NEW ZEALAND DATA SHEET

1. PRODUCT NAME

BOTOX® (botulinum toxin type A) purified neurotoxin complex 50 units (U), 100 units (U) or 200 units (U) powder for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of BOTOX® injection contains either 50 units (U), 100 units (U) or 200 units (U) of botulinum toxin type A as a haemagglutinin complex.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

A sterile, vacuum-dried preparation. Powder for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BOTOX® (botulinum toxin type A) purified neurotoxin complex is indicated:

- for the treatment of overactive bladder with symptoms of urinary incontinence, urgency and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication
- for the treatment of urinary incontinence due to neurogenic detrusor overactivity (e.g. spinal cord injury or multiple sclerosis) in adults who have an inadequate response to or are intolerant of an anticholinergic medication
- for the prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month with headache lasting 4 hours a day or longer, of which at least 8 days are with migraine)
- for the treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VIIth nerve disorders in patients 12 years of age and above
- to reduce the subjective symptoms and objective signs of spasmodic torticollis (cervical dystonia) in adults
- treatment of focal spasticity in children two years and older
- for the treatment of primary hyperhidrosis of the axillae
- for the treatment of focal spasticity in adults
- for the treatment of upper facial rhytides, including forehead, crow’s feet and glabellar lines.

4.2 Dose and method of administration

Route of Administration

Intramuscular injection.

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

May be subcutaneous for blepharospasm.

Intradermal for hyperhidrosis of the axillae.

General

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 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 the refrigerator and use within twenty-four hours. Discard any remaining solution. Do not freeze reconstituted BOTOX®.

Optimum dose levels and the number of injection sites per muscle have not been established for all indications. The exact dosage and number of injection sites should be tailored to the patient's needs based on the size, number and location of muscles involved, severity of the disease, presence of local muscle weakness, response to previous treatment and the patient's medical condition. In general, dosing of BOTOX® should be individualised for each patient and always start with the minimal effective dose. The dosing interval should typically not be more frequent than every three months.

Bladder Dysfunction

Patients should not have an urinary tract infection at the time of treatment. Prophylactic antibiotics should be administered 1 - 3 days pre-treatment, on the treatment day and 1 - 3 days post-treatment. It is recommended that patients discontinue anti-platelet therapy at least 3 days before the injection procedure. Patients on anti-coagulant therapy need to be managed appropriately to decrease the risk of bleeding.

Overactive Bladder

An intravesical instillation of diluted local anaesthetic with or without sedation may be used prior to injection, as 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 sterile saline solution (see **DILUTION TABLE – Table 6**). 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 visualisation for the injections but over-distension should be avoided.

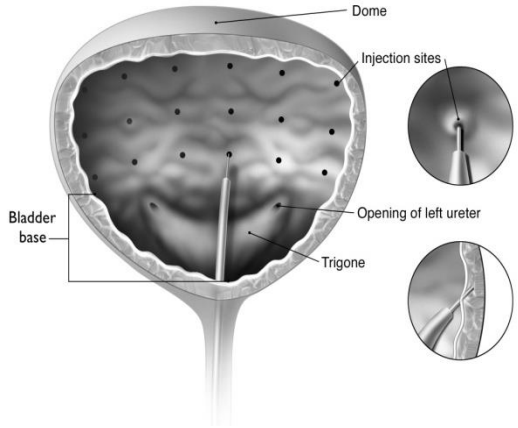
The injection needle should be filled (primed) with approximately 1 mL of reconstituted BOTOX® prior to the start of injections (depending on the needle length) to remove any air.

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 1 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 visualisation 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 re-injection when the clinical effect of the previous injection has diminished (median duration in Phase 3 clinical trials was 166 days [~24 weeks]) but no sooner than 3 months from the prior bladder injection.

Figure 1



Neurogenic Detrusor Overactivity

An intravesical instillation of diluted local anaesthetic with or without sedation, or general anaesthesia, may be used prior to injection, as 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 U vials of BOTOX®, each with 6 mL of 0.9% non-preserved sterile 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 sterile 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 visualisation 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 30 injections of 1 mL (~6.7 U) each (total volume of 30 mL) should be spaced approximately 1 cm apart (see figure 1 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 visualisation should be drained. The patient should be observed for at least 30 minutes post-injection.

Clinical improvement generally occurs within 2 weeks. Patients should be considered for re-injection when the clinical effect of the previous injection has diminished (median duration in Phase 3 clinical trials was 256 - 295 days (36 - 42 weeks) for BOTOX® 200 U) but no sooner than 3 months from the prior bladder injection.

Chronic Migraine

The recommended dose for treating chronic migraine is 155 U to 195 U administered intramuscularly (i.m.) using a 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 Table 1 below. A 1-inch needle may be needed in the neck region for patients with extremely 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. 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 Table 1 below.

The recommended re-treatment schedule is every 12 weeks.

Table 1: BOTOX® Dosing by Muscle for Chronic Migraine

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

[a] *1 IM injection site = 0.1 mL = 5 U BOTOX®*

[b] *Dose distributed bilaterally for minimum dose*

Cervical Dystonia (spasmodic torticollis)

Dosing must be tailored to the individual patient based on the patient's head and neck position, localisation of pain, muscle hypertrophy, patient's body weight and patient response.

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. 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).

A 25-, 27- or 30-gauge needle should be used for superficial muscles and a needle of appropriate length may be used for deeper musculature. For cervical dystonia, localisation of the involved muscles with electromyographic guidance may be useful.

Table 2 below is intended to provide dosing guidelines for injection of BOTOX® in the treatment of cervical dystonia.

Table 2: Dosage Guide

Classification of Cervical Dystonia	**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 - 2 sites 25 - 75 U; 1 - 3 sites 25 - 100 U; 1 - 8 sites
Type II Head rotation only	Sternocleidomastoid	25 - 100 U; at least 2 sites if >25 U given
Type III Head tilted 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 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 dose and sites injected must be individualised for each patient.

Table 3 below shows the median dose of BOTOX® injected per muscle in a clinical trial in which dose was determined by the practitioner based on the presentation of the individual cervical dystonia patient.

Table 3: BOTOX® Dosing by Muscle for Cervical Dystonia

Muscle(s)	**Range of Medians* (U)**	**Minimum - Maximum Dose, U/muscle****
Sternocleidomastoid	50	15 - 190
Trapezius	50 - 60	5 - 200
Levator scapulae	50	10 - 180
Splenius capitis/cervicis	90	10 - 240
Scalene	40	5 - 90

* Two medians were given: for those patients who received one injection cycle (n = 121) and for those patients who received two injection cycles (n = 90). When only one number is given, the medians were the same for both groups of patients.

** Limiting the dose injected into the sternocleidomastoid muscle to less than 100 U may decrease the occurrence of dysphagia (see **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

In initial controlled clinical trials to establish safety and efficacy for cervical dystonia, doses of BOTOX® ranged from 140 to 280 U. In more recent trials, the doses have ranged from 95 to 360 U (with an approximate mean of 240 U). As with any medicinal treatment, initial dosing should begin at the lowest effective dose.

In general, a total dose of 360 U every two months should not be exceeded for the treatment of cervical dystonia. The time-to-retreatment will vary between patients, however data from controlled clinical trials indicates that symptoms may start to re-emerge at approximately 8-10 weeks post-injection. Clinical improvement generally occurs within the first two weeks after injection. The maximum clinical benefit generally occurs approximately six weeks post-injection. The duration of therapeutic effect reported in 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.

Repeat doses should be administered when the clinical effect of a previous injection diminishes, though usually not more frequently than every two months. “Booster” injections are not recommended.

Strabismus

BOTOX® is intended for injection into extraocular muscles utilising 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.

An injection of BOTOX® is prepared by drawing into a sterile tuberculin syringe an amount of the properly diluted toxin (see **DILUTION TABLE – Table 6**) slightly greater than the intended dose. Air bubbles in the syringe barrel are expelled and the syringe is attached to the electromyographic injection needle, preferably a one and a half inch, 27-gauge needle. Injection volume in excess of the intended dose is expelled through the needle into an appropriate waste container to assure patency of the needle and to confirm that there is no syringe-needle leakage. A new, sterile needle and syringe should be used to enter the vial on each occasion for dilution or removal of BOTOX®.

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 volume of BOTOX® injected for treatment of strabismus should be between 0.05 mL to 0.15 mL per muscle.

Strabismus dosage: The initial doses of the diluted BOTOX® (see **DILUTION TABLE – Table 6**) typically create paralysis of injected muscles beginning one to two days after injection and increases in intensity during the first week. Paralysis lasts for 2 - 6 weeks and gradually resolves over a similar time period.

Overcorrections lasting over 6 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 because of mechanical factors such as large deviations or restrictions or because of lack of binocular motor fusion to stabilise the alignment.

1. 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 dioptres: 1.25 U to 2.5 U in any one muscle.

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

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

2. 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 maybe increased up to twice the amount of 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.

Blepharospasm

An injection of BOTOX® is prepared by drawing into a sterile 1.0 mL tuberculin syringe an amount of the properly diluted toxin (see **DILUTION TABLE – Table 6**) slightly greater than the intended dose. A new, sterile needle and syringe should be used to enter the vial on each occasion for dilution or removal of BOTOX®.

For blepharospasm, diluted BOTOX® (see **DILUTION TABLE – Table 6**) is injected using a sterile, 27 - 30-gauge needle with or without electromyographic guidance. 1.25 U to 2.5 U (0.05 mL to 0.1 mL volume at each site) injected into the medial and lateral pre-tarsal orbicularis oculi of the upper lid and into the lateral pre-tarsal orbicularis oculi of the lower lid is the initial recommended dose. Pre-tarsal injections are often appropriate and may vary based on the patient's presentation. In the upper lid, maximising the distance of the injection from 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 may occur easily in the soft eyelid tissue. This may be reduced by applying light pressure at the injection site immediately after the injection.

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 as needed.

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 a minimal increase in benefit from injecting more than 5.0 U per site.

Some tolerance may be found when BOTOX® is used in treating blepharospasm if treatments are given any more frequently than every three months. The effect is rarely permanent.

The cumulative dose of BOTOX® in a two-month period should not exceed 200 U.

VIIth Nerve Disorders

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

The cumulative dose of BOTOX® in a two-month period should not exceed 200 U.

Focal Spasticity in Children two years and older

The exact dose and number of injection sites should be tailored to the child's needs based on the size, number and location of muscles involved, the severity of spasticity, presence of local muscle weakness and the patient's response to previous treatment. In clinical trials, the dose per muscle ranged from 0.5 - 2.0 U/kg body weight in the upper limb and 2.0 - 4.0 U/kg body weight in the lower limb per treatment session. For the treatment of equinus foot deformity, the total dose is up to 4 U/kg or 200 U (whichever is the lesser amount) divided into two sites in each medial and lateral head of the gastrocnemius muscle. In other muscles, the dose per muscle ranged from 3.0 - 8.0 U/kg body weight and did not exceed 300 U divided among selected muscles at any treatment session. 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.

A 27- or 30-gauge needle should be used with an appropriate needle length to reach the targeted muscles. For focal spasticity, localisation techniques include electromyography, muscle ultrasound or electrical stimulation.

Clinical improvement generally occurs within the first two weeks after injection. Repeat doses should be administered when the clinical effect of a previous injection diminishes but typically not more frequently than every three months. The maximum degree of muscle spasticity at the time of re-injection may necessitate alterations in the dose of BOTOX® and muscles to be injected.
Table 4 below is intended to give dosing guidelines for injection of BOTOX® in the treatment of focal spasticity in children aged 2 years and older. The maximum cumulative dose should generally not exceed 8.0 U/kg body weight and up to a maximum of 300 U divided among selected muscles at any treatment session or in a 3-month interval.

Table 4: BOTOX® Dosing by Muscle for Focal Spasticity in Children

Muscles in upper limb	Dosage in U/kg/muscle
Biceps brachii	0.5 - 2.0 U
Brachialis	0.5 - 2.0 U
Brachioradialis	0.5 - 2.0 U
Flexor carpi ulnaris	0.5 - 2.0 U
Flexor carpi radialis	0.5 - 2.0 U
Pronator teres	0.5 - 2.0 U
Pronator quadratus	0.5 - 2.0 U
Flexor digitorum profundus	0.5 - 2.0 U
Flexor digitorum sublimis	0.5 - 2.0 U
Flexor pollicis longus	0.5 - 2.0 U
Flexor pollicis brevis	0.5 - 2.0 U

Opponens pollicis	0.5 - 2.0 U
Adductor pollicis	0.5 - 2.0 U
Muscles in lower limb	**Dosage in U/kg/muscle**
Hip adductor group (adductor longus, adductor brevis, adductor magnus, medial hamstrings)	4.0 U
Gastrocnemius	2.0 - 4.0 U

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. Clinical trials support a maximum dose of 360 U divided among selected muscles (typically in the flexor muscles of the elbow, wrist and fingers) for treating upper limb spasticity and a maximum dose of 400 U divided among selected muscle groups for treating adult lower limb spasticity at any treatment session. Clinical improvement in muscle tone generally occurs within two weeks following treatment with the peak effect seen four to six weeks following treatment. In clinical trials, patients were re-injected at 12-to-16-week intervals. The degree of muscle spasticity at the time of re-injection may necessitate alterations in the dose of BOTOX® and muscles to be injected.

Table 5 below is intended to provide dosing guidelines for injection of BOTOX® in the treatment of focal spasticity.

Table 5: BOTOX® Dosing by Muscle for Focal Spasticity in Adults

Muscle	**Total Dosage; Number of Sites**
Upper Limb	
Biceps brachii	100 - 200 U; up to 4 sites
Flexor digitorum profundus	15 - 50 U; 1 - 2 sites
Flexor digitorum sublimis	15 - 50 U; 1 - 2 sites
Flexor carpi radialis	15 - 60 U; 1 - 2 sites
Flexor carpi ulnaris	10 - 50 U; 1 - 2 sites
Adductor pollicis	20 U; 1 - 2 sites
Flexor pollicis longus	20 U; 1 - 2 sites
Lower Limb	
Posterior tibialis	70 - 100 U; 1 - 2 sites
Soleus	80 - 125 U; 1 - 2 sites
Flexor hallucis longus	50 U; 2 sites
Flexor digitorum longus/brevis	50 - 100 U; 2 - 4 sites
Gastrocnemius medial/lateral	50 - 200 U; 2 - 4 sites

A 25-, 27- or 30-gauge needle should be used with an appropriate needle length to reach the targeted muscles. For focal spasticity, localisation techniques include electromyography, muscle ultrasound or electrical stimulation.

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

Primary Hyperhidrosis of the Axillae

The hyperhidrotic area to be injected may be defined using standard staining techniques, e.g. Minor's iodine-starch test. BOTOX® is reconstituted with 0.9% non-preserved sterile saline solution (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. Each dose is injected to a depth of approximately 2 mm and at a 45-degree angle to the skin surface with the bevel side up to minimise leakage and ensure the injections remain intradermal.

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 a 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 the effects from previous injections subside but usually not more frequently than every two months.

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® should be reconstituted with 0.9% non-preserved sterile saline solution (100 U/2.5 mL) and injected using a sterile 30-gauge needle. A volume of 0.1 mL (4 U) is administered in each of 5 injection sites, 2 injections in each corrugator muscle and 1 injection in the procerus muscle for a total dose of 20 U.

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

Improvement of the severity of glabellar lines generally occurs within one week after treatment. The effect was demonstrated for up to 4 months.

Crow's Feet

BOTOX® should be injected bilaterally at 3 sites in the lateral aspect of the orbicularis oculi (i.e. total of 6 injections), where most lines are seen when a smile is forced. In general, 2 - 6 U is recommended per injection site at a 2 - 3 mm depth, for a total dose of 6 - 18 U per side.

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

Forehead Lines

BOTOX® should be injected intramuscularly at each of 4 injection sites in the frontalis muscle. In general, 2 - 6 U is recommended per injection site every 1 - 2 cm along either side of a deep forehead crease, for a total dose of 8 - 24 U.

Injections should be at least 2 - 3 cm above the eyebrow to reduce the risk of brow ptosis.

Dilution Technique

It is good practice to perform vial reconstitution and syringe preparation over plastic-lined paper towels to catch any spillage. To reconstitute vacuum-dried BOTOX® injection, use sterile normal saline without a preservative; 0.9% w/v non-preserved, sterile sodium chloride injection is the recommended diluent. Draw up the proper amount of diluent in the appropriate size syringe. Since BOTOX® is denatured by bubbling or similar violent agitation, inject the diluent into the vial gently. Discard the vial if a vacuum does not pull the diluent into the vial. Record the date and time of reconstitution on the space on the label. BOTOX® should be administered within 24 hours after reconstitution in the vial.

During this time period, reconstituted BOTOX® should be stored in a refrigerator (2°C to 8°C). Reconstituted BOTOX® should be clear, colourless to slightly yellow and free of particulate matter. Parenteral medicines should be inspected visually for particulate matter and discolouration prior to administration and whenever the solution and the container permit. The product and recommended diluent do not contain a preservative and are for single use only.

For reconstitution technique for intradetrusor injections for neurogenic detrusor overactivity, please refer to **DOSE AND METHOD OF ADMINISTRATION** under the sub-heading **NEUROGENIC DETRUSOR OVERACTIVITY**.

Table 6: Dilution Table for 50 U, 100 U and 200 U

Diluent Added (0.9% non-preserved sterile Sodium chloride Injection)		**50 U Vial**	**100 U Vial**	**200 U Vial**
		Resulting dose (U/0.1 mL)	**Resulting dose (U/0.1 mL)**	**Resulting dose (U/0.1 mL)**
0.5 mL		10	20	40
1 mL		5	10	20
2 mL		2.5	5	10
4 mL		1.25	2.5	5
5 mL		N/A	2	4
8 mL		N/A	1.25	2.5
10 mL		N/A	1	2

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).

Lack of Response

In the absence of the desired effect after the first treatment session, i.e. no significant clinical improvement from baseline by one month after injection, the following actions should be considered:

- Analysis of potential causes of lack of effect, e.g. inappropriate selection of muscles to be injected; insufficient dose; poor injection technique; muscles inaccessible to injection; underlying structural abnormalities such as muscle contractures or bone disorders; relative weakness of antagonist muscles; change in pattern of muscle involvement; patient perception of benefit compared with initial results; inappropriate storage or reconstitution and/or formation of toxin-neutralising antibodies.

- Re-evaluation of the appropriateness of treatment with botulinum toxin type A.

For the second treatment session, in the absence of any undesirable effects after the first treatment session, the physician should consider the following:

- adjust the dose, taking into account the analysis of the earlier treatment failure;
- use of EMG guidance as appropriate; and
- maintain a three-month interval between the two treatment sessions.

In the event of treatment failure or diminished effect following repeat injections, taking into account dose adjustments and targeting of injections, alternative treatment methods should be considered.

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 and have demonstrable levels of neutralising antibodies is less than 5%, though in a long-term juvenile cerebral palsy trial, 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 previously been responders; 19 continued to respond; 7 became clinical non-responders and no further data is available in 5 patients.

In the pivotal trials, none of the 615 overactive bladder patients with analysed specimens developed the presence of neutralising antibodies to BOTOX®. Following on from these pivotal and open-label extension trials, specimens analysed from patients showed that no neutralising antibodies developed in any of the 954 patients (0.0%) who had received BOTOX® 100 U doses. Only 3 of 260 patients (1.2%) developed neutralising antibodies after subsequently receiving at least one BOTOX® 150 U dose, of which one of these three patients continued to experience clinical benefit.

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

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 be no more frequent than every two months). The maximum dose should not be exceeded in any two-month period for adult spasticity patients and patients with cervical dystonia. In treating paediatric patients, the maximum cumulative dose should generally not exceed 8 U/kg up to a maximum of 300 U, in a 3-month interval. 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.

Paediatric Use

The safety and effectiveness of BOTOX® in the treatment of urinary incontinence due to overactive bladder, urinary incontinence due to neurogenic detrusor overactivity and prophylaxis of headaches in adults with chronic migraine have not been established in patients below the age of 18 years.

Safety and effectiveness in children below the age of 12 years have not been established for the indications of blepharospasm, strabismus, VIIth nerve disorder, cervical dystonia, upper facial lines (forehead, crow's feet and glabellar lines) or primary hyperhidrosis of the axillae, nor in children below 2 years of age for cerebral palsy.

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. Some of these patients had risk factors including significant neuromuscular debility, dysphagia, aspiration pneumonia, seizures and cardiovascular disease. Post-marketing reports of possible distant effects from the site of injection have been very rarely reported in paediatric patients with co-morbidities, predominantly 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.

New onset or recurrent seizures have also been reported, typically in children who are predisposed to experiencing these events. The exact relationship of these events to the BOTOX® injection has not been established.

Use in the Elderly

Overall, with the exception of Overactive Bladder (see below), clinical trials of BOTOX® did not identify differences in responses between the elderly and younger patients. Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range.

Overactive Bladder

Of 1242 patients in placebo-controlled clinical trials 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 trials, 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 younger patients. Similarly, no overall difference in effectiveness was observed between these age groups in placebo-controlled pivotal clinical trials.

4.3 Contraindications

BOTOX® injection is contraindicated

- in individuals with known hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- in patients with myasthenia gravis or Eaton Lambert syndrome.
- in the presence of infection at the proposed injection site(s).

Bladder Dysfunction

Intradetrusor injection of BOTOX® is contraindicated in patients who have a urinary tract infection and in patients with acute urinary retention who are not routinely catheterising.

Due to the risk of urinary retention, intradetrusor injection of BOTOX® is also contraindicated in patients who are not willing and/or able to initiate catheterisation post-treatment, if required.

4.4 Special warnings and precautions for use

General

The recommended dosages and frequencies of administration for BOTOX® injection should not be exceeded.

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.

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 are consistent with the mechanism of action of botulinum toxin and have been reported hours to weeks after injection. Symptoms 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 these symptoms can also occur in patients who have underlying conditions and co-morbidities 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 there have been reports of death, although an exact relationship to BOTOX® has not been established. Advise patients or caregivers to seek immediate medical attention if any of these symptoms occur.

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.

Theoretically, the effect of botulinum toxin type A may be potentiated by aminoglycoside antibiotics or spectinomycin or any other medicines that interfere with neuromuscular transmission (e.g. tubocurarine-type muscle relaxants). Caution should be exercised when BOTOX® injection is used with aminoglycosides (e.g. streptomycin, tobramycin, neomycin, gentamycin, netilmycin, kanamycin, amikacin), spectinomycin, polymyxins, tetracyclines, lincomycin or any other medicines which interfere with neuromuscular transmission.

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® injection.

Individuals with peripheral motor neuropathic diseases (e.g. amyotrophic lateral sclerosis or motor neuropathy) should only receive BOTOX® injection with extreme caution. Patients with neuromuscular junction disorders may be at an increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of BOTOX®. Published medical literature has reported 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.

The safe and effective use of BOTOX® injection depends upon proper storage of the product, selection of the correct dose and proper reconstitution and administration techniques. Physicians administering BOTOX® injection should be familiar with the relevant anatomy of the area involved and any alterations to the anatomy due to prior surgical procedures. 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 the 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 may be useful for the treatment of hemifacial spasm, cervical dystonia (spasmodic torticollis) and for the treatment of dynamic equinus foot deformity due to spasticity in juvenile cerebral palsy patients.

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. As with all biological products, adrenaline and other precautions as necessary should be available should an anaphylactic reaction occur. 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.

Caution should be exercised when BOTOX® is used in the presence of inflammation at the proposed injection site(s) or when excessive weakness or atrophy is present in the target muscles.

As with any injection, procedure-related injury could occur. An injection could result in localised infection, pain, inflammation, paraesthesia, hypoaesthesia, tenderness, swelling/oedema, erythema and/or bleeding/bruising. Needle-related pain and/or anxiety resulted in vasovagal responses, including transient symptomatic hypotension and syncope.

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.

DUE TO THE LACK OF AN INTERNATIONAL UNIT, BOTOX® IS NOT THERAPEUTICALLY EQUIVALENT TO ANY OTHER BOTULINUM TOXIN TYPE A PREPARATIONS. THE POTENCIES OF BOTOX® AND OTHER BOTULINUM TOXIN TYPE A PREPARATIONS ARE BASED ON DIFFERENT ASSAY METHODS. IN VIEW OF THIS LACK OF HARMONISATION OF UNIT SYSTEMS FOR BOTULINUM TOXIN TYPE A, EXTREME CAUTION IS REQUIRED IF IT SHOULD PROVE NECESSARY TO SUBSTITUTE THE BOTULINUM TYPE A TOXIN OF ONE PHARMACEUTICAL COMPANY BY ANOTHER. THE EFFECT OF ADMINISTERING DIFFERENT BOTULINUM NEUROTOXIN SEROTYPES AT THE SAME TIME OR WITHIN SEVERAL MONTHS OF EACH OTHER IS UNKNOWN. EXCESSIVE NEUROMUSCULAR WEAKNESS MAY BE EXACERBATED BY ADMINISTRATION OF ANOTHER BOTULINUM TOXIN PRIOR TO THE RESOLUTION OF THE EFFECTS OF A PREVIOUSLY ADMINISTERED BOTULINUM TOXIN.

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) is also considered extremely remote. No cases of viral diseases or CJD have ever been identified for albumin.

Bladder Dysfunction

Appropriate medical caution should be exercised when 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. Initiation of catheterisation should be considered if post-void residual urine volume exceeds 200 mL and discontinuation should be considered when post-void residual falls below 200 mL. Patients should be instructed to contact their physician if they experience difficulties in voiding as catheterisation may be required.

Neurogenic Detrusor Overactivity

In these patients, autonomic dysreflexia associated with the procedure could occur which may require prompt medical therapy. From clinical data, the incidence rate of autonomic dysreflexia was 1.5% in the BOTOX® group, compared with 0.4% in the placebo group.

Chronic Migraine

The safety and effectiveness of BOTOX® have not been established for the prophylaxis of headaches in adults with episodic migraine (14 headache days or fewer per month).

Strabismus

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.

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 dioptres, 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.

Blepharospasm

Reduced blinking following BOTOX® injection into the orbicularis muscle can lead to corneal exposure, persistent epithelial defect 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 closure of the eye by patching or other means.

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

Cervical Dystonia (spasmodic torticollis)

The most frequently reported adverse event following treatment of cervical dystonia patients with all types of botulinum toxins is dysphagia. 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. Consequent to the dysphagia, there is the potential for aspiration, dyspnoea and occasionally the need for tube feeding. In rare cases, dysphagia followed by aspiration pneumonia and death has been reported.

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

Limiting the dose injected into the sternocleidomastoid muscle to less than 100 U may decrease the occurrence of dysphagia. Patients with smaller neck muscle mass, or patients who receive bilateral injections into the sternocleidomastoid muscle, have been reported to be at a greater risk of dysphagia. Injections into the levator scapulae may be associated with an increased risk of upper respiratory infection and dysphagia. Dysphagia is attributable to the localised diffusion of the toxin to the oesophageal musculature.

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

Spasticity

BOTOX® is a treatment of focal spasticity that has only been studied in association with usual standard of care regimens and is not intended as a replacement for these treatment modalities.

BOTOX® treatment is not likely to be effective in improving range of motion at a joint affected by a known fixed contracture. Identification of the treatment goals and clinical examination to identify the specific muscles causing spasticity is necessary and use of electromyography, muscle ultrasound or electrical stimulation may facilitate the accuracy of the BOTOX® injections.

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

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

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

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

Primary Hyperhidrosis of the Axillae

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.

Upper Facial Rhytides (forehead lines, crow's feet and glabellar 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 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.

4.5 Interactions with other medicines and other forms of interaction

Theoretically, the effect of botulinum toxin type A may be potentiated by aminoglycoside antibiotics or any other medicines that interfere with neuromuscular transmission (e.g. neuromuscular blocking agents). Caution should be exercised when BOTOX® injection is used in patients taking any of these medicines (see **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

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.

4.6 Fertility, pregnancy and lactation

Pregnancy: Pregnancy Category B3

When pregnant mice and rats were injected intramuscularly during the period of organogenesis, at 4 U/kg there was reduced weight gain compared with controls and reduced foetal ossification at a single site. Higher doses (8 or 16 U/kg) were associated with reductions in foetal body weights and/or delayed ossification but there was no evidence for teratogenicity.

Pregnant rabbits were particularly sensitive to BOTOX® injection. In a range-finding study, intramuscular administration twice during the period of organogenesis resulted in abortions (2 U/kg) and maternal deaths (4 and 6 U/kg). Daily intramuscular administration during the period of organogenesis resulted in reduced foetal weights (0.25 and 0.5 U/kg), increased resorptions (0.5 U/kg); the No-Observed-Effect-Level (NOEL) was 0.125 U/kg, although all doses produced maternal toxicity.

Intramuscular treatment of rats with a maternotoxic dose of BOTOX® (16 U/kg) injection, twice during gestation and once during the lactation period, resulted in an increased post-implantation loss and reduced pup weights but post-weaning pup development was unaffected.

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® treatment should not be used during pregnancy unless the benefits clearly outweigh the potential risks. If the use of BOTOX® injection is determined to be warranted during pregnancy, or if the patient becomes pregnant whilst taking BOTOX®, the patient should be apprised of the potential risks.

Use in Lactation

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

In general, adverse reactions 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 weakness represents the expected pharmacological action of botulinum toxin in muscle tissue. However, weakness of adjacent muscles and/or muscles remote from the site of injection has been reported.

Overactive Bladder

Table 7 presents the most frequently reported adverse reactions in double-blind, placebo-controlled, pivotal Phase 3 trials within 12 weeks of injection for overactive bladder.

Table 7: Adverse Reactions Reported by ≥1% of BOTOX®-treated Patients and More Frequent than in Placebo-treated Patients Within the First 12 Weeks, in Double-blind, Placebo-controlled, Pivotal Phase 3 Clinical Trials

Adverse Reactions by System Organ Class	BOTOX® 100 U (N=552)	Placebo (N=542)
Infections and infestations		
Urinary tract infection	17.9%	5.5%
Bacteriuria	4.3%	2.0%
Renal and urinary disorders		
Dysuria	9.1%	6.6%
Urinary retention	5.6%	0.4%
Investigations		
Residual urine volume*	3.1%	0.2%

*****Elevated PVR not requiring catheterisation

During the complete treatment cycle, the following adverse reactions with BOTOX® 100 U injection were reported: urinary tract infections (25.5%), dysuria (10.9%), bacteriuria (8.0%), urinary retention (5.8%), residual urine volume (3.4%) and pollakiuria (2.0%).

Events considered to be procedure-related by the investigator reported at any time following initial injection were dysuria (5.8%) and haematuria (2.2%).

Catheterisation was initiated in 6.5% of patients following treatment with BOTOX® 100 U versus 0.4% of patients in the placebo group. Median duration of CIC was 63 days with BOTOX® 100 U versus 11 days in the placebo group as detailed in Table 8 below:

Table 8: Initiation of CIC Post-treatment for Any Reason and for Urinary Retention (Placebo-controlled Pivotal Trial Safety Population; Treatment Cycle 1)

Parameter	100 U BOTOX® (N = 552)	Placebo (N = 542)
Initiation of CIC (for any reason) at any time during treatment cycle 1		
Proportion of patients	36/552 (6.5%)	2/542 (0.4%)
Initiation of catheterisation due to urinary retention at any time during treatment cycle 1[a]		
Proportion of patients	32/552 (5.8%)	2/542 (0.4%)
Median duration (days)	63	11

CIC = clean intermittent catheterisation

[a] Based upon reporting an AE of urinary retention which is defined as an elevation of PVR that requires catheterisation

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

Neurogenic Detrusor Overactivity

Table 9 presents the most frequently reported adverse reactions in double-blind trials within 12 weeks of injection for neurogenic detrusor overactivity.

Table 9: Adverse Reactions Reported by ≥1% of BOTOX®-treated Patients and More Frequent than in Placebo-treated Patients Within the First 12 Weeks, in Double-blind, Placebo-controlled Clinical Trials

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

The following rates with BOTOX® 200 U were reported during the complete treatment cycle (median duration of 44 weeks of exposure): urinary tract infections (49.2%), urinary retention (17.2%), fatigue (6.1%) and insomnia (3.1%).

In these neurogenic patients, the following additional adverse reactions were reported during the complete treatment cycle: constipation (4.2%), muscular weakness (3.8%), fall (3.1%), gait disturbance (2.7%), muscle spasm (2.3%) and bladder diverticulum (1.1%).

Procedure-related events in the BOTOX® 200 U group included: haematuria (3.8%), dysuria (2.3%) and autonomic dysreflexia (1.5%).

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

No difference on the multiple sclerosis (MS) exacerbation annualised 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 trials.

Among patients who were not catheterising at baseline prior to treatment, catheterisation for urinary retention was initiated in 30.6% following treatment with BOTOX® 200 U versus 6.7% following treatment with placebo (Table 10).

Table 10: Initiation of CIC Post-treatment for Any Reason and for Urinary Retention (Placebo-controlled Trial Safety Population; Treatment Cycle 1)

Parameter	BOTOX® 200 U (N = 108)	Placebo (N = 104)
Initiation of CIC (for any reason) at any time during treatment cycle 1[a]		
Proportion of patients	42/108 (38.9%)	18/104 (17.3%)
Initiation of catheterisation due to urinary retention at any time during treatment cycle 1[b]		
Proportion of patients	33/108 (30.6%)	7/104 (6.7%)
Median duration (days)	289.0	358.0

CIC = clean intermittent catheterisation

[a] Based on patient bladder diary data

[b] Based on investigator reporting "Catheterisation due to Urinary Retention"

A placebo-controlled, double-blind, post-approval trial with BOTOX® 100 U (Study 191622-117) was conducted in MS patients with urinary incontinence due to neurogenic detrusor overactivity. These patients were not adequately managed with at least one anticholinergic agent and not catheterising at baseline. Table 11 below presents the most frequently reported adverse reactions within 12 weeks of injection.

Table 11: Adverse Reactions Reported by ≥1% of BOTOX®-treated Patients and More Frequent than in Placebo-treated Patients Within the First 12 Weeks (Study 191622-117)

Adverse Reactions by System Organ Class	BOTOX® 100 U (N=66)	Placebo (N=78)
Infections and infestations		
Urinary tract infection	17 (25.8%)	5 (6.4%)
Bacteriuria	6 (9.1%)	4 (5.1%)
Renal and urinary disorders		
Urinary retention	10 (15.2%)	1 (1.3%)
Dysuria	3 (4.5%)	1 (1.3%)
Investigations		
Residual urine volume*	11 (16.7%)	1 (1.3%)

* Elevated PVR not requiring catheterisation

During the complete treatment cycle (median duration of 51 weeks of exposure), the following adverse events were reported with BOTOX® 100 U: urinary tract infections (39.4%), bacteriuria (18.2%), urinary retention (16.7%), residual urine volume* (16.7%) and dysuria (9.1%).

Procedure-related events included: dysuria (4.5%) and haematuria (3.0%).

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

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

The median duration of post-injection catheterisation for those who developed urinary retention was 64 days for BOTOX® 100 U and 2 days for placebo.

Chronic Migraine

Safety data were compiled from two chronic migraine double-blind, placebo-controlled trials involving 687 patients treated with BOTOX® injection. The following adverse reactions were reported.

The frequency is defined as follows: Very Common (≥ 1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very Rare (<1/10,000).

Nervous system disorders
Common: Headache, migraine, facial paresis

Eye disorders
Common: Eyelid ptosis

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

General disorders and administration site conditions
Common: Injection site pain

Gastrointestinal disorders
Uncommon: Dysphagia

Migraine, including worsening migraine, was reported in 3.8% of BOTOX® and 2.6% of placebo (saline) patients, typically occurring within the first month after treatment. These reactions did not consistently re-occur 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 (saline).

Strabismus

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. Extraocular muscles adjacent to the injection site are often affected, causing ptosis or vertical deviation, especially with higher doses of BOTOX® injection. The incidence rates of these side effects in 2058 adults who received 3650 injections for horizontal strabismus are listed below:

Ptosis	15.7%
Vertical deviation	16.9%

The incidence of ptosis was much less after inferior rectus injection (0.9%) and much greater after superior rectus injection (37.7%).

The incidence rates of these side effects persisting for over 6 months in an enlarged series of 5587 injections of horizontal muscles in 3104 patients are listed below:

Ptosis lasting over 180 days	0.3%
Vertical deviation greater than 2 prism dioptres lasting over 180 days	2.1%

In these patients, the injection procedure itself caused 9 scleral perforations. A vitreous haemorrhage occurred and later cleared in one case. No retinal detachment or visual loss occurred in any case. Sixteen retrobulbar haemorrhages occurred. Decompression of the orbit after 5 minutes was necessary to restore retinal circulation in one case. There was no visual loss from retrobulbar haemorrhage in any of these cases but in five eyes there was pupillary change consistent with ciliary ganglion damage (Adies pupil).

Blepharospasm

In clinical trials of 1684 patients who received 4258 treatments (involving multiple injections) for blepharospasm, the incidence rates of adverse reactions per treated eye are listed below:

Ptosis	11.0%
Irritation/Tearing (including dry eye, lagophthalmos and photophobia)	10.0%
Ectropion, keratitis, diplopia reported rarely and entropion	incidence less than 1%

Ecchymosis occurs easily in the soft eyelid tissue. This can be prevented by applying pressure at the injection site immediately after injection. Diffuse skin rash and local swelling of the eyelid skin lasting for several days following eyelid injection were reported infrequently in clinical trials.

In the two cases of VIIth nerve disorder (one case of an aphakic eye) reduced blinking from BOTOX® injection of the orbicularis muscle led to serious corneal exposure, persistent epithelial defect and corneal ulceration. Perforation requiring corneal grafting occurred in one case, an aphakic eye. Avoidance of injection into the lower lid area to avoid ectropion may reduce this hazard. Vigorous treatment of any corneal epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses or closure of the eye by patching or other means.

Two patients previously incapacitated by blepharospasm experienced cardiac collapse attributed to over-exertion within three weeks following BOTOX® treatment. Sedentary patients should be cautioned to resume activity slowly and carefully following the administration of BOTOX® injection.

Acute angle closure glaucoma has been reported very rarely following periorbital injections of botulinum toxin (see **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

VIIth Nerve Disorders (hemifacial spasm)

Adverse effects reported after injection of BOTOX® have included blurring of vision, facial droop, dizziness and tiredness, in addition to those listed above for blepharospasm.

Cervical Dystonia (spasmodic torticollis)

The following adverse events were reported in BOTOX®-treated patients compared with placebo-treated patients and are listed in descending order of incidence: pain (32%), focal weakness (17%) and dysphagia (13%) being the most common. Soreness, malaise, general weakness, upper respiratory infection, nausea, headache, drowsiness, stiffness, dry mouth, dizziness, rhinitis, flu syndrome, numbness and hypertonia were all reported in 2 to 10% of patients. Other treatment-related adverse events reported during clinical trials with BOTOX® injection for cervical dystonia included diplopia, ptosis, dyspnoea and fever.

Table 12: Safety Data from Placebo-controlled, Double-blind Clinical Trials *

Adverse event	BOTOX® (n = 231)	Placebo (n = 224)
Pain†	32%	21%
Weakness, focal	17%	4%
Dysphagia	13%	3%
Soreness	9%	3%
Malaise	6%	2%
Weakness, general	6%	1%
Upper respiratory infection	5%	3%
Nausea	5%	1%
Headache	5%	3%
Drowsiness	4%	1%
Stiffness	3%	0%
Dry mouth	3%	0.4%
Dizziness	3%	1%
Rhinitis	3%	0%
Hypertonia	2%	0%
Flu syndrome	3%	4%
Numbness	2%	1%
Diplopia	1%	0%
Fever	1%	0%
Ptosis	0.4%	0%
Dyspnoea	0.4%	0%
Voice alteration	0.4%	0%

*This data was compiled from all reported adverse events in Allergan placebo-controlled, double-blind trials including the meta-analysis of five Oculinum trials completed prior to 1992.

†Pain mainly represents local pain at injection site, but also includes neck pain, back pain and general muscle ache.

In an open label trial, 18.6% (13/70) of patients reported dysphagia after treatment with a mean dose of 240.5 U BOTOX®. Dysphagia and symptomatic general weakness may be attributable to an extension of the pharmacology of BOTOX® resulting from the spread of the toxin outside the injected muscles. Dysphagia is usually reported as mild to moderate severity in most patients. However, in an occasional patient it may be associated with more severe problems (see **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Dysphonia has also been reported in the literature in patients who have been treated for cervical dystonia. Rhinitis has also been reported.

Focal Spasticity in Children two years and older

The safety of BOTOX® used for the treatment of focal spasticity was evaluated from clinical trials for the treatment of dynamic equinus foot deformity, upper limb spasticity and lower limb spasticity. As is expected for any intramuscular injection procedure, localised pain, discomfort, bruising and oedema was associated with the injection in these patients. All treatment-related adverse events were mild to moderate in severity and were self-limiting.

In children treated for upper limb spasticity, the most frequently reported treatment-related adverse events included local and general weakness, trigger finger, clumsiness, hypokinesia, falling, increased frequency of micturition, joint dislocation and muscle spasms. The percent of patients who experienced these events at least once during the trial are summarised below:

Table 13: Adverse events reported in children treated for upper limb spasticity

	BOTOX® (n = 74)
Muscular weakness, local	5.4%
Muscular weakness, general	2.7%
Trigger finger	2.7%
Clumsiness	1.4%
Falling	1.4%
Hypokinesia	1.4%
Increased frequency of micturition	1.4%
Joint dislocation	1.4%
Muscle spasms	1.4%

Other adverse events reported commonly or very commonly in these trials were convulsions, nasopharyngitis, pneumonia, vomiting and contusion.

In children treated for dynamic equinus foot deformity due to spasticity in juvenile cerebral palsy, the adverse events most frequently reported as treatment-related included falling, leg pain, leg (local) weakness and general weakness. The percentage of patients who experienced these events at least once during the trial are summarised below:

Table 14: Most frequently reported adverse events reported in children treated for dynamic equinus foot deformity

	BOTOX® (n = 215)
Falling	9.3%
Leg pain	2.3%
Weakness, local	2.3%
Weakness, general	2.3%

Falling may be attributable to a change in ankle position and gait pattern and/or local weakness. Local weakness represents the expected pharmacological action of botulinum toxin.

Other treatment-related adverse reactions reported in 1% of patients were: leg cramps, fever, knee pain, ankle pain, pain at the injection site post-treatment and lethargy. Urinary incontinence has also been reported.

In children treated for spasticity of the hip adductor muscles, there were no adverse events reported in the trials evaluated.

Focal Spasticity in Adults

The safety of BOTOX® was evaluated in 339 unique patients who received treatment for upper limb spasticity associated with stroke in double-blind and open label trials. In general, the majority of adverse events reported were mild to moderate in severity and were typically self-limiting.

The following events were reported as treatment-related in 1 - 4% of patients and are listed in decreasing order of incidence: arm pain and hypertonia.

Fever and flu syndrome were also reported in approximately 1% of patients. The following events were reported as treatment-related in less than 1% of patients and are listed in decreasing order of incidence: hyperaesthesia, arthralgia, asthenia, bursitis, dermatitis, headache, injection site hypersensitivity, malaise, nausea, paraesthesia, postural hypotension and pruritus.

The safety of BOTOX® was evaluated in 82 patients who received a single treatment for lower limb spasticity associated with stroke in either a double-blind or an open label trial. The following treatment-related adverse events were reported: accidental injury (1.2%), incoordination (1.2%) and paraesthesia (1.2%). Adverse events reported were mild to moderate in severity.

Of the 56 patients who received BOTOX® in the double-blind phase of the trial, 44 went on to receive a second injection in the open-label trial. Additional treatment-related adverse reactions reported were: hypertonia (4.5%), asthenia (2.3%), headache (2.3%) and hyperkinesia (2.3%).

The most frequently reported adverse reactions identified in additional studies for adult lower limb spasticity, including Study 191622-116, 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 displayed below:

Table 15: Adverse events identified in additional studies for adult lower limb spasticity treatment

Adverse Reactions by System Organ Class	All BOTOX® (N=538)	Placebo (N=422)
General disorders and administration site conditions Peripheral oedema	13 (2.4%)	5 (1.2%)
Musculoskeletal and connective tissue disorders Arthralgia	19 (3.5%)	5 (1.2%)

Primary Hyperhidrosis of the Axillae

The safety of BOTOX® was evaluated in 287 patients who received at least 1 treatment exposure for focal hyperhidrosis of the axilla in double-blind and open-label trials. Adverse events reported as treatment-related in greater than 1% of BOTOX®-treated patients are listed in decreasing order of incidence: perceived increase in non-axillary sweating (4.5%), injection site pain (1.7%), pain (1.4%) and vasodilation (hot flushes) (1.0%). Body odour has also been reported.

Glabellar Lines

Safety of BOTOX® for the treatment of glabellar lines was evaluated in two multicentre, double-blind, placebo-controlled, parallel group trials (n = 535; 405 in the BOTOX®-treated group and 130 in the placebo-treated group). Most adverse events reported were of mild to moderate severity and all were

transient. The most frequently reported treatment-related adverse events were headache (9.4% in the BOTOX® group and 15.4% in the placebo group) and blepharoptosis (3.2% in the BOTOX® group). Blepharoptosis is consistent with the pharmacological action of BOTOX® and may be injection-technique-related.

Adverse events reported as treatment-related in 1 - 3% of BOTOX®-treated patients, listed in decreasing order of incidence were: injection site pain/burning/stinging (2.5%), face pain (2.2%), erythema (1.7%), local muscle weakness (1.7%), injection site oedema (1.5%), ecchymosis (1.0%), skin tightness (1.0%), paraesthesia (1.0%) and nausea (1.0%).

Crow's Feet

The safety of BOTOX® for the treatment of crow's feet was evaluated in two multicentre, double-blind, placebo-controlled, parallel group trials (246 in the BOTOX®-treated groups (6 U to 18 U/side) and 80 in the placebo-treated group). Most adverse events reported were of mild to moderate severity and all were transient. The most frequently reported treatment-related adverse events were injection site haemorrhage i.e. bruising at the injection site (8.1% in the BOTOX® 6 U to 18 U/side groups and 10.0% in the placebo group) and headache (3.7% in the BOTOX® 6 U to 18 U/side groups and 2.5% in the placebo group). Flu syndrome was reported in 1.6% of BOTOX®-treated patients (6 U to 18 U/side) and in none of the placebo-treated patients. All other adverse events reported as treatment-related in the BOTOX® groups were reported in less than 1% of patients.

Other trials have reported the incidence of injection site bruising to be between 4 - 25% of BOTOX®-treated patients, with similar rates noted for placebo treated patients. Other adverse events related to BOTOX® treatment included temporary droop of the lateral portion of the lower eyelid (5%) which is consistent with the pharmacological action of BOTOX® and may be injection technique-related.

Forehead Lines

In a clinical trial where BOTOX® was administered to 59 patients with horizontal forehead lines (8 U to 24 U into the frontalis), the following treatment-related adverse events were reported: headache (22.0%), bruising (10.2%), eyebrow ptosis (10.2%), eyelid swelling (20.3%), aching/itching forehead (5.1%), nausea (3.4%), feeling of tension (1.7%), flu-like symptoms/cold (1.7%) and other (6.8%). All adverse events were mild or moderate in severity and no serious adverse events were reported.

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 skin rash, urticaria, soft tissue oedema and dyspnoea (see **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

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 the **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** and **UNDESIRABLE EFFECTS** sections: 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; dry eye; hypoacusis; tinnitus; vertigo; facial palsy; facial paresis; brachial plexopathy; radiculopathy; syncope; hypoaesthesia; malaise; myalgia; myasthenia gravis; paraesthesia; localised muscle twitching/involuntary muscle contractions; rash; erythema multiforme; pruritus; dermatitis psoriasiform; hyperhidrosis and alopecia; including madarosis.

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 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. Local weakness is usually well tolerated and resolves spontaneously without intervention. However, dysphagia may result in loss of airway protection and aspiration pneumonia.

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

Should symptoms (muscular weakness, ptosis, diplopia, blurred vision, facial weakness, swallowing and speech disorders, constipation, aspiration pneumonia, difficulty breathing or respiratory depression) occur post-injection or oral ingestion, the person should be medically monitored for up to several weeks. These patients should be considered for further medical evaluation and appropriate medical therapy immediately instituted which may include hospitalisation. Advise patients or caregivers to seek immediate medical attention if any of these symptoms occur. Specific anti-toxin to botulinum toxin is only likely to be effective if given within thirty minutes of the botulinum toxin injection.

If the musculature of the oropharynx and oesophagus are affected, aspiration may occur which may lead to the 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Neuromuscular blocking agent**, ATC code:** M03AX01

BOTOX® (botulinum toxin type A) purified 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.

One Unit of BOTOX® corresponds to the calculated median intraperitoneal lethal dose (LD_{50}) in mice, performed in a mouse potency assay. This assay method is specific to Abbvie's product, BOTOX®. Due to specific method details such as the vehicle, dilution scheme and laboratory protocols for the various mouse LD_{50} assays, units of biological activity of BOTOX® cannot be compared to or converted into units of any other botulinum toxin activity.

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. 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 sensitisation 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.

Bladder Dysfunction (Overactive Bladder and Neurogenic Detrusor Overactivity)

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.

Overactive Bladder

Two double-blind, placebo-controlled, randomised, multi-centre, 24-week Phase 3 clinical trials were conducted in patients with OAB with symptoms of urinary incontinence, urgency and frequency. A total of 1105 patients, whose symptoms had not been adequately managed with anticholinergic therapy (inadequate response or intolerable side effects), were randomised to receive either 100 U of BOTOX® (n = 557) or placebo (n = 548).

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

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.

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

Neurogenic Detrusor Overactivity

In two Phase 3 trials, significant improvements compared to placebo in the primary efficacy variable of change from baseline in weekly frequency of urinary incontinence episodes were observed for BOTOX® (200 U and 300 U) 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 (including avoidance limiting behaviour, psychosocial impact and social embarrassment) were also observed. No additional benefit of BOTOX® 300 U over 200 U was demonstrated.

The efficacy and safety profile of BOTOX® was studied in 51 patients **≥** 65 years of age and is consistent with that observed in the overall trial population in the pivotal trials.

A placebo-controlled, double-blind, randomised post-approval 52-week trial (Study 191622-117) was conducted in MS patients with urinary incontinence due to neurogenic detrusor overactivity who were not adequately managed with at least one anticholinergic agent and not catheterising at baseline. These patients were randomised to receive either 100 U 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 U) at the primary efficacy time point at week 6. Significant improvements in urodynamic parameters were also observed.

Chronic Migraine

The presumed mechanism for headache prophylaxis is by blocking peripheral signals to the central nervous system, which inhibits central sensitisation, as confirmed by clinical trials. Limited nonclinical data also suggest that BOTOX® may reduce sensitisation processes but the actual mechanism of action for headache prophylaxis is not known.

Blepharospasm

The paralytic effect on muscles injected with BOTOX® is useful in reducing the excessive, abnormal contractions associated with blepharospasm. Typically, patients with blepharospasm show improvement lasting an average of 12.5 weeks prior to the need for re-treatment.

Strabismus

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

Cervical Dystonia (spasmodic torticollis)

When injected into neck muscles, BOTOX® acts to provide relief from both objective signs and subjective symptoms of cervical dystonia (spasmodic torticollis). These improvements may include reduced pain/discomfort, reduced head rotation, reduced shoulder elevation, decreased size and strength of hypertrophic muscles and functional disability improvement. Based on the results of early publications in naïve patients, 40 to 58% of patients with cervical dystonia respond with a significant

improvement in their symptoms after initial treatment with BOTOX®. Among patients who have previously benefited from BOTOX® injection for cervical dystonia, approximately 91% can expect improvement for any given treatment period based on patient withdrawal data in a recent trial.

Focal Spasticity in Adults and Children two years and older

BOTOX® treatment reduces both the objective signs and subjective symptoms of spasticity. Improvements include reduction in muscle tone, increase in range of motion, reduction in pain and a reduction of spasticity related functional disability.

The efficacy and safety of BOTOX® for the treatment of lower limb spasticity was also evaluated in a randomised, multi-centre, double-blind, placebo-controlled study (Study 191622-116). This study included 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. A total dose of 300 U of BOTOX® or placebo was injected intramuscularly and divided between the gastrocnemius, soleus and tibialis posterior, with optional injection of up to an additional 100 U divided among the flexor hallucis longus, flexor digitorum longus, flexor digitorum brevis, extensor hallucis and rectus femoris (400 U total dose). Electromyography, muscle ultrasound or electrical stimulation was employed to assist in proper muscle localisation. Patients were followed for 12 weeks.

The primary endpoint was the average change from baseline of weeks 4 and 6 MAS ankle score and a key secondary endpoint was the average CGI (Physician Global Assessment of Response) at weeks 4 and 6. The MAS uses a similar scoring system as the Ashworth Scale. The CGI evaluated the response to treatment in terms of how the patient was doing in his/her life using a 9-point scale from -4 = very marked worsening to +4 = very marked improvement.

Statistically and clinically significant between-group differences for BOTOX® over placebo were demonstrated for the primary efficacy measures of MAS and key secondary measure of CGI and are presented in Table 16.

Table 16: Primary and Key Secondary Efficacy Endpoints

	BOTOX® 300 to 400 U (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

*Statistically significantly different from placebo ($p<0.05$)

Statistically significant improvements in MAS change from baseline (Figure 2) and CGI by Physician (Figure 3) for BOTOX® were observed at weeks 2, 4 and 6, compared to placebo.

Figure 2: Modified Ashworth Scale Ankle Score for Study 191622-116 – Mean Change from Baseline by Visit

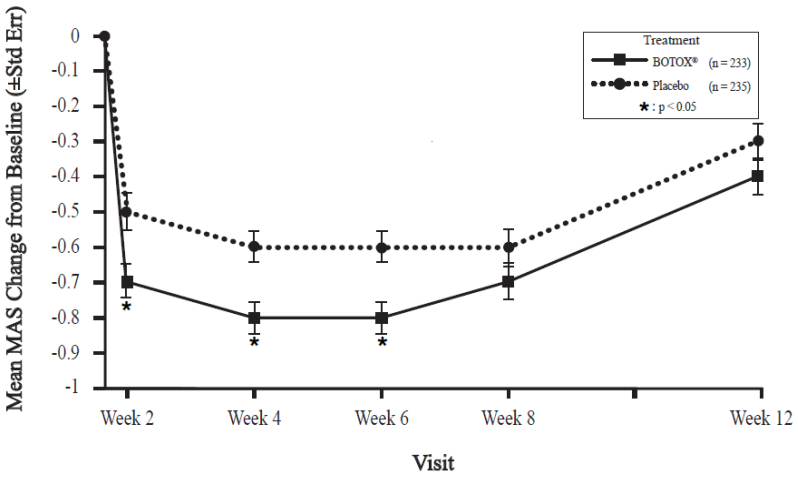
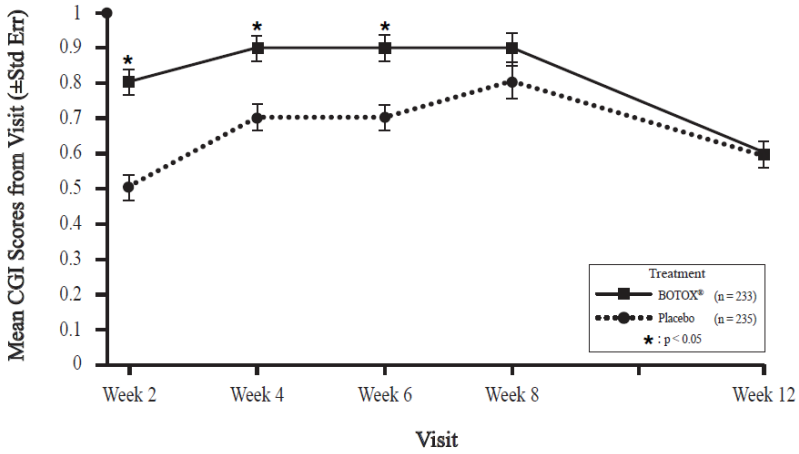


Figure 3: Clinical Global Impression by Physician for Study 191622-116 – Mean Scores by Visit



Primary Hyperhidrosis of the Axillae

The proposed mechanism of action of BOTOX® in hyperhidrosis is the inhibition of cholinergically driven excessive sweating, by locally blocking the autonomic sympathetic cholinergic nerve fibres innervating sweat glands. This is achieved by injecting the toxin in the vicinity of the sweat glands which are located within the dermis of the skin. Injections for this indication must therefore be given intradermally. Hyperhidrosis is typically treated by multiple intradermal injections given in a grid-like pattern over the affected area.

In a double-blind, placebo-controlled clinical trial of 320 patients, the responder rate was 95% at week 1 and 93.8% at the primary endpoint of week 4, as assessed by the objective gravimetric evaluations. The objective of treatment is to reduce sweating to a physiologically normal level which patients find tolerable. Anhidrosis is not the target.

Glabellar Lines

When injected into the corrugator and/or procerus muscles, BOTOX® weakens the overactive underlying muscle contraction, decreasing the severity of the glabellar lines and improving appearance. In controlled clinical trials, onset of action was rapid and lasted at least 4 months for many subjects.

Crow's Feet

Crow's feet are well established, deep, radiating, horizontal and oblique furrows at the temporal aspect of each eye and are the direct result of the contraction of the lateral fibres of the orbicularis oculi muscles. In controlled clinical trials, injections of BOTOX® into the lateral orbital area resulted in rapid onset of action (effect of BOTOX® was apparent at the first assessment timepoint of 7 days) and reduced the severity of wrinkling in this area for up to 17 weeks.

Forehead Lines

Horizontal forehead lines are associated with chronic functional activity of the frontalis muscle. At two weeks post-injection, 84 - 95% of BOTOX®-treated patients were considered by investigators as treatment responders; 75 - 80% of patients felt they had improvement (16 or 24 U at four sites in the frontalis muscle). Higher doses of BOTOX® resulted in greater efficacy and longer duration of effect. Injections of BOTOX® reduced the severity of horizontal forehead lines for up to 24 weeks as determined by a trained observer.

5.2 Pharmacokinetic properties

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

Distribution studies in rats indicate minimal muscular diffusion of ^{125}I-botulinum neurotoxin A complex in the gastrocnemius muscle after injection, followed by rapid systemic metabolism and urinary excretion. The amount of radiolabelled 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.

Auto-radiographic results after intramuscular injection of ^{125}I-botulinum neurotoxin A complex into the proximal inner surface of the upper eyelids of rabbits also indicate slow muscular diffusion.

In vitro studies of isolated rat synaptosome fragments indicated that botulinum toxin has a high affinity for cholinergic terminals where it binds to the pre-synaptic membrane.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of BOTOX® injection. BOTOX® is not structurally related to any known carcinogens. There has been no clinical evidence of cumulative adverse events following repeated injection of BOTOX®. BOTOX® was inactive in *in vitro* tests for gene mutation and in *in vitro* and *in vivo* tests for clastogenicity.

Intramuscular BOTOX® doses of 4 U/kg (males) and 8 U/kg (females) did not affect rat fertility. Decreased fertility occurred with higher doses but these also resulted in signs of toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Human albumin: 0.25 mg for 50 U, 0.5 mg for 100 U or 1.0 mg for 200 U
Sodium chloride: 0.45 mg for 50 U, 0.9 mg for 100 U or 1.8 mg for 200 U

6.2 Incompatibilities

Incompatibility studies were not assessed as part of the registration of BOTOX®. BOTOX® should therefore not be mixed with other medicinal products.

6.3 Shelf-life

The shelf life of all strengths of the BOTOX® packaged product (50 U, 100 U and 200 U) is 36 months when stored at 2 °C to 8 °C.

Administer BOTOX® within 24 hours after the vial is removed from the refrigerator and reconstituted. During these 24 hours, reconstituted BOTOX® injection should be stored in a refrigerator. If reconstituted BOTOX® injection is further diluted in a syringe for intradetrusor injections, it should be used immediately. It should be clear, colourless or slightly yellow and free of particulate matter. It is for single use only.

6.4 Special precautions for storage

Store the vacuum-dried product in a refrigerator between 2 ºC – 8 °C.

For storage conditions after reconstitution of the medicine, see section 6.3.

6.5 Nature and contents of container

BOTOX® (botulinum toxin type A) purified neurotoxin complex is a sterile, vacuum-dried preparation. It is supplied in a clear glass vial with a rubber stopper and tamper-proof aluminium seal, containing a white powder for reconstitution. Each vial contains 50 U, 100 U or 200 U of vacuum-dried *Clostridium botulinum* toxin type A.

Each vial contains 50 U*, 100 U or 200 U* of botulinum toxin type A, packaged individually.

*- not marketed

6.6 Special precautions for disposal

All vials, including expired vials, or equipment used with the medicine should be disposed of carefully as is done with all medical waste. Unused vials should be reconstituted with a small amount of water and then autoclaved. Any unused vials or equipment (such as syringes) should be autoclaved (120ºC for 30 minutes) or the residual BOTOX® inactivated using dilute hypochlorite solution (0.5% or 1%) for 5 minutes.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

AbbVie Limited
6th Floor, 156-158 Victoria St
Wellington, 6011
New Zealand
Toll free telephone: 0800 659 912

9. DATE OF FIRST APPROVAL

October 1991

10. DATE OF REVISION OF TEXT

18 May 2023

SUMMARY TABLE OF CHANGES

Sections changed	Summary of new information
All	Sponsor details updated