Contraction (cmH_20)			
Mean Baseline	51.3	50.9	
Mean Change at Week 6[b]	**-35.1**	**-2.4**	**p<0.001**
Incontinence Quality of Life Total Score[c,d]			
Mean Baseline	33.95	35.06	
Mean Change at Week 6[b]	**+26.90**	**+10.81**	**p<0.001**
Mean Change at Week 12	+31.42	+9.05	p<0.001

* Percentage of dry patients (without incontinence) throughout week 6 was 36.3% (200 Unit BOTOX® group) and 10.1% (placebo)

[a] Primary endpoint

[b] Secondary endpoints

[c] I-QOL total score scale ranges from 0 (maximum problem) to 100 (no problem at all).

[d] In the pivotal studies, the pre-specified minimally important difference (MID) for I-QOL total score was 8 points based on MID estimates of 4-11 points reported in neurogenic detrusor overactivity patients.

Table Primary and Secondary Endpoints at Baseline and Change from Baseline in Study 2

	BOTOX® 200 Units (N=92)	**Placebo (N=92)**	**p-values**
Weekly Frequency of Urinary Incontinence*			
Mean Baseline	32.5	36.7	
Mean Change at Week 2	-18.8	-9.7	p<0.001
Mean Change at Week 6[a]	**-21.8**	**-13.2**	**p=0.002**
Mean Change at Week 12	-20.5	-12.2	p=0.002
Maximum Cystometric Capacity (mL)			
Mean Baseline	247.3	249.4	
Mean Change at Week 6[b]	**+157.0**	**+6.5**	**p<0.001**
Maximum Detrusor Pressure during 1st Involuntary Detrusor Contraction (cmH_20)			
Mean Baseline	51.7	41.5	
Mean Change at Week 6[b]	**-28.5**	**+6.4**	**p<0.001**
Incontinence Quality of Life Total Score[c,d]			
Mean Baseline	37.46	35.72	
Mean Change at Week 6[b]	**+24.43**	**+11.71**	**p<0.001**
Mean Change at Week 12	+25.08	+8.56	p<0.001

* Percentage of dry patients (without incontinence) throughout week 6 was 38.0% (200 Unit BOTOX® group) and 7.6% (placebo)

[a] Primary endpoint

[b] Secondary endpoints

[c] I-QOL total score scale ranges from 0 (maximum problem) to 100 (no problem at all).

[d] In the pivotal studies, the pre-specified minimally important difference (MID) for I-QOL total score was 8 points based on MID estimates of 4-11 points reported in neurogenic detrusor overactivity patients.

Table **Primary and Secondary Endpoints at Baseline and Change from Baseline in Pooled Pivotal Studies (Studies 1 and 2)**

	BOTOX® 200 Units (N=227)	**Placebo (N=241)**	**p-values**
Weekly Frequency of Urinary Incontinence*			
Mean Baseline	32.4	31.5	
Mean Change at Week 2	-17.7	-9.0	p<0.001
Mean Change at Week 6[a]	**-21.3**	**-10.5**	**p<0.001**
Mean Change at Week 12	-20.6	-9.9	p<0.001
Maximum Cystometric Capacity (mL)			
Mean Baseline	250.2	253.5	
Mean Change at Week 6[b]	**+153.6**	**+11.9**	**p<0.001**
Maximum Detrusor Pressure during 1st Involuntary Detrusor Contraction (cmH_20)			
Mean Baseline	51.5	47.3	
Mean Change at Week 6[b]	**-32.4**	**+1.1**	**p<0.001**
Incontinence Quality of Life Total Score[c,d]			
Mean Baseline	35.37	35.32	
Mean Change at Week 6[b]	**+25.89**	**+11.15**	**p<0.001**
Mean Change at Week 12	+28.89	+8.86	p<0.001

* Percentage of dry patients (without incontinence) throughout week 6 was 37.0% for the 200 Unit BOTOX® group, and 9.1% for placebo, respectively.

[a] Primary endpoint

[b] Secondary endpoints

[c] I-QOL total score scale ranges from 0 (maximum problem) to 100 (no problem at all).

[d] In the pivotal studies, the pre-specified minimally important difference (MID) for I-QOL total score was 8 points based on MID estimates of 4-11 points reported in neurogenic detrusor overactivity patients.

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

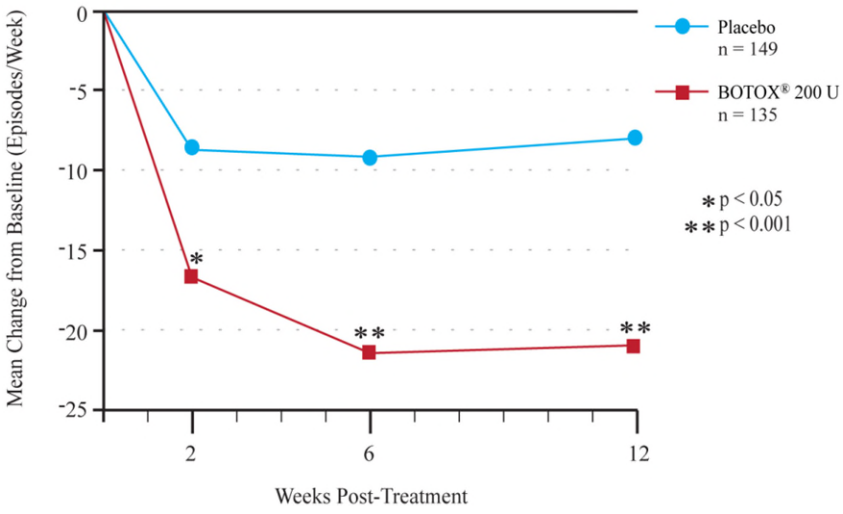


Figure **Mean Change from Baseline in Weekly Frequency of Urinary Incontinence Episodes During Treatment Cycle 1 in Study 2**

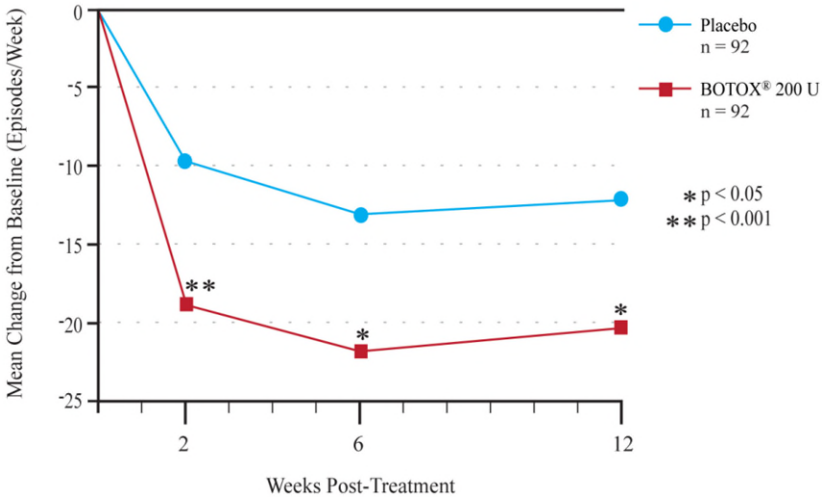
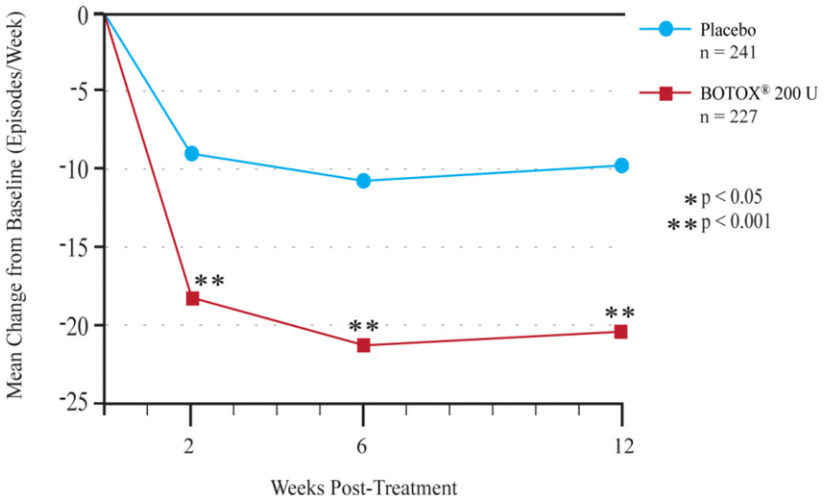


Figure **Mean Change from Baseline in Weekly Frequency of Urinary Incontinence Episodes During Treatment Cycle 1 in Pooled Pivotal Studies (Studies 1 and 2)**



The median duration of response in the two pivotal studies, based on patient request for re-treatment, 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).

For all efficacy endpoints, patients experienced consistent response with re-treatment.

In the pivotal studies (300 Units and 200 Units), 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.

POST APPROVAL STUDY (117)

A placebo controlled, double-blind post-approval study was conducted in multiple sclerosis (MS) patients with urinary incontinence due to neurogenic detrusor overactivity who were not adequately managed with at least one anticholinergic agent and not catheterizing at baseline. These patients were randomized to receive either 100 Units of BOTOX® (n=66) or placebo (n=78).

Significant improvements compared to placebo in the primary efficacy variable of change from baseline in daily frequency of incontinence episodes were observed for BOTOX® (100 Units) at the primary efficacy time point at week 6, including the percentage of dry patients. Significant improvements in urodynamic parameters, and Incontinence Quality of Life questionnaire (I-QOL), including avoidance limiting behavior, psychosocial impact and social embarrassment were also observed (see Table below).

Table Primary and Secondary Endpoints at Baseline and Change from Baseline in Post Approval Study (117)

	BOTOX® 100 Units (N=66)	**Placebo (N=78)**	**p-values**
Daily Frequency of Urinary Incontinence*			
Mean Baseline	4.2	4.3	
Mean Change at Week 2	-2.9	-1.2	p<0.001
Mean Change at Week 6[a]	**-3.3**	**-1.1**	**p<0.001**
Mean Change at Week 12	-2.8	-1.1	p<0.001
Maximum Cystometric Capacity (mL)			
Mean Baseline	246.4	245.7	
Mean Change at Week 6[b]	**+127.2**	**-1.8**	**p<0.001**
Maximum Detrusor Pressure during 1st Involuntary Detrusor Contraction (cmH_20)			
Mean Baseline	35.9	36.1	
Mean Change at Week 6[b]	**-19.6**	**+3.7**	**p=0.007**
Incontinence Quality of Life Total Score[c,d]			
Mean Baseline	32.4	34.2	
Mean Change at Week 6[b]	**+40.4**	**+9.9**	**p<0.001**
Mean Change at Week 12	+38.8	+7.6	p<0.001

* Percentage of dry patients (without incontinence) throughout week 6 was 53.0% (100 Unit BOTOX® group) and 10.3% (placebo)

[a] Primary endpoint

[b] Secondary endpoints

[c] I-QOL total score scale ranges from 0 (maximum problem) to 100 (no problem at all).

[d] The pre-specified minimally important difference (MID) for I-QOL total score was 11 points based on MID estimates of 4-11 points reported in neurogenic detrusor overactivity patients.

The median duration of response in Post Approval Study, based on patient request for re-treatment, was 362 days (~52 weeks) for BOTOX® 100 Unit dose group compared to 88 days (~13 weeks) with placebo.

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 during a 28-day baseline, had ≥15 headache days, with 50% being migraine/probable migraine, and ≥4 headache episodes were studied in 2 phase 3 clinical trials. These patients were randomized to placebo or to 155 Units-195 Units BOTOX® injections every 12 weeks, for the 2-cycle, double-blind phase. They could receive 3 additional open-label cycles for a maximum of 5 injection cycles. Patients were allowed to use acute headache treatments (65.5% overused acute treatments during the baseline period). BOTOX® treatment demonstrated statistically significant ($p<0.001$) and clinically meaningful improvements from baseline compared to placebo for 50% reduction in headache days, mean frequency of moderate/severe headache days and total cumulative hours of headache on headache days (see Table below).

Results of the Headache Impact Test (HIT-6) and Migraine-Specific Quality of Life (MSQ) questionnaires indicated BOTOX® treatment showed improved functioning, vitality, psychological distress and overall quality of life.

Table Week 24 (Primary Timepoint) Key Efficacy Endpoints for Pooled Phase 3 Studies

Efficacy per 28 days	Pooled Studies 191622-079 & 191622-080		
	BOTOX® (N=688)	Placebo (N=696)	p- value
Change from baseline in frequency of headache days	-8.4	-6.6	<0.001
Change from baseline in frequency of migraine/probable migraine days	-8.2	-6.2	<0.001
Change from baseline in number of moderate/severe headache days	-7.7	-5.8	<0.001
Change from baseline in total cumulative hours of headache on headache days	-119.67	-80.49	<0.001
Change from baseline in frequency of headache episodes	-5.2	-4.9	0.009
Proportion of patients with severe HIT-6 category scores	67.6%	78.2%	<0.001
Change from baseline in total HIT-6 scores	-4.8	-2.4	<0.001
Percentage of patients with 50% reduction in headache days	47.1%	35.1%	<0.001

Table Week 24 (Primary Timepoint) Key Efficacy Endpoints for Phase 3 Studies

Efficacy per 28 days	Study 191622-079			Study 191622-080		
	BOTOX® (N=341)	Placebo (N=338)	p-value	BOTOX® (N=347)	Placebo (N=358)	p-value
Change from baseline in frequency of headache days	-7.8	-6.4	0.006	-9.0	-6.7	<0.001
Change from baseline in frequency of migraine/probable migraine days	-7.6	-6.1	0.002	-8.7	-6.3	<0.001
Change from baseline in number of moderate/severe headache days	-7.2	-5.8	0.004	-8.3	-5.8	<0.001
Change from baseline in total cumulative hours of headache on headache days	-106.70	-70.40	0.003	-132.41	-90.01	<0.001
Change from baseline in frequency of headache episodes	-5.2	-5.3	0.344	-5.3	-4.6	0.003
Proportion of patients with severe HIT-6 category scores	68.9%	79.9%	0.001	66.3%	76.5%	0.003
Change from baseline in total HIT-6 scores	-4.7	-2.4	<0.001	-4.9	-2.4	<0.001
Percentage of patients with 50% reduction in headache days	43.5%	36.0%	0.082	50.5%	34.4%	<0.001

Upper Facial Rhytides

Glabellar Lines

In two multicenter, double-blind, placebo-controlled, parallel-group studies of identical design, patients with moderate to severe glabellar lines evaluated at maximum frown were randomized to receive BOTOX® (n=405) or placebo (n=132). In these studies, the severity of glabellar lines was significantly reduced for up to 120 days in the BOTOX® group compared to the placebo group as measured by investigator rating of glabellar line severity at maximum frown and at rest, and by subject's global assessment of change in appearance of glabellar lines. Thirty days after injection, 80% of BOTOX® treated patients were considered by investigators as treatment responders (glabellar line severity score of mild or none), and 89% of patients felt they had moderate or better improvement, compared to 3.0% and 6.8% of placebo-treated patients respectively.

A third, open-label study was also conducted to support the continued efficacy of repeat BOTOX® injections. At the completion of the double-blind studies, patients were able to enter this open-label phase with repeat treatments given at 120 day intervals. Therapeutic effect was maintained over the three injection cycles assessed with results showing increased efficacy following multiple injection sessions.

Forehead Lines

822 patients with moderate to severe forehead lines (FHL) and glabellar lines (GL) seen at maximum contraction, either alone (N=254, Study 1) or also with moderate to severe crow's feet lines (CFL) seen at maximum smile (N=568, Study 2), were enrolled and included in the primary populations for analyses of

all primary and secondary efficacy endpoints. In the clinical studies, forehead lines were treated in conjunction with glabellar lines.

For both investigator and patient assessments, the proportion of patients achieving none or mild forehead lines seen at maximum eyebrow elevation following BOTOX® injections was greater than patients treated with placebo at day 30, the timepoint of the primary efficacy endpoint (Table below). The proportions of patients achieving at least a 1-grade improvement in forehead line severity from baseline at rest, and achieving none or mild upper facial line severity at maximum contraction are also provided.

Table Day 30: Investigator and Patient Assessment of Forehead Lines and Upper Facial Lines at Maximum Contraction and Rest

Clinical Study	Endpoint	BOTOX®	Placebo	BOTOX®	Placebo
		Investigator Assessment		Patient Assessment	
Study 191622-142 40 U (20 U forehead lines + 20 U glabellar lines)	Forehead Lines at Max Contraction[a]	94.8% (184/194)	1.7% (1/60) p < 0.0005	87.6% (170/194)	0.0% (0/60) p < 0.0005
	Forehead Lines at Rest[b]	86.2% (162/188)	22.4% (13/58) p < 0.0001	89.7% (174/194)	10.2% (6/59) p < 0.0001
Study 191622-143 40 U (20 U forehead lines + 20 U glabellar lines)	Forehead Lines at Max Contraction[a]	90.5% (201/222)	2.7% (3/111) p < 0.0005	81.5% (181/222)	3.6% (4/111) p < 0.0005
	Forehead Lines at Rest[b]	84.1% (185/220)	15.9% (17/107) p < 0.0001	83.6% (184/220)	17.4% (19/109) p < 0.0001
Study 191622-143 64 U (20 U forehead lines + 20 U glabellar lines + 24 U crow's feet lines)	Forehead Lines at Max Contraction[a]	93.6% (220/235)	2.7% (3/111) p < 0.0005	88.9% (209/235)	3.6% (4/111) p < 0.0005
	Upper Facial Lines at Max Contraction[c]	56.6% (133/235)	0.9% (1/111) p < 0.0001	n/a	

[a] Proportion of patients achieving none or mild FHL severity at maximum eyebrow elevation
[b] Proportion of patients with at least a 1-grade improvement from baseline of FHL severity at rest
[c] Proportion of responders defined as the same patient achieving none or mild in forehead lines, glabellar lines, and crow's feet lines for each facial region at maximum contraction

A total of 116 and 150 patients received 3 cycles over 1 year of BOTOX® 40 Units (20 Units FHL with 20 Units GL) and 64 Units (20 Units FHL, 20 Units GL, and 24 Units CFL), respectively. The response rate for FHL improvement was similar across all treatment cycles.

Using the Facial Lines Outcomes (FLO-11) Questionnaire, improvements in patient-reported perceptions of how bothered they were from their forehead lines, looking older than their actual age, and attractiveness were observed in a significantly (p<0.001) greater proportion of BOTOX® 40 Units (20 Units FHL with 20 Units GL) and 64 Units (20 Units FHL, 20 Units GL, and 24 Units CFL) patients compared to placebo at the primary timepoint of day 30 in Studies 1 and 2 (see Table 52 below).

Table **Responder Rates – Improvement in FLO-11 Items 1, 4, and 5 at Day 30 of Treatment Cycle 1 (Studies 1 and 2)**

Study 1			Study 2			
BOTOX® 20 Units FHL with 20 Units GL) (N=194)	**Placebo (N=60)**	**p-value (40 Units vs. placebo)**	**BOTOX® (20 Units FHL with 20 Units GL) (N=222)**	**BOTOX® (20 Units FHL, 20 Units GL, 24 Units CFL) (N=235)**	**Placebo (N=111)**	**p-value (40 Units vs. placebo and 64 Units vs. placebo)**
Improvement in Impact Item 1 ***(When I look in the mirror I am bothered by my facial lines)***						
83.5% (162/194)	3.3% (2/60)	0.0004	73.0% (162/222)	86.8% (204/235)	10.8% (12/111)	< 0.0001
Improvement in Impact Item 4 ***(I look older than my actual age because of my facial lines)***						
80.4% (156/194)	11.7% (7/60)	< 0.0001	68.9% (153/222)	79.6% (187/235)	9.9% (11/111)	< 0.0001
Improvement in Impact Item 5 ***(My facial lines make me look less attractive than I want to look)***						
84.0% (163/194)	10.0% (6/60)	< 0.0001	70.7% (157/222)	83.0% (195/235)	14.4% (16/111)	< 0.0001

Using the Facial Lines Satisfaction Questionnaire (FLSQ), 78.1% (150/192) of patients in Study 1 and 62.7% (138/220) in Study 2 reported improvements in appearance-related and emotional impacts (as defined by items pertaining to feeling older, negative self-esteem, looking tired, feeling unhappy, looking angry) with BOTOX® 40 Units (20 Units FHL with 20 Units GL) treatment compared to patients treated with placebo 19.0% (11/58) in Study 1 and 18.9% (21/111) in Study 2 at day 30 (p<0.0001 in both studies).

On the same questionnaire, 90.2% (174/193) of patients in Study 1 and 79.2 (175/221, 40 Units), or 86.4% (203/235, 64 Units) in Study 2 reported they were "very satisfied"/ "mostly satisfied" with BOTOX® 40 Units or 64 Units compared to patients treated with placebo (1.7% (1/58), 3.6% (4/110) in Study 1 and Study 2, respectively), at the primary timepoint of day 60 using the FLSQ (p < 0.0001 in both studies).

In the pivotal studies, 3.8% (31/822) of patients were 65 years of age or older. Responder rates in this subgroup were similar to those in the overall population, but comparisons are difficult to make due to the small number of patients.

Crow's Feet Lines

Injection of BOTOX® into the lateral orbital area reduced the severity of wrinkling in this area (crow's feet) for up to 16 weeks. 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 (6-18 unit treatment groups). There was no significant difference between doses. Benefits of a second injection lasted longer than the first.

PRECLINICAL SAFETY DATA

Reproductive and Developmental Toxicity
BOTOX® was not found to be selectively toxic to the embryo or fetus in any species tested. The maternal effect levels for these species occurred at or below the dose levels which induced fetal effects, indicating a lack of selective fetal toxicity. Maternal effects observed at this dosage were primarily due to the anticipated pharmacological actions of BOTOX®. Developmental effects (decreased body weight, delayed ossification) in mouse, rat and rabbit fetuses were observed at dosages that ranged from 0.5 to 16 Units/kg depending on the schedule of injections, daily or periodical. No drug-related gross external, soft tissue or skeletal malformations were observed in mouse, rat or rabbit fetuses at the highest doses tested in the definitive studies.

Animal Toxicology
The following preclinical safety studies of BOTOX® have been performed: Acute toxicity, toxicity on repeated injection, local tolerance, mutagenicity, antigenicity, and human blood compatibility. These studies revealed no special hazard for humans at clinically relevant dose levels. The published intramuscular LD_{50} in monkeys is 39 Units/kg.

Specific preclinical toxicological studies relevant to the BPH (intra- and peri-prostatic injections) and OAB (intradetrusor injections) indications have been conducted. Data from an intraprostatic multiple-dose study in monkeys revealed the development of bladder stones in 1/6 animals dosed with 12 Units/kg BOTOX® and 2/6 animals dosed with 20 Units/kg BOTOX®.

In a single-dose peri-prostatic injection study a bladder stone was observed in 1 of 4 monkeys given two 3.4 Units/kg BOTOX® injections (6.8 Units/kg total) into the prostatic urethra and proximal rectum.

No bladder stones have been observed to date in the completed single dose intradetrusor study in rat and the completed repeat dose intradetrusor toxicology study in monkeys. Bladder stones are an uncommon finding in nonhuman primates. Due to anatomical differences between monkeys and humans in the seminal vesicles and ejaculatory ducts in relationship to the prostate, these effects may be considered species specific and thus not relevant to human risk assessment.

No systemic toxicity was observed following a single intradetrusor injection of <50 Units/kg BOTOX® in rats. To simulate inadvertent injection, a single dose of BOTOX® (~7 Units/kg) was administered into the

prostatic urethra and proximal rectum, the seminal vesicle and urinary bladder wall, or the uterus of monkeys (~3 Units/kg) without adverse clinical effects. In a 9 month repeat dose intradetrusor study (4 injections), ptosis was observed at 24 Units/kg, and mortality was observed at doses ⩾24 Units/kg; no adverse effects were observed at 12 Units/kg.

Juvenile Animal Data

In a study in which juvenile rats received intramuscular injection of BOTOX® (0, 8, 16, or 24 Units/kg) every other week from postnatal day 21 for 12 weeks, changes in bone size/geometry associated with decreased bone density and bone mass were observed at all doses, secondary to limb disuse, lack of muscle contraction, and decreased body weight gain. The changes were less severe at the lowest dose tested, with signs of reversibility at all dose levels. The no-effect dose for adverse developmental effects in juvenile animals (8 Units/kg) is similar to the maximum adult dose (400 Units) and lower than the maximum pediatric dose (340 Units) on a body weight (kg) basis.

Information for Patients Counselling:

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.

How Supplied

BOTOX® is supplied in a single use vial. Each vial contains vacuum-dried *Clostridium botulinum* type A neurotoxin complex in the following size: 50 Units, 100 Units and 200 Units.

Storage Conditions

Unopened vial: Store at 2-8°C in a refrigerator.

Reconstituted vial: Store at 2-8°C in a refrigerator for up to 24 hours prior to use.

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

Shelf life: 3 years

Handling and Disposal

All vials, including expired vials, or equipment used in direct contact with the drug should be disposed of as medical waste. In cases when deactivation of the toxin is desired (e.g., spills), the use of dilute hypochlorite solution (0.5% or 1%) for five minutes is recommended prior to disposal as medical waste.

Manufactured by:
Allergan Pharmaceuticals Ireland, Westport, Co. Mayo, Ireland.

Product Registration Holder:
ABBVIE SDN BHD
Level 9 Menara Lien Hoe
No.8 Persiaran Tropicana
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