SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

BOTOX
50 Allergan Units
Powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Botulinum toxin* type A, 50 Allergan Units/vial.
* from *Clostridium botulinum*
Botulinum toxin units are not interchangeable from one product to another.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection.
BOTOX product appears as a thin white deposit that may be difficult to see on the base of the vial.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

BOTOX is indicated for:

Neurologic disorders:

BOTOX is indicated for the symptomatic treatment of:

- treatment **of focal spasticity**, including:

  - elbow, wrist and hand in **paediatric cerebral palsy patients,** two years of age or older as an adjunct to rehabilitative therapy
  - ankle and foot in ambulant **paediatric cerebral palsy** patients, two years of age or older as an adjunct to rehabilitative therapy
  - **upper limb spasticity** in adults
  - ankle and foot disability due to **lower limb spasticity** in adults
- symptomatic relief of **blepharospasm, hemifacial spasm** and **idiopathic cervical dystonia** (spasmodic torticollis)
- prophylaxis of headaches in adults with **chronic migraine** (headaches on at least 15 days per month of which at least 8 days are with migraine)

Bladder disorders:

- management of **bladder dysfunctions** in adult patients who are not adequately managed with anticholinergics
  - **overactive bladder** with symptoms of urinary incontinence, urgency and frequency
  - **neurogenic detrusor overactivity** with urinary incontinence due to subcervical spinal cord injury (traumatic or non-traumatic), or multiple sclerosis

Skin and skin appendage disorders

- management of severe **hyperhidrosis of the axillae**, which does not respond to topical treatment with antiperspirants or antihidrotics
- temporary improvement in the appearance of:
  - moderate to severe vertical lines between the eyebrows seen at maximum frown (glabellar lines) and/or,
  - moderate to severe lateral canthal lines (crow's feet lines) seen at maximum smile and/or,
  - moderate to severe forehead lines seen at maximum eyebrow elevation,
  - moderate to severe platysma prominence seen at maximum contraction,

when the severity has an important psychological impact in adult patients.

4.2 Posology and method of administration

Posology

Botulinum toxin units are not interchangeable from one product to another. Doses recommended in Allergan Units are different from other botulinum toxin preparations.

Elderly patients

Dosages for elderly patients are the same as for younger adults. Initial dosing should begin at the lowest recommended dose for the specific indication. Elderly patients with significant medical history and concomitant medications should be treated with caution.

There are limited data in patients older than 65 years managed with BOTOX for urinary incontinence with neurogenic detrusor overactivity, ankle and foot disability due to lower limb spasticity, as well as for facial lines and platysma prominence (see section 5.1).

Paediatric population

The safety and efficacy of BOTOX in indications other than those described for the paediatric population in section 4.1 have not been established. No recommendation on posology can be made for indications other than paediatric focal spasticity associated with cerebral palsy. For this indication, BOTOX should only be administered by appropriately qualified healthcare practitioners who are experienced in the assessment and treatment of paediatric focal spasticity and as part of a structured program of rehabilitation.

Currently available data in paediatric populations are described in section 4.2, 4.4, 4.8 and 5.1, as shown in the table below.

• Focal spasticity in paediatric patients	2 years (see section 4.2, 4.4 and 4.8)
• Blepharospasm/Hemifacial spasm/ Idiopathic Cervical dystonia	12 years (see section 4.4 and 4.8)
• Primary hyperhidrosis of the axillae	12 years (limited experience in adolescents between 12 and 17 years, see sections 4.4, 4.8 and 5.1)
• Paediatric neurogenic detrusor overactivity	5 - 17 years (see section 4.8 and 5.1)
• Paediatric overactive bladder	12 - 17 years (see section 4.8 and 5.1)

Method of Administration

BOTOX should only be administered by an appropriately qualified healthcare practitioner with expertise in the treatment of the relevant indication and the use of the required equipment, in accordance with national guidelines.

This product is for single use only and any unused solution should be discarded. The most appropriate vial size should be selected for the indication.

A decrease or increase in the BOTOX dose is possible by administering a smaller or larger injection volume. The smaller the injection volume the less discomfort and less spread of toxin in the injected muscle occurs. This is of benefit in reducing effects on nearby muscles when small muscle groups are being injected.

For instructions on reconstitution of the powder for solution for injection, handling and disposal of vials please refer to section 6.6.

Refer to specific guidance for each indication described below.

Generally valid optimum dose levels and number of injection sites per muscle have not been established for all indications. In these cases, individual treatment regimens should therefore be drawn up by an appropriately qualified healthcare practitioner. Optimum dose levels should be determined by titration but the recommended maximum dose should not be exceeded.

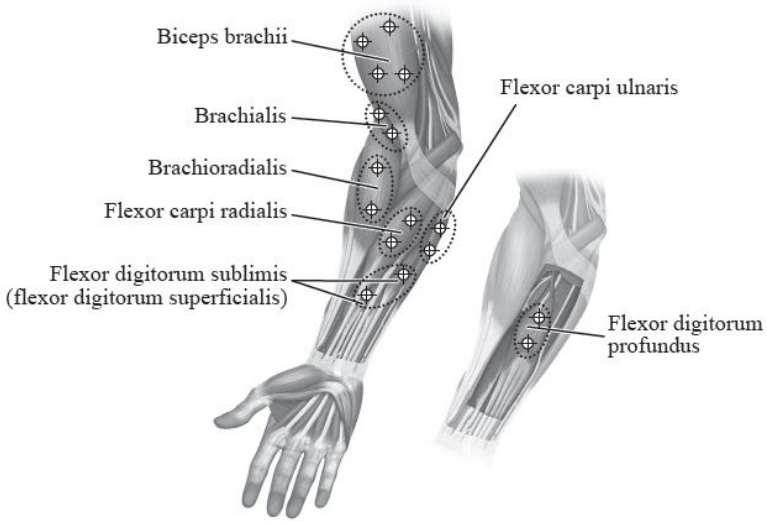
NEUROLOGIC DISORDERS

Focal spasticity of the upper limb in paediatric patients

Recommended needle: Appropriately sized sterile needle. Needle length should be determined based on muscle location and depth**.**

Administration guidance: Localisation of the involved muscles with techniques such as needle electromyographic (EMG) guidance, nerve stimulation, or ultrasound is recommended. Prior to injection, local anaesthesia or local anaesthesia in combination with minimal or moderate sedation may be used, per local site practice. The safety and efficacy of BOTOX in the treatment of paediatric spasticity has not been evaluated under general anaesthesia or deep sedation/analgesia.

The following diagram indicates the injection sites for paediatric upper limb spasticity:



Recommended dose: The recommended dose for treating paediatric upper limb spasticity is 3 Units/kg to 6 Units/kg body weight divided among the affected muscles.

BOTOX Dosing by Muscle for Paediatric Upper Limb Spasticity

Muscles Injected	BOTOX 3 Units/kg (maximum Units per muscle)	BOTOX 6 Units/kg (maximum Units per muscle)	Number of Injection Sites
Elbow Flexor Muscles			
Biceps	1.5 Units/kg (50 Units)	3 Units/kg (100 Units)	4
Brachialis	1 Unit/kg (30 Units)	2 Units/kg (60 Units)	2
Brachioradialis	0.5 Units/kg (20 Units)	1 Unit/kg (40 Units)	2
Wrist Muscles			
Flexor carpi radialis	1 Unit/kg (25 Units)	2 Units/kg (50 Units)	2
Flexor carpi ulnaris	1 Unit/kg (25 Units)	2 Units/kg (50 Units)	2
Finger Muscles			
Flexor digitorum profundus	0.5 Units/kg (25 Units)	1 Unit/kg (50 Units)	2
Flexor digitorum sublimis	0.5 Units/kg (25 Units)	1 Unit/kg (50 Units)	2

Maximum dose: The total dose of BOTOX administered per treatment session in the upper limb should not exceed 6 Units/kg body weight or 200 Units, whichever is lower. If it is deemed appropriate by the treating healthcare practitioner, the patient should be considered for re-injection when the clinical effect of the previous injection has diminished, no sooner than 12 weeks after the previous injection. When treating the upper and lower limbs in combination, the total dose should not exceed the lower of 10 Units/kg body weight or 340 Units, in a 12-week interval.

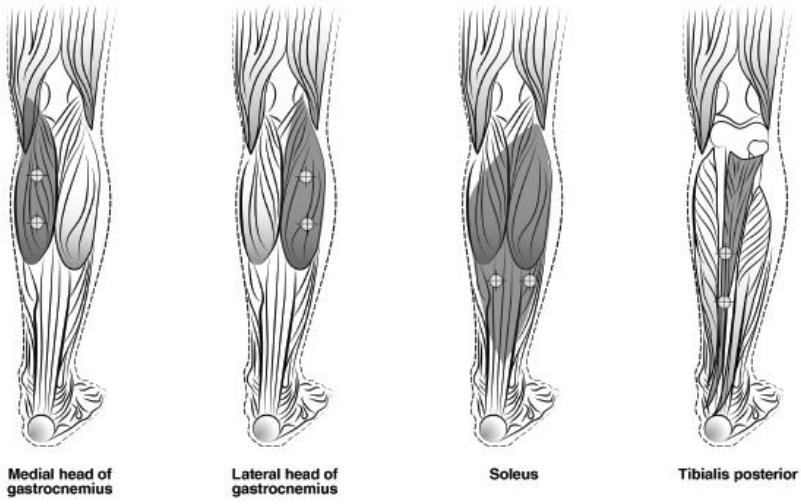
Additional information: Treatment with BOTOX is not intended to substitute for usual standard of care rehabilitation regimens. Clinical improvement generally occurs within the first two weeks after injection. Repeat treatment should be administered when the clinical effect of a previous injection diminishes but not more frequently than every 12 weeks.

Focal spasticity of the lower limb in paediatric patients

Recommended needle: Appropriately sized sterile needle. Needle length should be determined based on muscle location and depth.

Administration guidance: Localisation of the involved muscles with techniques such as needle electromyographic guidance, nerve stimulation, or ultrasound is recommended. Prior to injection, local anaesthesia or local anaesthesia in combination with minimal or moderate sedation may be used, per local site practice. The safety and efficacy of BOTOX in the treatment of paediatric spasticity has not been evaluated under general anaesthesia or deep sedation/analgesia.

The following diagram indicates the injection sites for paediatric lower limb spasticity:



Recommended dose: The recommended dose for paediatric lower limb spasticity is 4 Units/kg to 8 Units/kg body weight divided among the affected muscles.

BOTOX Dosing by Muscle for Paediatric Lower Limb Spasticity

Muscles Injected	BOTOX 4 Units/kg (maximum Units per muscle)	BOTOX 8 Units/kg (maximum Units per muscle)	Number of Injection Sites
Gastrocnemius medial head	1 Unit/kg (37.5 Units)	2 Units/kg (75 Units)	2
Gastrocnemius lateral head	1 Unit/kg (37.5 Units)	2 Units/kg (75 Units)	2
Soleus	1 Unit/kg (37.5 Units)	2 Units/kg (75 Units)	2
Tibialis Posterior	1 Unit/kg (37.5 Units)	2 Units/kg (75 Units)	2

Maximum dose: The total dose of BOTOX administered per treatment session in the lower limb should not exceed 8 Units/kg body weight or 300 Units, whichever is lower. If it is deemed appropriate by the treating healthcare practitioner, the patient should be considered for re-injection when the clinical effect of the previous injection has diminished, no sooner than 12 weeks after the previous injection. When treating both lower limbs or the upper and lower limbs in combination, the total dose should not exceed the lower of 10 Units/kg body weight or 340 Units, in a 12-week interval.

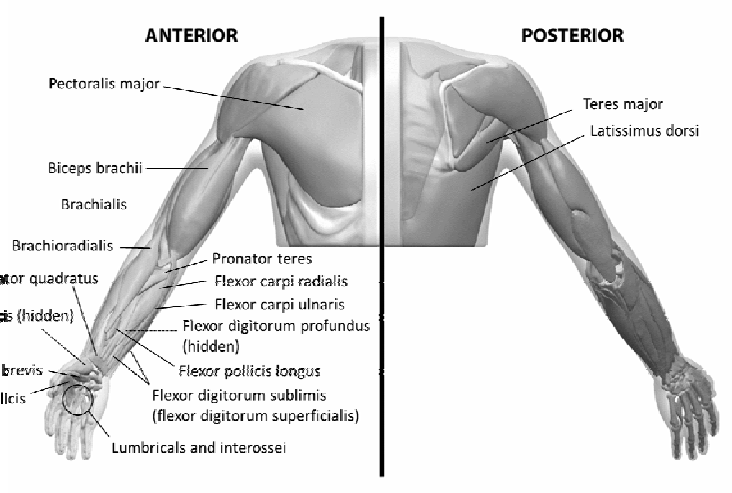
Additional information: Treatment with BOTOX is not intended to substitute for usual standard of care rehabilitation regimens. Clinical improvement generally occurs within the first two weeks after injection. Repeat treatment should be administered when the clinical effect of a previous injection diminishes but not more frequently than every 12 weeks.

Focal upper limb spasticity in adults

Recommended needle: Sterile 25, 27 or 30 gauge needle. Needle length should be determined based on muscle location and depth.

Administration guidance: Localisation of the involved muscles with techniques such as electromyographic guidance, nerve stimulation, or ultrasound is recommended. Multiple injection sites may allow BOTOX to have more uniform contact with the innervation areas of the muscle and are especially useful in larger muscles.

The following diagram indicates the injection sites for adult upper limb spasticity:



Recommended dose:

The recommended dose for treating adult upper limb spasticity is up to 400 Units divided among the affected muscles as listed in the following table.

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

Muscle	**Recommended Dose; Number of Sites**
Shoulder*	
Pectoralis major	75 – 125 Units; 3 sites
Teres major	30 – 50 Units; 2 sites
Latissimus dorsi	45 – 75 Units; 3 sites
Elbow	
Biceps brachii	70 Units; 2 sites
Brachioradialis	45 Units; 1 site
Brachialis	45 Units; 1 site
Forearm	
Pronator quadratus	10 – 50 Units; 1 site
Pronator teres	15 – 25 Units; 1 site
Wrist	
Flexor carpi radialis	15 – 60 Units; 1-2 sites
Flexor carpi ulnaris	10 – 50 Units; 1-2 sites
Fingers/Hand	
Flexor digitorum profundus	15 – 50 Units; 1-2 sites
Flexor digitorum sublimis/superficialis	15 – 50 Units; 1-2 sites
Lumbricals**	5 – 10 Units;1 site
Interossei**	5 – 10 Units;1 site
Thumb	
Adductor pollicis	20 Units; 1-2 sites

Flexor pollicis longus	20 Units; 1-2 sites
Flexor pollicis brevis	5 – 25 Units; 1 site
Opponens pollicis	5 – 25 Units; 1 site

*When injecting the shoulder muscles in combination, the recommended maximum dose is 250 U.
**When injecting both lumbricals and/or interossei, the recommended maximum dose is 50 U per hand.

Maximum dose: 400 Units in total

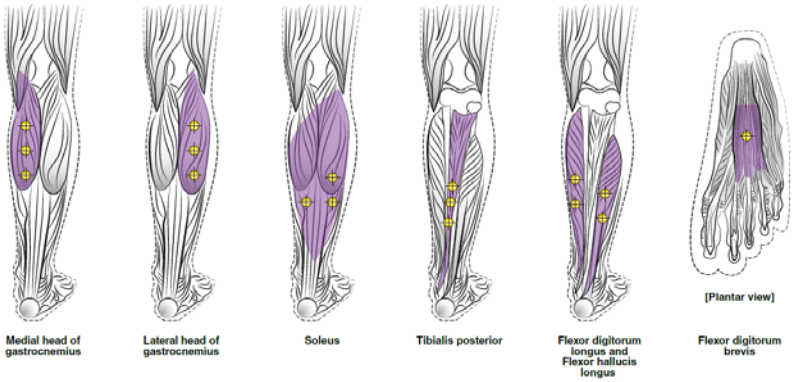
Additional information: If it is deemed appropriate by the treating healthcare practitioner, the patient should be considered for re-injection when the clinical effect of the previous injection has diminished. Re-injections should occur no sooner than 12 weeks after the previous injection. The degree and pattern of muscle spasticity at the time of re-injection may necessitate alterations in the dose of BOTOX and muscles to be injected. The lowest effective dose should be used.

Focal lower limb spasticity in adults

Recommended needle: Sterile 25, 27 or 30 gauge needle. Needle length should be determined based on muscle location and depth.

Administration guidance: Localisation of the involved muscles with techniques such as electromyographic guidance, nerve stimulation, or ultrasound is recommended. Multiple injection sites may allow BOTOX to have more uniform contact with the innervation areas of the muscle and are especially useful in larger muscles.

The following diagrams indicate the injection sites for adult lower limb spasticity:



Recommended dose: 300 Units to 400 Units divided among up to 6 muscles, as listed in the following table.

Muscle	Recommended Dose Total Dosage; Number of Sites
Gastrocnemius Medial head Lateral head	 75 Units; 3 sites 75 Units; 3 sites
Soleus	75 Units; 3 sites
Tibialis posterior	75 Units; 3 sites
Flexor hallucis longus	50 Units; 2 sites
Flexor digitorum longus	50 Units; 2 sites
Flexor digitorum brevis	25 Units; 1 site

Maximum dose: 400 Units in total

Additional information: If it is deemed appropriate by the treating healthcare practitioner, the patient should be considered for re-injection when the clinical effect of the previous injection has diminished, no sooner than 12 weeks after the previous injection.

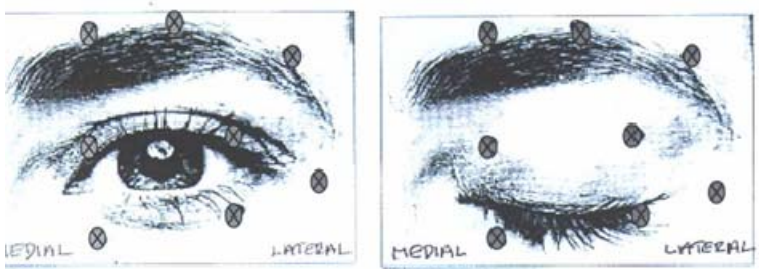
Blepharospasm/hemifacial spasm

Recommended needle: Sterile, 27-30 gauge/0.40-0.30 mm needle.

Administrative guidance: Electromyographic guidance is not necessary.

Recommended dose: The initial recommended dose is 1.25-2.5 Units (0.05-0.1 ml volume at each site) injected into the medial and lateral orbicularis oculi of the upper lid and the lateral orbicularis oculi of the lower lid. Additional sites in the brow area, the lateral orbicularis and in the upper facial area may also be injected if spasms here interfere with vision.

The following diagrams indicate the possible injection sites:



Maximum dose: The initial dose should not exceed 25 Units per eye. In the management of blepharospasm total dosing should not exceed 100 Units in total every 12 weeks.

Additional information:

Avoiding injection near 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.

In general, the initial effect of the injections is seen within three days and reaches a peak at one to two weeks post-treatment. Each treatment lasts approximately three months, following which the procedure can be repeated indefinitely. Normally no additional benefit is conferred by treating more frequently than every three months.

At repeat treatment sessions, the dose may be increased up to two-fold if the response from the initial treatment is considered insufficient – usually defined as an effect that does not last longer than two months. However, there appears to be little benefit obtainable from injecting more than 5 Units per site.

Patients with hemifacial spasm or VIIth nerve disorders should be treated as for unilateral blepharospasm, with other affected facial muscles being injected as needed. Electromyographic control may be necessary to identify affected small circumoral muscles.

Cervical dystonia

Recommended needle:

A 25, 27 or 30 gauge/0.50-0.30 mm needle may be used for superficial muscles, and a 22 gauge needle may be used for deeper musculature.

Administrative guidance:

The treatment of cervical dystonia typically may include injection of BOTOX into the sternocleidomastoid, levator scapulae, scalene, splenius capitis, semispinalis, longissimus and/or the trapezius muscle(s). This list is not exhaustive as any of the muscles responsible for controlling head position may be involved and therefore require treatment. The muscle mass and the degree of hypertrophy are factors to be taken into consideration when selecting the appropriate dose. Muscle activation patterns can change spontaneously in cervical dystonia without a change in the clinical presentation of dystonia.

In case of any difficulty in isolating the individual muscles, injections should be made under electromyographic assistance.

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.

Recommended dose: Dosing must be tailored to the individual patient based on the patient's head and neck position, location of pain, muscle hypertrophy, patient's body weight, and patient response.
Initial dosing in a naïve patient should begin at the lowest effective dose.

To minimise the incidence of dysphagia, the sternomastoid should not be injected bilaterally.

The following doses are recommended:

Type I Head **rotated** toward side of shoulder elevation	Sternomastoid Levator scapulae Scalene Splenius capitis Trapezius	50 – 100 Units; at least 2 sites 50 Units; 1 - 2 sites 25 – 50 Units; 1 – 2 sites 25 – 75 Units; 1 – 3 sites 25 – 100 Units; 1 – 8 sites
Type II Head rotation only	Sternomastoid	25 – 100 Units; at least 2 sites if >25 Units given
Type III Head **tilted** toward side of shoulder elevation	Sternomastoid Levator scapulae Scalene Trapezius	25 – 100 Units at posterior border; at least 2 sites if >25 Units given 25 – 100 Units; at least 2 sites 25 – 75 Units; at least 2 sites 25 – 100 Units; 1- 8 sites
Type IV Bilateral **posterior** cervical muscle spasm with elevation of the face	Splenius capitis and cervicis	50 – 200 Units; 2 – 8 sites, treat bilaterally (This is the total dose and not the dose for each side of the neck)

Maximum dose: No more than 50 Units should be given at any one injection site.
No more than 100 Units should be given to the sternomastoid.
No more than 200 Units in total should be injected for the first course of therapy, with adjustments made in subsequent courses dependent on the initial response, up to a maximum total dose of 300 Units.

Additional information: Treatment intervals of less than 10 weeks are not recommended.

Chronic migraine

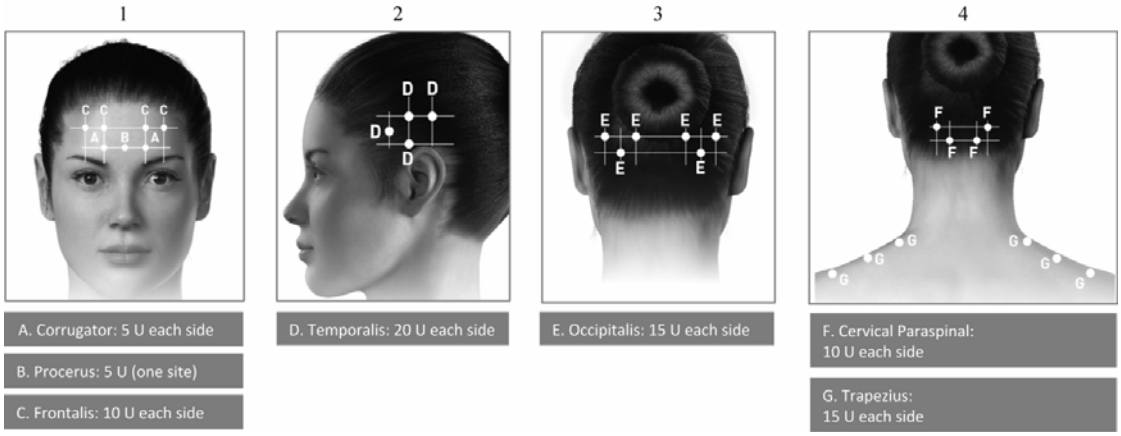
Recommended needle: Sterile 30 gauge, 0.5 inch needle.

A 1 inch needle may be needed in the neck region for patients with extremely thick neck muscles.

Administration guidance:

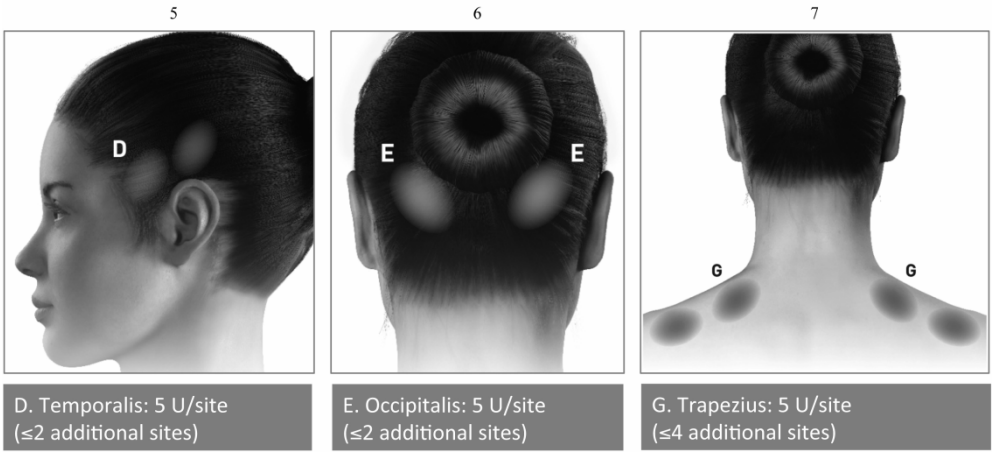
Injections should be divided across 7 specific head/neck muscle areas as specified in the diagrams below. With the exception of the procerus muscle, which should be injected at 1 site (midline), all muscles should be injected bilaterally with half the number of injection sites administered to the left, and half to the right side of the head and neck.

The following diagrams indicate the injection sites:



If there is a predominant pain location(s), additional injections to one or both sides may be administered in up to 3 specific muscle groups (occipitalis, temporalis and trapezius), up to the maximum dose per muscle as indicated in the table below.

The following diagrams indicate recommended muscle groups for optional additional injections:



Recommended dose:

155 Units to 195 Units administered intramuscularly as 0.1 ml (5 Units) injections to 31 and up to 39 sites.

	Recommended Dose
Head/Neck Area	**Total Dosage (number of sites*)**
Corrugator**	10 Units (2 sites)
Procerus	5 Units (1 site)
Frontalis**	20 Units (4 sites)
Temporalis**	40 Units (8 sites) up to 50 Units (up to 10

	sites)
Occipitalis**	30 Units (6 sites) up to 40 Units (up to 8 sites)
Cervical Paraspinal Muscle Group**	20 Units (4 sites)
Trapezius**	30 Units (6 sites) up to 50 Units (up to 10 sites)
Total Dose Range:	**155 Units to 195 Units 31 to 39 sites**

*1 IM injection site = 0.1 ml = 5 Units BOTOX
**Dose distributed bilaterally

Additional information: The recommended re-treatment schedule is every 12 weeks.

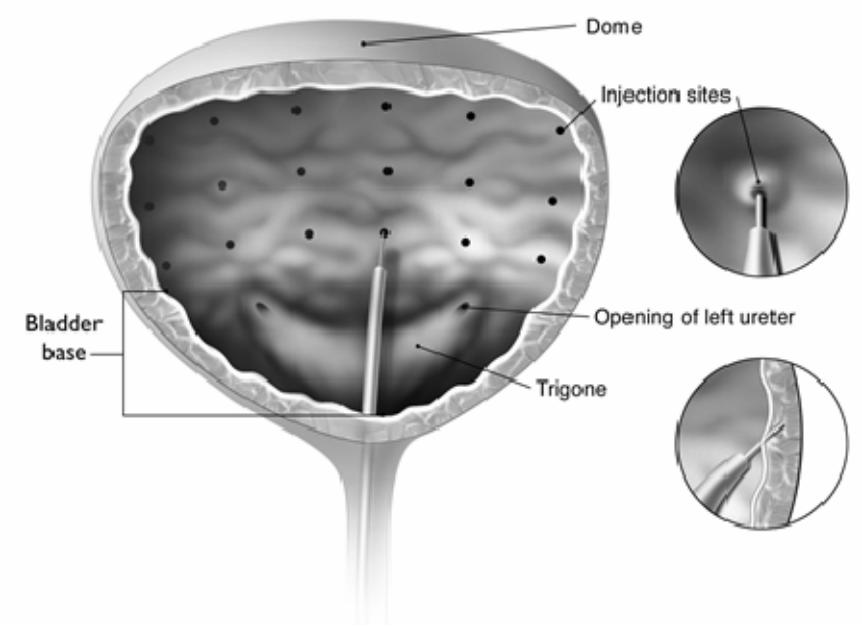
BLADDER DISORDERS

Overactive bladder

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

Administration guidance: The reconstituted solution of BOTOX (100 Units/10 ml) is injected via a flexible or rigid cystoscope, avoiding the trigone and base. The bladder should be instilled with enough saline to achieve adequate visualisation for the injections and avoid backflow of the product, but over-distension should be avoided.

The needle should be inserted approximately 2 mm into the detrusor, and 20 injections of 0.5 ml each (total volume 10 ml) should be spaced approximately 1 cm apart (see figure below). For the final injection, approximately 1 ml of sterile unpreserved normal saline (0.9% sodium chloride for injection) should be injected so the full dose is delivered.



Recommended dose: The recommended dose is 100 Units of BOTOX, as 0.5 ml (5 Units) injections across 20 sites in the detrusor muscle.

Additional information: For the patient preparation and monitoring, see section 4.4.

After the injections are given, the saline used for bladder wall visualisation should not be drained so that the 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.

Patients should be considered for reinjection when the clinical effect of the previous injection has diminished but no sooner than 3 months from the prior bladder injection.

Urinary incontinence due to neurogenic detrusor overactivity

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

Administration guidance: The reconstituted solution of BOTOX (200 Units/30 ml) is injected via a flexible or rigid cystoscope, avoiding the trigone and base. The bladder should be instilled with enough saline to achieve adequate visualisation for the injections and avoid backflow of the product, but over-distension should be avoided.

The needle should be inserted approximately 2 mm into the detrusor, and 30 injections of 1 ml each

	(total volume 30 ml) should be spaced approximately 1 cm apart (see figure above). For the final injection, approximately 1 ml of sterile unpreserved normal saline (0.9% sodium chloride for injection) should be injected so the full dose is delivered. After the injections are given, the saline used for bladder wall visualisation should be drained.
Recommended dose:	The recommended dose is 200 Units of BOTOX, as 1 ml (~6.7 Units) injections across 30 sites in the detrusor muscle.
Additional information:	For the patient preparation and monitoring, see section 4.4. Patients should be considered for reinjection when the clinical effect of the previous injection has diminished, but no sooner than 3 months from the prior bladder injection. No urodynamic data beyond 2 treatments and no histopathological data after repeated treatment are currently available. Patients should not receive multiple treatments in the event of limited symptomatic improvement.

SKIN AND SKIN APPENDAGE DISORDERS

Primary hyperhidrosis of the axillae

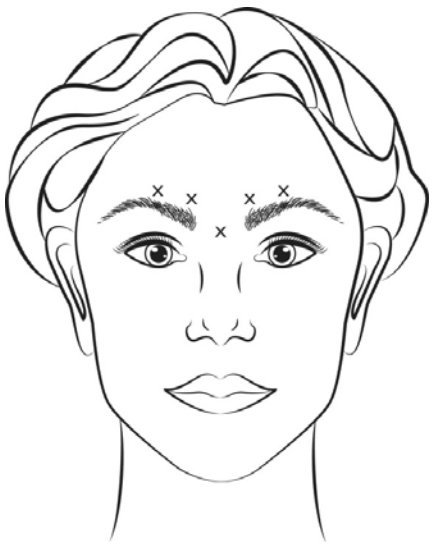
Recommended needle:	Sterile 30 gauge needle.
Administration guidance:	The hyperhidrotic area to be injected may be defined by using standard staining techniques, e.g. Minor´s iodine-starch test.
Recommended dose:	50 Units of BOTOX is injected intradermally to each axilla, evenly distributed in multiple sites approximately 1-2 cm apart. The recommended injection volume for intradermal injection is 0.1-0.2 ml.
Maximum dose:	Doses other than 50 Units per axilla cannot be recommended.
Additional information:	Clinical improvement generally occurs within the first week after injection and persists for 4-7 months. Repeat injection of BOTOX can be administered when the clinical effect of a previous injection diminishes and the treating healthcare practitioner deems it necessary. Injections should not be repeated more frequently than every 16 weeks.

Glabellar lines seen at maximum frown

Recommended needle: Sterile 30 gauge needle.

Administration guidance: Before injection, the thumb or index finger is to be placed firmly below the orbital rim in order to prevent extravasation below the orbital rim. The needle should be oriented superiorly and medially during the injection. In addition, injections near the levator palpebrae superioris muscle must be avoided, particularly in patients with larger brow-depressor complexes (depressor supercilii). Injections in the corrugator muscle must be done in the central part of that muscle, a distance of at least 1 cm above the arch of the eyebrows (see figure).

Care should be taken to ensure that BOTOX is not injected into a blood vessel when it is injected in the glabellar lines seen at maximum frown, see section 4.4.



Recommended dose: A volume of 0.1 ml (4 Units) is administered in each of the 5 injection sites (see Figure): 2 injections in each corrugator muscle and 1 injection in the procerus muscle for a total dose of 20 Units.

Maximum dose: In order to reduce the risk of eyelid ptosis, the maximum dose of 4 Units for each injection site as well as the number of injection sites should not be exceeded.

Additional Information Treatment intervals should not be more frequent than every three months. In the event of treatment failure or diminished effect following repeat injections, alternative treatment methods should be employed.

In case of insufficient dose a second treatment session should be initiated by adjusting the total dose up to 40 or 50 Units, taking into account the analysis of the previous treatment failure (see information in All indications).

The efficacy and safety of repeat injections of BOTOX for the treatment of glabellar lines beyond 12 months has not been evaluated.

Crow's feet lines seen at maximum smile

Recommended needle: Sterile 30 gauge needle.

Administration guidance: Injections should be given with the needle tip bevel up and oriented away from the eye. The first injection (A) should be made approximately 1.5 to 2.0 cm temporal to the lateral canthus and just temporal to the orbital rim. If the lines in the crow's feet region are above and below the lateral canthus, inject as shown in Figure 1. Alternatively, if the lines in the crow's feet region are primarily below the lateral canthus, inject as shown in Figure 2.

In order to reduce the risk of eyelid ptosis, injections should be made temporal to the orbital rim, thereby maintaining a safe distance from the muscle controlling eyelid elevation.

Figure 1:

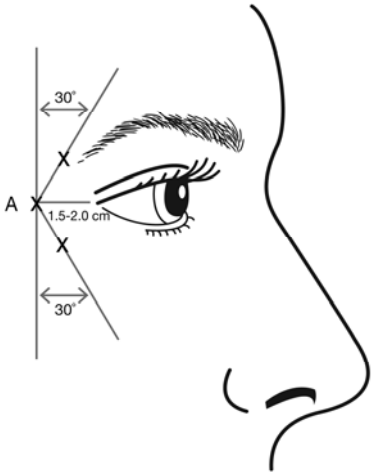
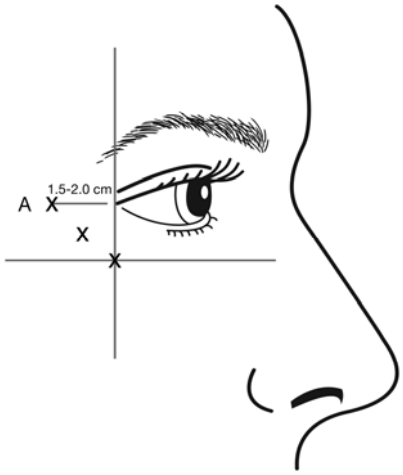


Figure 2:



Care should be taken to ensure that BOTOX is not injected into a blood vessel when it is injected in the crow's feet lines seen at maximum smile (see section 4.4).

Recommended dose: A volume of 0.1 ml (4 Units) is administered in each of the 3 injection sites per side (total of 6 injection sites) in the lateral orbicularis oculi muscle, for a

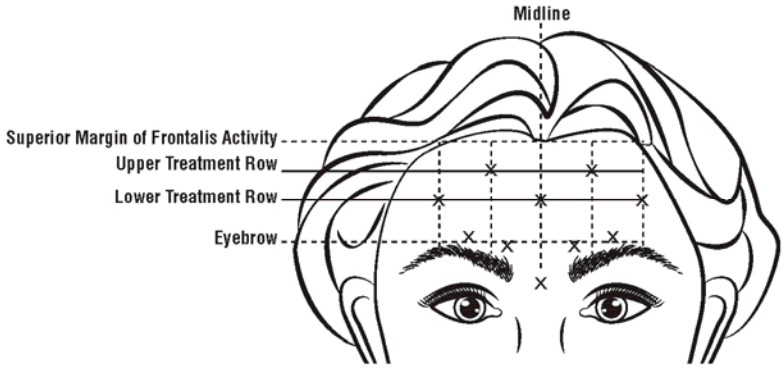
	total dose of 24 Units in a total volume of 0.6 ml (12 Units per side). For simultaneous treatment with glabellar lines seen at maximum frown, the dose is 24 Units for crow's feet lines seen at maximum smile and 20 Units for glabellar lines (see Administration guidance for glabellar lines) for a total dose of 44 Units in a total volume of 1.1 ml.
Maximum dose:	In order to reduce the risk of eyelid ptosis, the maximum dose of 4 Units for each injection site as well as the number of injection sites should not be exceeded.
Additional information:	Treatment intervals should not be more frequent than every 3 months. The efficacy and safety of repeat injections of BOTOX for the treatment of crow's feet lines beyond 12 months has not been evaluated.

Forehead Lines seen at maximum eyebrow elevation

Recommended needle:	Sterile 30 gauge needle.
Administration guidance:	To identify the location of the appropriate injection sites in the frontalis muscle, assess the overall relationship between the size of the subject's forehead, and the distribution of frontalis muscle activity should be assessed. The following horizontal treatment rows should be located by light palpation of the forehead at rest and maximum eyebrow elevation: • Superior Margin of Frontalis Activity: approximately 1 cm above the most superior forehead crease • Lower Treatment Row: midway between the superior margin of frontalis activity and the eyebrow, at least 2 cm above the eyebrow • Upper Treatment Row: midway between the superior margin of frontalis activity and lower treatment row The 5 injections should be placed at the intersection of the horizontal treatment rows with the following vertical landmarks:

- On the lower treatment row at the midline of the face, and 0.5 – 1.5 cm medial to the palpated temporal fusion line (temporal crest); repeat for the other side.
- On the upper treatment row, midway between the lateral and medial sites on the lower treatment row; repeat for the other side.

Figure 3:



Care should be taken to ensure that BOTOX is not injected into a blood vessel when it is injected in the forehead lines seen at maximum eyebrow elevation (see section 4.4).

Recommended dose:

A volume of 0.1 ml (4 Units) is administered in each of the 5 injection sites in the frontalis muscle, for a total dose of 20 Units in a total volume of 0.5 ml (see Figure 3).

The total dose for treatment of forehead lines (20 Units) in conjunction with glabellar lines (20 Units) is 40 Units/1.0 ml.

For simultaneous treatment with glabellar lines and crow's feet lines, the total dose is 64 Units, comprised of 20 Units for forehead lines, 20 Units for glabellar lines (see Recommended dose for Glabellar Lines and Figure), and 24 Units for crow's feet lines (see Recommended dose for Crow's Feet Lines and Figures 1 and 2).

Additional information:

Treatment intervals should not be more frequent than every 3 months.

The efficacy and safety of repeat injections of BOTOX for the treatment of forehead lines beyond 12 months has not been evaluated.

Platysma Prominence seen at maximum contraction

Recommended needle: Appropriately sized sterile needle (recommended range 30-33 gauge needle).

Administration guidance: Identify the treatment location: For each side, the 4 jawline injections to the upper platysma muscle should be approximately 1 to 2 cm inferior and parallel to the lower mandibular border. The anterior injection site should be in line with the oral commissure, and the posterior injection site should be slightly anterior to the angle of the mandible. The remaining 2 injections should be equidistant (approximately 1 to 2 cm apart) between the anterior and posterior injection points (see Figures 4 and 5).

For each vertical neck band, 1 to 2 per side, distribute 5 injections vertically approximately 1 to 2 cm apart (see Figures 4 and 5). The most superior injection site should be approximately 1 to 2 cm inferior to the jawline injections.

The platysma muscle is a thin muscle sheet just below the surface of the skin. Therefore, all platysma muscle injections should be administered superficially and intramuscularly with the needle perpendicular to the surface of the skin. For vertical neck band injections, each band should be identified while the patient is contracting their platysma. Gently pinch the band to isolate the muscle from nearby anatomical structures during administration (see Table below).

Figure 4: Injection Sites for Platysma Prominence (2 Bands)

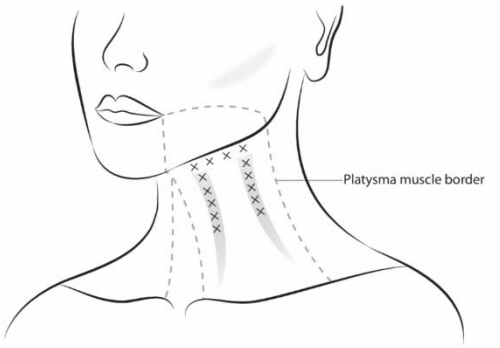
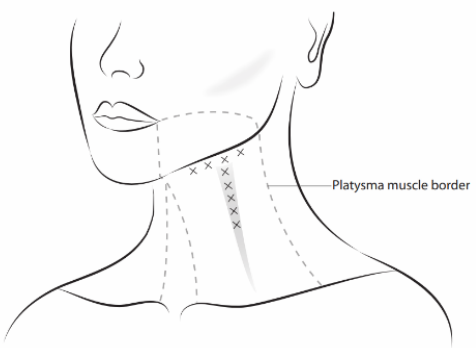


Figure 5: Injection Sites for Platysma Prominence (1 Band)



To reduce injection-related complications, including facial paresis and dysphagia, injection should be at least 1 cm inferior to the lower mandibular border and do not inject into structures deep to the platysma muscle, particularly in the anterior region of the neck.

Care should be taken to ensure that BOTOX is not injected into a blood vessel when it is injected in the platysma muscles seen at maximum contraction (see section 4.4).

Recommended dose:

Using an appropriately sized sterile syringe, needle and aseptic technique, 2 Units/0.05 ml of reconstituted BOTOX is injected into each of the 4 sites in the upper segment of platysma muscle, below the jawline on each side. In addition, 1 Unit/0.025 ml of reconstituted BOTOX is injected into each of the 5 sites along each vertical neck band, 1 to 2 vertical neck bands per side.

Dosing for Platysma Prominence

<table>
<tr><th>Jawline Injection (Inferior to the Lower Mandibular Border)</th><th colspan="2">Vertical Neck Band Injection</th><th>Total Dose (Number of Injection Sites)</th></tr>
<tr><td rowspan="3">2 Units/0.05 ml into each of the 4 sites on each side (16 Units in 8 sites)</td><td rowspan="3">1 Unit/0.025 ml into each of the 5 sites per band (1 to 2 bands/side)</td><td>1 band on both sides (10 Units in 10 sites)</td><td>26 Units (18 sites)</td></tr>
<tr><td>1 band on one side, and 2 bands on the other side (15 Units in 15 sites)</td><td>31 Units (23 sites)</td></tr>
<tr><td>2 bands on both sides (20 Units in 20 sites)</td><td>36 Units (28 sites)</td></tr>
</table>

Maximum dose:

No more than 2 Units should be given for each injection site at the jawline, and no more than 1 Unit should be given for each injection site along the vertical neck bands. The number of injection sites should not be exceeded.

Depending on platysma prominence severity, the total dose should not exceed 26 Units (1 band/side), 31 Units (1 band on one side, 2 bands on the other

	side), or 36 Units (2 bands/side) (see Table above and Figures 4 and 5).
Additional information:	Treatment intervals should not be more frequent than every 3 months. The efficacy and safety of dosing with BOTOX more frequently than every 3 months for the treatment of platysma prominence have not been evaluated. The efficacy and safety of repeat injections of BOTOX for the treatment of platysma prominence beyond 12 months have not been evaluated.

ALL INDICATIONS:

In case of treatment failure after the first treatment session, i.e. absence, at one month after injection, of significant clinical improvement from baseline, the following actions should be taken:

- Clinical verification, which may include electromyographic examination in a specialist setting, of the action of the toxin on the injected muscle(s);
- Analysis of the causes of failure, e.g. bad selection of muscles to be injected, insufficient dose, poor injection technique, appearance of fixed contracture, antagonist muscles too weak, formation of toxin-neutralising antibodies;
- Re-evaluation of the appropriateness of treatment with botulinum toxin type A;
- In the absence of any undesirable effects secondary to the first treatment session, instigate a second treatment session as following: i) adjust the dose, taking into account the analysis of the earlier treatment failure; ii) use EMG; and iii) maintain a three-month interval between the two treatment sessions.

In the event of treatment failure or diminished effect following repeat injections alternative treatment methods should be employed.

When treating adult patients for multiple indications, the maximum cumulative dose should not exceed 400 Units in a 12-week interval.

In treating paediatric patients, including when treating for multiple indications, the maximum cumulative dose should not exceed the lower of 10 Units/kg body weight or 340 Units, in a 12-week interval.

4.3 Contraindications

- known hypersensitivity to botulinum toxin type A or to any of the excipients listed in section 6.1;
- presence of infection at the proposed injection site(s).

For the management of bladder disorders:
- urinary tract infection at the time of treatment;
- acute urinary retention at the time of treatment, in patients who are not routinely catheterising;
- patients who are not willing and/or able to initiate catheterisation post-treatment if required;
- presence of bladder calculi.

4.4 Special warnings and precautions for use

The recommended dosages and frequencies of administration of BOTOX should not be exceeded due to the potential for overdose, exaggerated muscle weakness, distant spread of toxin and the formation of neutralising antibodies. Initial dosing in treatment naïve patients should begin with the lowest recommended dose for the specific indication.

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially "sodium free".

Prescribers and patients should be aware that side effects can occur despite previous injections being well tolerated. Caution should therefore be exercised on the occasion of each administration.

Side effects related to spread of toxin distant from the site of administration have been reported (see section 4.8), sometimes resulting in death, which in some cases was associated with dysphagia, pneumonia and/or significant debility.
The symptoms are consistent with the mechanism of action of botulinum toxin and have been reported hours to weeks after injection. The risk of symptoms is probably greatest in patients who have underlying conditions and comorbidities that would predispose them to these symptoms, including children and adults treated for spasticity, and are treated with high doses.

Patients treated with therapeutic doses may also experience exaggerated muscle weakness.

Elderly and debilitated patients should be treated with caution. Generally, clinical studies of BOTOX did not identify differences in responses between the elderly and younger patients except for facial lines (see section 5.1). Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range.

Consideration should be given to the risk-benefit implications for the individual patient before embarking on treatment with BOTOX.

Dysphagia has also been reported following injection to sites other than the cervical musculature (see section 4.4 'Cervical Dystonia').

BOTOX should only be used with extreme caution and under close supervision in patients with subclinical or clinical evidence of defective neuromuscular transmission

e.g. myasthenia gravis or Lambert-Eaton Syndrome in patients with peripheral motor neuropathic diseases (e.g. amyotrophic lateral sclerosis or motor neuropathy) and in patients with underlying neurological disorders. Such patients may have an increased sensitivity to agents such as BOTOX, even at therapeutic doses, which may result in excessive muscle weakness and an increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise. The botulinum toxin product should be used under specialist supervision in these patients and should only be used if the benefit of treatment is considered to outweigh the risk. Patients with a history of dysphagia and aspiration should be treated with extreme caution.

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

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.

The relevant anatomy, and any alterations to the anatomy due to prior surgical procedures, must be understood prior to administering BOTOX and injection into vulnerable anatomic structures must be avoided.

Pneumothorax associated with injection procedure has been reported following the administration of BOTOX near the thorax.
Caution is warranted when injecting in proximity to the lung (particularly the apices) or other vulnerable anatomic structures.

Serious adverse events including fatal outcomes have been reported in patients who had received off-label injections of BOTOX directly into salivary glands, the oro-lingual-pharyngeal region, oesophagus and stomach. Some patients had pre-existing dysphagia or significant debility.

Serious and/or immediate hypersensitivity reactions have been rarely reported including anaphylaxis, serum sickness, urticaria, soft tissue oedema, and dyspnoea. Some of these reactions have been reported following the use of BOTOX either alone or in conjunction with other products associated with similar reactions. If such a reaction occurs further injection of BOTOX should be discontinued and appropriate medical therapy, such as epinephrine, immediately instituted. One case of anaphylaxis has been reported in which the patient died after being injected with BOTOX inappropriately diluted with 5 ml of 1% lidocaine.

As with any injection, procedure-related injury could occur. An injection could result in localised infection, pain, inflammation, paraesthesia, hypoaesthesia, tenderness, swelling, erythema, and/or bleeding/bruising. Needle-related pain and/or anxiety may result in vasovagal responses, e.g. syncope, hypotension, etc.

Caution should be exercised when BOTOX is used in the presence of inflammation at the proposed injection site(s) or when excessive weakness or atrophy is present in the target muscle. Caution should also be exercised when BOTOX is used for treatment of patients with peripheral motor neuropathic diseases (e.g., amyotrophic lateral sclerosis or motor neuropathy).

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.

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 botulinum toxin injection has not been established. The reports in children were predominantly from cerebral palsy patients treated for spasticity.

Formation of neutralising antibodies to botulinum toxin type A may reduce the effectiveness of BOTOX treatment by inactivating the biological activity of the toxin. Results from some studies suggest that BOTOX injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation. When appropriate, the potential for antibody formation may be minimised by injecting with the lowest effective dose given at the longest clinically indicated intervals between injections.

Clinical fluctuations during the repeated use of BOTOX (as with all botulinum toxins) may be a result of different vial reconstitution procedures, injection intervals, muscles injected and slightly differing potency values given by the biological test method used.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Paediatric use
The safety and efficacy of BOTOX in indications other than those described for the paediatric population in section 4.1 has not been established. Post-marketing reports of possible distant spread of toxin have been very rarely reported in paediatric patients with comorbidities, predominantly with cerebral palsy. In general the dose used in these cases was in excess of that recommended (see section 4.8).

There have been rare spontaneous reports of death sometimes associated with aspiration pneumonia in children with severe cerebral palsy after treatment with botulinum toxin, including following off-label use (e.g. neck area). 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. Treatment in patients with poor underlying health status should be administered only if the potential benefit to the individual patient is considered to outweigh the risks.

NEUROLOGIC DISORDERS

Focal spasticity in adult and paediatric patients
BOTOX is a treatment of focal spasticity that has only been studied in association with usual standard of care regimens, and is not intended as a replacement for these treatment modalities. BOTOX is not likely to be effective in improving range of motion at a joint affected by a fixed contracture.

BOTOX should only be used for the treatment of focal spasticity in adult patients if muscle tone reduction is expected to result in improved function (e.g. improvements in gait), or improved symptoms (e.g. reduction in muscle spasms or pain), and/or to facilitate care. Improvement in active function may be limited if BOTOX treatment is initiated longer than 2 years or in patients with Modified Ashworth Scale (MAS) < 3.

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

There have been post-marketing reports of death (sometimes associated with aspiration pneumonia) and of possible distant spread of toxin in children with co-morbidities, predominantly cerebral palsy following treatment with botulinum toxin. See warnings under section 4.4, 'Paediatric use'.

Blepharospasm
Reduced blinking following botulinum toxin injection into the orbicularis muscle can lead to corneal exposure, persistent epithelial defect, and corneal ulceration, especially in patients with VII nerve disorders. Careful testing of corneal sensation in eyes previously operated upon, avoidance of injection into the lower lid area to avoid ectropion, and vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.

Ecchymosis occurs easily in the soft eyelid tissues. This can be minimised by applying gentle pressure at the injection site immediately after injection.

Because of the anticholinergic activity of botulinum toxin, caution should be exercised when treating patients at risk for angle closure glaucoma, including patients with anatomically narrow angles.

Cervical dystonia
Patients with cervical dystonia should be informed of the possibility of experiencing dysphagia which may be very 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.

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

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

Chronic migraine
No efficacy has been shown for BOTOX in the prophylaxis of headaches in patients with episodic migraine (headaches on < 15 days per month).

BLADDER DISORDERS

Patient preparation and monitoring
Prophylactic antibiotics should be administered to patients with sterile urine or asymptomatic bacteriuria in accordance with local standard practice.

The decision to discontinue anti-platelet therapy should be subject to local guidance and benefit/risk consideration for the individual patient. Patients on anti-coagulant therapy need to be managed appropriately to decrease the risk of bleeding.

Appropriate medical caution should be exercised when performing the cystoscopy. The patient should be observed for at least 30 minutes post-injection.

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

Overactive bladder
Prior to injection an intravesical instillation of diluted local anaesthetic, with or without sedation, may be used, per local site practice. If a local anaesthetic instillation is performed, the bladder should be drained and rinsed with sterile saline before the next steps of the injection procedure.

Urinary incontinence due to neurogenic detrusor overactivity
BOTOX injection can be performed under general or local anaesthesia with or without sedation. If a local anaesthetic intravesical instillation is performed, the bladder should be drained and rinsed with sterile saline before the next steps of the injection procedure.

Autonomic dysreflexia associated with the procedure can occur and greater vigilance is required in patients known to be at risk.

SKIN AND SKIN APPENDAGE DISORDERS

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

Glabellar lines seen at maximum frown and/or crow's feet lines seen at maximum smile and/or forehead lines seen at maximum eyebrow elevation or platysma prominence seen at maximum contraction
It is mandatory that BOTOX is used for one single patient treatment only during a single session. The excess of unused product must be disposed of as detailed in section 6.6. Particular precautions should be taken for product preparation and administration as well as for the inactivation and disposal of the remaining unused solution (see section 6.6).

The use of BOTOX is not recommended in individuals under 18 years. There are limited phase 3 clinical data with BOTOX in patients older than 65 years.

Care should be taken to ensure that BOTOX is not injected into a blood vessel when it is injected in the glabellar lines seen at maximum frown, in the crow's feet lines seen at maximum smile, in the forehead lines seen at maximum eyebrow elevation, or in the platysma muscles seen at maximum contraction, see section 4.2. When injecting in the platysma muscles, should accidental intravascular injection into the carotid artery or jugular vein occur, monitor the patient closely for signs and symptoms as described under accidental injection in section 4.9.

There is a risk of eyelid ptosis following treatment, refer to Section 4.2 for administration instructions on how to minimise this risk.

4.5 Interaction with other medicinal products and other forms of interaction

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

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.

No interaction studies have been performed. No interactions of clinical significance have been reported.

There are no data available on the concomitant use of anticholinergics with BOTOX injections in the management of overactive bladder.

4.6 Fertility, Pregnancy and lactation

Pregnancy
There are no adequate data from the use of botulinum toxin type A in pregnant women. Studies in animals have shown reproductive toxicity (see Section 5.3). The potential risk for humans is unknown. BOTOX is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding
There is no information on whether BOTOX is excreted in human milk. The use of BOTOX during breast-feeding cannot be recommended.

Fertility
There are no adequate data on the effects on fertility from the use of botulinum toxin type A in women of childbearing potential. Studies in male and female rats have shown fertility reductions (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, BOTOX may cause asthenia, muscle weakness, somnolence, dizziness and visual disturbance, which could affect driving and the operation of machinery.

4.8 Undesirable effects

a) General

In controlled clinical trials adverse events considered by the investigators to be related to BOTOX were reported in 35% patients with blepharospasm, 28% with cervical dystonia, 8% with paediatric spasticity, 11% with primary hyperhidrosis of the axillae, 9% in adults with focal spasticity of the upper limb, 11% in adults with focal spasticity of the lower limb, 26% with overactive bladder, 32% in adults with neurogenic detrusor overactivity and 6.2% in paediatric patients with neurogenic detrusor overactivity. In clinical trials for chronic migraine, the incidence was 26% with the first treatment and declined to 11% with a second treatment.

In controlled clinical trials for glabellar lines seen at maximum frown, adverse events considered by the investigators to be related to BOTOX were reported in 23% (placebo 19%) of patients. In treatment cycle 1 of the pivotal controlled clinical trials for crow's feet lines seen at maximum smile, such events were reported in 8% (24 Units for crow's feet lines alone) and 6% (44 Units: 24 Units for crow's feet lines administered simultaneously with 20 Units for glabellar lines) of patients compared to 5% for placebo.

In treatment cycle 1 of clinical trials for forehead lines seen at maximum eyebrow elevation, adverse events considered by the investigators to be related to BOTOX were reported in 20.6% of patients treated with 40 Units (20 Units to the frontalis with 20 Units to the glabellar complex), and 14.3% of patients treated with 64 Units (20 Units to the frontalis with 20 Units to the glabellar complex and 24 Units to the lateral canthal lines areas), compared to 8.9% of patients who received placebo.

In treatment cycle 1 of clinical trials for platysma prominence seen at maximum contraction, adverse events considered by investigators to be related to BOTOX were reported in 4.7% of patients treated with 26 Units, 31 Units, or 36 Units, compared to 5.0% of patients who received placebo.

Adverse reactions may be related to treatment, injection technique or both. In general, adverse reactions occur within the first few days following injection and, while generally transient, may have a duration of several months or, in rare cases, longer.

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

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. Fever and flu syndrome have also been reported after injections of botulinum toxin.

b) Adverse reactions - frequency by indication

The frequency of adverse reactions reported in the clinical trials 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); Not known (cannot be estimated from the available data).

NEUROLOGIC DISORDERS

Focal spasticity of the upper limb in paediatric patients

System Organ Class	Preferred Term	Frequency
Infections and infestations	Upper respiratory tract infection	Common
Gastrointestinal disorders	Nausea	Common
Musculoskeletal and connective tissue disorders	Muscular weakness	Common
General disorders and administration site conditions	Injection site pain	Common

Focal spasticity of the lower limb in paediatric patients

System Organ Class	Preferred Term	Frequency
Skin and subcutaneous tissue disorders	Rash	Common
Musculoskeletal and connective tissue disorders	Muscular weakness	Uncommon
General disorders and administration site conditions	Gait disturbance, injection site pain	Common
Injury, poisoning and procedural complications	Ligament sprain, skin abrasion	Common

Focal upper limb spasticity in adult patients

System Organ Class	Preferred Term	Frequency
Gastrointestinal disorders	Nausea	Common
Musculoskeletal and connective tissue disorders	Pain in extremity, muscular weakness	Common
General disorders and administration site conditions	Fatigue, peripheral oedema	Common

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

Injection of BOTOX for spasticity of the upper limb in patients with decreased pulmonary function has been associated with small but statistically significant decreases in forced vital capacity (FVC) and/or forced expiratory volume 1 second (FEV1) that were subclinical and were not correlated with any adverse clinical pulmonary reactions.

Focal lower limb spasticity in adult patients

System Organ Class	Preferred Term	Frequency
Skin and subcutaneous tissue disorders	Rash	Common
Musculoskeletal and connective tissue disorders	Arthralgia, musculoskeletal stiffness, muscular weakness	Common
General disorders and administration site conditions	Peripheral oedema	Common
Injury, poisoning and procedural complications	Fall	Common

Blepharospasm/hemifacial spasm

System Organ Class	Preferred Term	Frequency
Nervous system disorders	Dizziness, facial paresis, facial palsy	Uncommon
Eye disorders	Eyelid ptosis	Very Common
	Punctate keratitis, lagophthalmos, dry eye, photophobia, eye irritation, lacrimation increase	Common
	Keratitis, ectropion, diplopia, entropion, visual disturbance, blurred vision	Uncommon
	Eyelid oedema	Rare
	Corneal ulceration, corneal epithelium defect, corneal perforation	Very Rare
Skin and subcutaneous tissue disorders	Ecchymosis	Common
	Rash/dermatitis	Uncommon
General disorders and administration site conditions	Irritation, face oedema	Common
	Fatigue	Uncommon

Cervical dystonia

System Organ Class	Preferred Term	Frequency
Infections and infestations	Rhinitis, upper respiratory infection	Common
Nervous system disorders	Dizziness, hypertonia, hypoaesthesia, somnolence, headache	Common
Eye disorders	Diplopia, eyelid ptosis	Uncommon
Respiratory, thoracic and mediastinal disorders	Dyspnoea, dysphonia	Uncommon
Gastrointestinal disorders	Dysphagia	Very common
	Dry mouth, nausea	Common
Musculoskeletal and connective tissue disorders	Muscular weakness	Very common
	Musculoskeletal stiffness and musculoskeletal soreness	Common
General disorders and administration site conditions	Pain	Very common
	Asthenia, influenza-like illness, malaise	Common
	Pyrexia	Uncommon

Chronic migraine

System Organ Class	Preferred Term	Frequency
Nervous system disorders	Headache*, migraine*, including worsening of migraine, facial paresis	Common
Eye disorders	Eyelid ptosis	Common
	Eyelid oedema	Uncommon
Gastrointestinal disorders	Dysphagia	Uncommon
Skin and subcutaneous tissue disorders	Pruritis, rash	Common
	Pain of skin	Uncommon
Musculoskeletal and connective tissue disorders	Neck pain, myalgia, musculoskeletal pain, musculoskeletal stiffness, muscle spasms, muscle tightness, muscular weakness	Common
	Pain in jaw	Uncommon
	Mephisto sign (lateral elevation of eyebrows)	Not known
General disorders and administration site conditions	Injection site pain	Common

* In placebo-controlled trials, headache and migraine, including serious cases of intractable or worsening of headache/migraine, were reported more frequently with BOTOX (9%) than with placebo (6%). They typically occurred within the first month after the injections and their incidence declined with repeated treatments.

BLADDER DISORDERS

Adult overactive bladder

System Organ Class	Preferred Term	Frequency
Infections and infestations	Urinary tract infection	Very common
	Bacteriuria	Common
Renal and urinary disorders	Dysuria†	Very common
	Urinary retention, pollakiuria, leukocyturia	Common
Investigations	Residual urine volume*	Common

**elevated post-void residual urine volume (PVR) not requiring catheterisation*
†procedure-related adverse reactions

In the phase 3 clinical trials urinary tract infection was reported in 25.5% of patients treated with BOTOX 100 Units and 9.6% of patients treated with placebo. Urinary retention was reported in 5.8% of patients treated with BOTOX 100 Units and in 0.4% of patients treated with placebo. Clean intermittent catheterisation was initiated in 6.5% of patients following treatment with BOTOX 100 Units versus 0.4% in the placebo group.

Overall, 42.5% of patients (n = 470) were ≥ 65 years of age and 15.1% (n = 167) were ≥ 75 years of age. No overall difference in the safety profile following BOTOX treatment was observed between patients ≥ 65 years compared to patients < 65 years in these studies, with the exception of urinary tract infection where the incidence was higher in elderly patients in both the placebo and BOTOX groups compared to the younger patients.

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

Paediatric overactive bladder

System Organ Class	Preferred Term	Frequency
Infections and infestations	Urinary tract infection	Common
Renal and urinary disorders	Dysuria*, urethral pain*	Common
Gastrointestinal disorders	Abdominal pain, abdominal pain lower	Common

** procedure-related adverse reaction*

In one double-blind, parallel-group, randomised, multi-centre clinical study conducted in 55 patients aged 12 to 17 years, the adverse reactions were generally comparable with the known safety profile in adult overactive bladder however events of urethral and abdominal pain were also noted in this small paediatric OAB study.

See sections 4.2 and 5.1.

Adult urinary incontinence due to neurogenic detrusor overactivity

System Organ Class	Preferred Term	Frequency
Infections and infestations	Urinary tract infection[a, b], bacteriuria[b]	Very Common
Investigations	Residual urine volume**[b]	Very Common
Psychiatric disorders	Insomnia†[a]	Common
Gastrointestinal disorders	Constipation†[a]	Common
Musculoskeletal and connective tissue disorders	Muscular weakness†[a], muscle spasm[a]	Common
Renal and urinary disorders	Urinary retention[a, b]	Very Common
	Haematuria*[a, b], bladder diverticulum[a], dysuria*[b]	Common
General disorders and administration site conditions	Fatigue†[a], gait disturbance†[a]	Common
Injury, poisoning and procedural complications	Autonomic dysreflexia*[a], fall†[a]	Common

** procedure-related adverse reactions*
*** elevated PVR not requiring catheterisation*
† only in multiple sclerosis
a Adverse reactions occurring in the Phase 2 and pivotal Phase 3 clinical trials
b Adverse reactions occurring in the post-approval study of BOTOX 100U in MS patients not catheterising at baseline

In the phase 3 clinical trials, urinary tract infection was reported in 49% of patients treated with BOTOX 200 Units and in 36% of patients treated with placebo (in multiple sclerosis patients: 53% vs. 29%, respectively; in spinal cord injury patients: 45% vs. 42%, respectively). Urinary retention was reported in 17% of patients treated with BOTOX 200 Units and in 3% of patients treated with placebo (in multiple sclerosis patients: 29% vs. 4%, respectively; in spinal cord injury patients: 5% vs. 1%, respectively). Among patients who were not catheterising at baseline prior to treatment, catheterisation was initiated in 39% following treatment with BOTOX 200 Units versus 17% on placebo. The risk of urinary retention increased in patients older than 65 years.

No change in the type and frequency of adverse reactions was observed following 2 treatments.

In the post-approval study of BOTOX 100 Units in MS patients not catheterising at baseline, 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 Units versus 2.6% on placebo (refer to section 5.1).

Paediatric neurogenic detrusor overactivity

System Organ Class	**Preferred Term**	**Frequency**
Infections and infestations	Bacteriuria	Very Common
	Urinary tract infection, leukocyturia	Common
Renal and urinary disorders	Haematuria	Common

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

See sections 4.2 and 5.1.

SKIN AND SKIN APPENDAGE DISORDERS

Primary hyperhidrosis of the axillae

System Organ Class	**Preferred Term**	**Frequency**
Nervous system disorders	Headache, paraesthesia	Common
Vascular disorders	Hot flushes	Common
Gastrointestinal disorders	Nausea	Uncommon
Skin and subcutaneous tissue disorders	Hyperhidrosis (non axillary sweating), abnormal skin odour, pruritus, subcutaneous nodule, alopecia	Common
Musculoskeletal and connective tissue disorders	Pain in extremity	Common
	Muscular weakness, myalgia, arthropathy	Uncommon
General disorders and administration site conditions	Injection site pain	Very common
	Pain, injection site oedema, injection site haemorrhage, injection site hypersensitivity, injection site irritation, asthenia, injection site reactions	Common

Increase in non axillary sweating was reported in 4.5% of patients within 1 month after injection and showed no pattern with respect to anatomical sites affected. Resolution was seen in approximately 30% of the patients within four months.

Weakness of the arm has been also reported uncommonly (0.7%) and was mild, transient, did not require treatment and recovered without sequelae. This adverse event may be related to treatment, injection technique, or both. In the uncommon event of muscle weakness being reported a neurological examination may be considered. In addition, a re-evaluation of injection technique prior to subsequent injection is advisable to ensure intradermal placement of injections.

In an uncontrolled safety study of BOTOX (50 Units per axilla) in paediatric patients 12 to 17 years of age (n= 144), adverse reactions occurring in more than a single

patient (2 patients each) comprised injection site pain and hyperhidrosis (non-axillary sweating).

Facial lines in adults

The following table represent the adverse reactions that have been reported during the double-blind, placebo-controlled clinical studies following injection of BOTOX for Glabellar lines, Crow's Feet Lines with or without Glabellar Lines, Forehead Lines and Glabellar Lines with or without Crow's Feet Lines.

System Organ Class	**Preferred Term**	**Glabellar Lines**	**Crow's Feet Lines with or without Glabellar Lines**	**Forehead Lines and Glabellar Lines with or without Crow's Feet Lines**
Infections and infestations	Infection	Uncommon	n/a	n/a
Psychiatric disorders	Anxiety	Uncommon	n/a	n/a
Nervous system disorders	Headache	Common	n/a	Common
	Paraesthesia	Common	n/a	n/a
	Dizziness	Uncommon	n/a	n/a
Eye disorders	Eyelid ptosis	Common	n/a	Common[1]
	Blepharitis, eye pain, visual disturbance (includes vision blurred)	Uncommon	n/a	n/a
	Eyelid oedema	Uncommon	Uncommon	n/a
Gastrointestinal disorders	Nausea	Common	n/a	n/a
	Oral dryness	Uncommon	n/a	n/a
Skin and subcutaneous tissue disorders	Erythema	Common	n/a	n/a
	Skin tightness	Common	n/a	Common
	Oedema (face, periorbital), photosensitivity reaction, pruritus, dry skin	Uncommon	n/a	n/a
	Brow Ptosis	n/a	n/a	Common[2]
Musculoskeletal and connective tissue disorders	Localised muscle weakness	Common	n/a	n/a
	Muscle twitching	Uncommon	n/a	n/a

	Mephisto sign (lateral elevation of eyebrows)	Uncommon	n/a	Common
General disorders and administration site conditions	Face pain, injection site oedema, ecchymosis, injection site irritation	Common	n/a	n/a
	Injection site bruising*	n/a	n/a	Common
	Injection site haematoma*	n/a	Common	Common
	Flu syndrome, asthenia, fever	Uncommon	n/a	n/a
	Injection site haemorrhage*	n/a	Uncommon	n/a
	Injection site pain	Common	Uncommon*	Uncommon*
	Injection site paraesthesia	n/a	Uncommon	n/a

n/a – not reported as adverse drug reaction
procedure-related adverse reactions
[1]The median time to onset of eyelid ptosis was 9 days following treatment
[2]The median time to onset of brow ptosis was 5 days following treatment

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

Platysma Prominence

The safety of BOTOX was evaluated in the double-blind, placebo-controlled clinical studies for the improvement of platysma prominence. No adverse reactions were reported by ≥1% of BOTOX treated subjects that were also more frequent than in placebo-treated subjects.

The safety of up to 4 BOTOX treatments for platysma prominence was also assessed. Eligible subjects who received BOTOX or placebo in the lead-in double-blind, placebo-controlled study received up to 3 additional BOTOX treatments in its open-label extension study. The following adverse reactions were reported during open-label treatment of platysma prominence:

System Organ Class	**Preferred Term**	**Frequency**
Gastrointestinal disorders	Dysphagia	Uncommon
Nervous System disorders	Facial paresis	Uncommon

No change was observed in the overall safety profile with repeat dosing of up to 4 BOTOX treatments.

c) Additional information

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 section 4.4 (Special warnings and precautions for use), and section 4.8 (Undesirable effects).

System Organ Class	**Preferred Term**

Immune system disorders	Anaphylaxis, angioedema, serum sickness, urticaria
Metabolism and nutrition disorders	Anorexia
Nervous system disorders	Brachial plexopathy, dysphonia, dysarthria, facial paresis, hypoaesthesia, muscle weakness, myasthenia gravis, peripheral neuropathy, paraesthesia, radiculopathy, seizures, syncope, facial palsy
Eye disorders	Angle-closure glaucoma (for treatment of blepharospasm), eyelid ptosis, lagophthalmos, strabismus, blurred vision, visual disturbance, dry eye, eyelid oedema
Ear and labyrinth disorders	Hypoacusis, tinnitus, vertigo
Cardiac disorders	Arrhythmia, myocardial infarction
Respiratory, thoracic and mediastinal disorders	Aspiration pneumonia (some with fatal outcome), dyspnoea, respiratory depression, respiratory failure
Gastrointestinal disorders	Abdominal pain, diarrhoea, constipation, dry mouth, dysphagia, nausea, vomiting
Skin and subcutaneous tissue disorders	Alopecia, brow ptosis, dermatitis psoriasiform, erythema multiforme, hyperhidrosis, madarosis, pruritus, rash
Musculoskeletal and connective tissue disorders	Muscle atrophy, myalgia, localised muscle twitching/involuntary muscle contractions
General disorders and administration site conditions	Denervation atrophy, malaise, pyrexia

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Overdose of BOTOX is a relative term and depends upon dose, site of injection, and underlying tissue properties. No cases of systemic toxicity resulting from accidental injection of BOTOX have been observed. Excessive doses may produce local, or distant, generalised and profound neuromuscular paralysis. No cases of ingestion of BOTOX have been reported.

Signs and symptoms of overdose are not apparent immediately post-injection. Should accidental injection or ingestion occur or overdose be suspected, the patient should be medically monitored for up to several weeks for progressive signs and symptoms of muscular weakness, which could be local or distant from the site of injection and may include ptosis, diplopia, dysphagia, dysarthria, generalised weakness or respiratory failure. These patients should be considered for further medical evaluation and appropriate medical therapy immediately instituted, which may include hospitalisation.

If the musculature of the oropharynx and oesophagus are affected, aspiration may occur which may lead to development of aspiration pneumonia. If the respiratory muscles become paralysed or sufficiently weakened, intubation and assisted respiration will be required until recovery takes place and may involve the need for a

tracheostomy and prolonged mechanical ventilation, in addition to other general supportive care.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC class M03A X01 and ATC class D11AX.

The active constituent in BOTOX is a protein complex derived from *Clostridium botulinum*. The protein consists of type A neurotoxin and several other proteins. Under physiological conditions it is presumed that the complex dissociates and releases the pure neurotoxin.

Clostridium botulinum toxin type A neurotoxin complex blocks peripheral acetyl choline release at presynaptic cholinergic nerve terminals.

Intramuscular injection of the neurotoxin complex blocks cholinergic transport at the neuromuscular junction by preventing the release of acetylcholine. The nerve endings of the neuromuscular junction no longer respond to nerve impulses and secretion of the chemotransmitter is prevented (chemical denervation). Re-establishment of impulse transmission is by newly formed nerve endings and motor end plates. Clinical evidence suggests that BOTOX reduces pain and neurogenic inflammation and elevates cutaneous heat pain thresholds in a capsaicin induced trigeminal sensitisation model. Recovery after intramuscular injection takes place normally within 12 weeks of injection as nerve terminals sprout and reconnect with the endplates.

After intradermal injection, where the target is the eccrine sweat glands, the effect lasted for about 4-7 months in patients treated with 50 Units per axilla.

There is limited clinical trial experience of the use of BOTOX in primary axillary hyperhidrosis in adolescents between the ages of 12 and 18. A single, year long, uncontrolled, repeat dose, safety study was conducted in US paediatric patients 12 to 17 years of age (N=144) with severe primary hyperhidrosis of the axillae. Participants were primarily female (86.1%) and Caucasian (82.6%). Participants were treated with a dose of 50 Units per axilla for a total dose of 100 Units per patient per treatment. However, no dose finding studies have been conducted in adolescents so no recommendation on posology can be made. Efficacy and safety of BOTOX in this group have not been established.

BOTOX blocks the release of neurotransmitters associated with the genesis of pain. The presumed mechanism for headache prophylaxis is by blocking peripheral signals to the central nervous system, which inhibits central sensitisation, as suggested by pre-clinical and clinical pharmacodynamic studies.

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

Clinical efficacy and safety

NEUROLOGIC DISORDERS

Focal spasticity of the upper limb in paediatric patients

The efficacy and safety of BOTOX for the treatment of upper limb spasticity in paediatric patients of ages 2 years and older was evaluated in a randomised, multi-centre, double-blind, placebo-controlled study. The study included 234 paediatric patients (77 BOTOX 6 Units/kg, 78 BOTOX 3 Units/kg and 79 placebo) with upper limb spasticity because of cerebral palsy (87%) or stroke (13%) and baseline MAS elbow or wrist score of at least 2. A total dose of 3 Units/kg (maximum 100 Units) or 6 Units/kg (maximum 200 Units) or placebo was injected intramuscularly and divided between the elbow or wrist and finger muscles. All patients received standardised occupational therapy. The use of electromyographic guidance, nerve stimulation, or ultrasound techniques was required to assist in proper muscle localisation for injections. The primary endpoint was the average of the change from baseline in MAS score of the principal muscle group (elbow or wrist) at weeks 4 and 6 and the key secondary endpoint was the average of the Clinical Global Impression of Overall Change by Physician (CGI) at weeks 4 and 6. The Goal Attainment Scale (GAS) by Physician for active and passive goals was evaluated as a secondary endpoint at weeks 8 and 12. Pain was assessed using the Faces Pain Scale (FPS) in a subset of patients. Patients were followed for 12 weeks.
Eligible patients could enter an open-label extension study, in which they received up to five treatments at doses up to 10 Units/kg (maximum 340 Units), when also treating the lower limb in combination with the upper limb.
Statistically significant improvements compared to placebo were demonstrated in patients treated with BOTOX 3 and 6 Units/kg for the primary endpoint and at all timepoints through week 12. The improvement in MAS score was similar across both BOTOX treatment groups. However, at no point was the difference from placebo ≥ 1 point on the MAS. See table below. Responder analysis treatment effect ranged from approximately 10-20%.

Primary and Secondary Efficacy Endpoints Results

	BOTOX 3 Units/kg (N=78)	BOTOX 6 Units/kg (N=77)	Placebo (N=79)
Mean Change from Baseline in Principal Muscle Group (Elbow or Wrist) on the MAS[a]			
Week 4 and 6 Average	-1.92*	-1.87*	-1.21
Mean Change from Baseline in Finger Flexor Muscle on the MAS[a]			
Week 4 and 6 Average	-1.46	-1.41	-1.02
Mean CGI Score[b]			
Week 4 and 6 Average	1.88	1.87	1.66
Mean GAS Score[c]			
Passive goals at Week 8	0.23	0.30	0.06
Passive goals at Week 12	0.31	0.71*	0.11
Active goals at Week 8	0.12	0.11	0.21
Active goals at Week 12	0.26	0.49	0.52
Mean Change from Baseline on FPS Score[d]	**N=11**	**N=11**	**N=18**
Week 4	-4.91	-3.17	-3.55
Week 6	-3.12	-2.53	-3.27

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

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

[b] The CGI evaluated the response to treatment in terms of how the patient was doing in his/her life using a 9-point scale (-4=very marked worsening to +4=very marked improvement).

[c] The GAS is a 6-point scale (-3[worse than start], -2 [equal to start], -1 [less than expected], 0 [expected goal], +1 [somewhat more than expected], +2 [much more than expected]).

[d] Pain was assessed in participants who were 4 years of age and older and had a pain score > 0 at baseline using Faces Pain Scale (FPS: 0 =no pain to 10 = very much pain).

Focal spasticity of the lower limb in paediatric patients

The efficacy and safety of BOTOX for the treatment of lower limb spasticity in paediatric patients of ages 2 years and above was evaluated in a randomised, multi-centre, double-blind, placebo-controlled study. The study included 384 paediatric patients (128 BOTOX 8 Units/kg, 126 BOTOX 4 Units/kg and 128 placebo) with lower limb spasticity because of cerebral palsy and ankle score of at least 2. A total dose of 4 Units/kg (maximum 150 Units) or 8 Units/kg (maximum 300 Units) or placebo was injected intramuscularly and divided between the gastrocnemius, soleus and tibialis posterior. All patients received standardised physical therapy. The use of electromyographic guidance, nerve stimulation, or ultrasound techniques was required to assist in proper muscle localisation for injections. The primary endpoint was the average of the change from baseline in MAS ankle score at weeks 4 and 6, and the key secondary endpoint was the average of the CGI at weeks 4 and 6. The GAS by Physician for active and passive functional goals was a secondary endpoint at weeks 8 and 12. Gait was assessed using the Edinburgh Visual Gait (EVG) at weeks 8 and 12 in a subset of patients. Patients were followed for 12 weeks.

Eligible patients could enter an open-label extension study, in which they received up to five treatments at doses up to 10 Units/kg (maximum 340 Units), if treating more than one limb.

Statistically significant improvements compared to placebo were demonstrated in patients treated with BOTOX 4 and 8 Units/kg for the primary endpoint and at most timepoints through Week 12. The improvement in MAS score was similar across both BOTOX treatment groups. However, at no point was the difference from placebo ≥1

point on the MAS. See table below. Responder analysis treatment effect was less than 15% at all time points.

Primary and Secondary Efficacy Endpoints Results

	BOTOX 4 Units/kg (N=125)	**BOTOX 8 Units/kg (N=127)**	**Placebo (N=129)**
Mean Change from Baseline in Plantar Flexors on the MAS[a]			
Week 4 and 6 Average	-1.01*	-1.06*	-0.80
Mean CGI Score[b]			
Week 4 and 6 Average	1.49	1.65*	1.36
Mean GAS Score[c]			
Passive goals at Week 8	0.18*	0.19*	-0.26
Passive goals at Week 12	0.27	0.40*	0.00
Active goals at Week 8	-0.03*	0.10*	-0.31
Active goals at Week 12	0.09	0.37*	-0.12
Mean Change from Baseline on EVG Score[d]			
Week 8	-2.11	-3.12*	-0.86
Week 12	-2.07	-2.57	-1.68

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

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

[b] The CGI evaluated the response to treatment in terms of how the patient was doing in his/her life using a 9-point scale (-4=very marked worsening to +4=very marked improvement).

[c] The GAS is a 6-point scale (-3[worse than start], -2 [equal to start], -1 [less than expected], 0 [expected goal], +1 [somewhat more than expected], +2 [much more than expected]).

[d] The EVG is an 11- item scale that assesses gait based on foot-stance (5 items), knee-stance (2 items), foot-swing (2 items) and knee-swing (2 items) using a 3-point ordinal scale (0 [normal], 1 [flexion 1 or extension 1], and 2 [flexion 2 or extension 2] for each item, respectively).

In paediatric lower limb spasticity patients with analysed specimens from one phase 3 study and the open-label extension study, neutralising antibodies developed in 2 of 264 patients (0.8%) treated with BOTOX for up to 5 treatment cycles. Both patients continued to experience clinical benefit following subsequent BOTOX treatments.

Focal upper limb spasticity in adult patients

The efficacy and safety of BOTOX for the treatment of adult upper limb spasticity was evaluated in 4 randomised, multi-centre, double-blind, placebo-controlled studies.

Study 1 included 126 adult patients (64 BOTOX and 62 placebo) with upper limb spasticity (Ashworth score of at least 3 for wrist flexor tone and at least 2 for finger flexor tone) who were at least 6 months post-stroke. BOTOX (a total dose of 200 Units to 240 Units) or placebo were injected intramuscularly into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and if necessary into the adductor pollicis and flexor pollicis longus.

Study 1 results on the primary endpoint and the key secondary endpoints are shown in the Table below.

Primary and Secondary Efficacy Endpoints Results at Week 6 in Study 1

	BOTOX 200 to 240 Units (N=64)	Placebo (N=62)
Mean Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale [a]	-1.7*	-0.5
Mean Physician Global Assessment of Response to Treatment[b]	1.8*	0.6
Mean Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale[a]	-1.3*	-0.5
Mean Change from Baseline in Thumb Flexor Muscle Tone on the Ashworth Scale[a]	-1.7*	-0.5

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

[a] The Ashworth Scale is a 5-point scale (0 [no increase in muscle tone], 1, 2, 3, and 4 [limb rigid in flexion or extension]) which measures the force required to move an extremity around a joint, with a reduction in score representing improvement in spasticity.

[b] The Physician Global Assessment evaluated the response to treatment in terms of how the patient was doing in his/her life using a scale from -4 = very marked worsening to +4 = very marked improvement.

Study 2 included 124 adult post-stroke patients with upper limb spasticity who received either 400 U BOTOX (240 U in wrist, finger and thumb flexors and 160 U in the elbow flexors; n=61) or 240 U BOTOX (wrist, finger and thumb flexors and placebo in the elbow flexors; n=63). Patients were followed for 12 weeks and then entered the open label phase during which they could receive up to 3 additional treatments of 400 U BOTOX, at minimum 12-week intervals, distributed among finger, thumb, wrist, or elbow flexors, forearm pronators, or shoulder adductors/internal rotators.

The main efficacy results for elbow flexors are shown below.

Efficacy Results for Elbow Flexors at Week 6 in Study 2

	BOTOX 400 U (160 U elbow) (N=61)	BOTOX 240 U (placebo elbow) (N=63)
MAS Elbow Flexors Responder Rate[a]	68.9%*	50.8%
Mean Change from Baseline in Elbow Flexor Muscle Tone on the MAS[b]	-1.1**	-0.7
Mean CGI score by Physician[c]	1.5	1.4
CGI by Physician Responder Rate[d]	82.0%	79.4%
Mean CGI score by Patient[c]	1.2	1.3
Mean Change from Baseline NRS Pain score in Elbow[e]	-0.9	-0.6
Mean Change from Baseline DAS Limb Position[f]	-0.6	-0.2

* difference from 240 U=18.1%; 95% Confidence Interval 1.1 to 35.0.

**nominal p value <0.05

[a] Proportion of patients with Modified Ashworth Scale (MAS) score ≥ 1-grade improvement.

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

[c] Clinical Global Impression of Overall Change (CGI) score, as rated by Physician or Patient, evaluates global improvement from -4 (very much worsened) to +4 (very much improved).

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

[e] Pain severity in the elbow was rated on a scale from 0 to 10, with 0 being "no pain" and 10 being "pain as bad as you can imagine".

[f] The Disability Assessment Scale (DAS) is a 4-point scale of 0 to 3, where 0 indicates no disability and 3 indicates severe disability.

A total of 84 patients from Study 2 received open-label treatments of BOTOX in the shoulder adductors/internal rotators. The results achieved at week 6 for the MAS in the shoulder muscles are shown below.

Efficacy Results for Shoulder at Week 6 of Open-label Treatment Cycles in Study 2

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

Study 3 enrolled 53 adult post-stroke patients with upper limb spasticity. Patients received a single fixed-dose, fixed-muscle treatment of either BOTOX 300 U (150 U elbow; 150 U shoulder), BOTOX 500 U (250 U elbow; 250 U shoulder), or placebo, divided across defined muscles of the elbow and shoulder in a single limb.

The main efficacy results are shown below.

Efficacy Results for Elbow and Shoulder at Week 6 in Study 3

	BOTOX 300 U (N=18)	**BOTOX 500 U (N=17)**	**Placebo (N=18)**
Mean Change from Baseline in Elbow Flexor Muscle Tone on the MAS	-1.47	-1.62*	-0.74
MAS Elbow Flexors Responder Rate[a]	72.2%	75.0%	47.1%
Mean Change from Baseline in Shoulder Muscle Tone on the MAS	-1.4	-1.6	-1.4

Mean Shoulder-Specific CGI Score by Physician[b]	1.22	1.21	1.04
Mean CGI score by Physician[c]	1.31	1.21	0.94

[*] Significantly different from placebo ($p \leq 0.05$)
[a] Proportion of patients with Modified Ashworth Scale (MAS) score ≥ 1-grade improvement.
[b] The shoulder-specific Clinical Global Impression of Overall Change by Physician (CGI) evaluates global improvement in the shoulder joint from -4 (very much worsened) to +4 (very much improved).
[c] CGI score evaluates global improvement from -4 (very much worsened) to +4 (very much improved).

Study 4 included a subgroup of 26 adult post-stroke patients with upper limb spasticity who received up to 2 treatments of BOTOX in up to 3 affected shoulder muscles (pectoralis major with or without teres major and latissimus dorsi). The main results are presented in the table below.

Efficacy Results for Shoulder at Week 10 post-2nd injection or Week 24 in Study 4

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

[a] The REsistance to PAssive movement Scale (REPAS) quantifies resistance to passive movement for passive arm and leg motions and is scored on a scale of 0 (no increase in tone) to 4 (limb rigid in flexion or extension), with a higher score denoting greater resistance to movement. REPAS for shoulder extension is presented here.
[b] Goal Attainment Scale (GAS) is a 6-point scale in which the physician rates goal attainment from -3 (worse than start), -2 (equal to start), -1 (less than expected), 0 (expected goal), +1 (somewhat more than expected) or +2 (much more than expected).

Across 4 studies in patients with adult upper limb spasticity, neutralising antibodies developed in 2 of 406 patients (0.49%) treated with BOTOX. One patient was not a clinical responder following any treatment cycle. The second patient experienced inconsistent clinical response both before and after seroconversion.

Focal lower limb spasticity in adult patients

The efficacy and safety of BOTOX was evaluated in a randomised, multi-centre, double-blind, placebo-controlled study which 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. BOTOX 300 to 400 Units or placebo were injected intramuscularly into the study mandatory muscles gastrocnemius, soleus, and tibialis posterior and optional muscles including flexor hallucis longus, flexor digitorum longus, flexor digitorum brevis, extensor hallucis, and rectus femoris.

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. Statistically and clinically significant differences were demonstrated between BOTOX and placebo for these measures as shown in the table below.
For the primary endpoint of average MAS ankle score at weeks 4 and 6, no improvement from baseline was observed for patients aged 65 and older in the BOTOX group compared to placebo.

	BOTOX 300 to 400 Units (N=233)	**Placebo (N=235)**
Mean Change from Baseline in Ankle Plantar Flexors in MAS Score		
Week 4 and 6 Average	-0.8*	-0.6
Mean Clinical Global Impression Score by Investigator		
Week 4 and 6 Average	0.9*	0.7
Mean Change from Baseline in Toe Flexors in MAS Score		
FHaL Week 4 and 6 Average	-1.02*	-0.6
FDL Week 4 and 6 Average	-0.88	- 0.77
Mean Change from Baseline in Ankle Plantar Flexors in MAS Score for Patients ≥ 65 years	**N=60**	**N=64**
Week 4 and 6 Average	-0.7	-0.7

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

Another double-blind, placebo-controlled, randomised, multicentre, phase 3 clinical study was conducted in adult post-stroke patients (average 6.5 years) with lower limb spasticity affecting the ankle. A total of 120 patients were randomised to receive either BOTOX (n=58; total dose of 300 Units) or placebo (n=62).

Significant improvement compared to placebo was observed in the primary endpoint for the overall change from baseline up to week 12 in the MAS ankle score, which was calculated using the area under the curve (AUC) approach. Significant improvements compared to placebo were also observed for the mean change from baseline in MAS ankle score at individual post-treatment visits at weeks 4, 6 and 8. The proportion of responders (patients with at least a 1-grade improvement) was also significantly higher (67%-68%) than in placebo-treated patients (31%-36%) at these visits.

BOTOX treatment was also associated with significant improvement in the investigator's clinical global impression (CGI) of functional disability compared to placebo although the difference was not significant for the patient's CGI.

Cervical dystonia

In initial controlled clinical trials to establish safety and efficacy for cervical dystonia, doses of reconstituted BOTOX ranged from 140 to 280 Units. In more recent studies, doses ranged from 95 to 360 Units (with an approximate mean of 240 Units). Clinical improvement generally occurs within the first two weeks after injection. The maximum clinical benefit generally occurs by six weeks post-injection. The duration of beneficial effect reported in clinical studies showed substantial variation (from 2 to

33 weeks) with a typical duration of approximately 12 weeks.

Chronic migraine

Chronic migraine patients without any concurrent headache prophylaxis who, during a 28-day baseline, had at least 4 episodes and ≥ 15 headache days (with at least 4 hours of continuous headache) with at least 50% being migraine/probable migraine, were studied in two Phase 3 clinical trials. Patients were allowed to use acute headache treatments and 66% overused acute treatments during the baseline period.

During the double-blind phase of the trials, the main results achieved after two BOTOX treatments administered at a 12-week interval are shown in the table below.

Mean change from baseline at Week 24	**BOTOX** N=688	**Placebo** N=696	**P-value**
Frequency of headache days	-8.4	-6.6	< 0.001
Frequency of moderate/severe headache days	-7.7	-5.8	< 0.001
Frequency of migraine/probable migraine days	-8.2	-6.2	< 0.001
% patients with 50% reduction in headache days	47%	35%	< 0.001
Total cumulative hours of headache on headache days	120	80	< 0.001
Frequency of headache episodes	-5.2	-4.9	0.009
Total HIT-6* scores	-4.8	-2.4	< 0.001

* Headache Impact Test

The treatment effect appeared smaller in the subgroup of male patients (n=188) than in the whole study population.

BLADDER DISORDERS

Adult overactive bladder

Two double-blind, placebo-controlled, randomised, 24-week phase 3 clinical studies were conducted in patients with overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. A total of 1105 patients (mean age of 60 years), whose symptoms had not been adequately managed with at least one anticholinergic therapy (inadequate response or intolerable side effects), were randomised to receive either 100 Units of BOTOX (n=557), or placebo (n=548), after having discontinued anticholinergics for more than one week.

Primary and Secondary Endpoints at Baseline and Change from Baseline in Pooled Pivotal Studies

	Botox 100 Units (N=557)	**Placebo (N=548)**	**P-value**
Daily Frequency of Urinary Incontinence Episodes			
Mean Baseline	5.49	5.39	
Mean Change† at Week 2	-2.66	-1.05	< 0.001
Mean Change† at Week 6	-2.97	-1.13	< 0.001
Mean Change† at Week 12[a]	-2.74	-0.95	< 0.001
Proportion with Positive Treatment Response using Treatment Benefit Scale (%)			
Week 2	64.4	34.7	< 0.001

Week 6	68.1	32.8	< 0.001
Week 12[a]	61.8	28.0	< 0.001
Daily Frequency of Micturition Episodes			
Mean Baseline	11.99	11.48	
Mean Change[†] at Week 12[b]	-2.19	-0.82	< 0.001
Daily Frequency of Urgency Episodes			
Mean Baseline	8.82	8.31	
Mean Change[†] at Week 12[b]	-3.08	-1.12	< 0.001
Incontinence Quality of Life Total Score			
Mean Baseline	34.1	34.7	
Mean Change[†] at Week 12[bc]	+21.3	+5.4	< 0.001
King's Health Questionnaire: Role Limitation			
Mean Baseline	65.4	61.2	
Mean Change[†] at Week 12[bc]	-24.3	-3.9	< 0.001
King's Health Questionnaire: Social Limitation			
Mean Baseline	44.8	42.4	
Mean Change[†] at Week 12[bc]	-16.1	-2.5	< 0.001
Percentage of patients achieving full continence at Week 12 (dry patients over a 3-day diary)	27.1%	8.4%	< 0.001
Percentage of patients achieving reduction from baseline in urinary incontinence episodes at Week 12			
at least 75%	46.0%	17.7%	
at least 50%	60.5%	31.0%	

[†] Least Squares (LS) mean changes are presented
[a] Co-primary endpoints
[b] Secondary endpoints
[c] Pre-defined minimally important change from baseline was +10 points for I-QOL and -5 points for KHQ

The median duration of response following BOTOX treatment, based on patient request for re-treatment, was 166 days (~24 weeks). The median duration of response, based on patient request for re-treatment, in patients who continued into the open label extension study and received treatments with only BOTOX 100 Units (N=438), was 212 days (~30 weeks).

A total of 839 patients were evaluated in a long-term open-label extension study. For all efficacy endpoints, patients experienced consistent response with re-treatments. The mean reductions from baseline in daily frequency of urinary incontinence were -3.07 (n=341), -3.49 (n=292), and -3.49 (n=204) episodes at week 12 after the first, second, and third BOTOX 100 Unit treatments, respectively. The corresponding proportions of patients with a positive treatment response on the Treatment Benefit Scale were 63.6% (n=346), 76.9% (n=295), and 77.3% (n=207), respectively.

In the pivotal studies, none of the 615 patients with analysed serum specimens developed neutralising antibodies after 1 – 3 treatments. In patients with analysed specimens from the pivotal phase 3 and the open-label extension studies, neutralising antibodies developed in 0 of 954 patients (0.0%) while receiving BOTOX 100 Unit doses and 3 of 260 patients (1.2%) after subsequently receiving at least one 150 Unit dose. One of these three patients continued to experience clinical benefit. Compared to the overall BOTOX treated population, patients who developed neutralising antibodies generally had shorter duration of response and consequently received treatments more frequently (see section 4.4).

Paediatric overactive bladder

Limited efficacy data are available from one double-blind, parallel-group, randomised, multi-centre clinical study (191622-137) in patients aged 12 to 17 years with overactive bladder with symptoms of urinary incontinence. A total of 55 (of the planned 108) patients who had an inadequate response to or were intolerant of at least one anticholinergic medication were enrolled, resulting in insufficient sample size to conclude effectiveness in this population. The patients were randomised to 25 Units, 50 Units or 100 Units, not to exceed 6 Units/kg body weight; N=18, N=17, N=20 for BOTOX 25 Units, BOTOX 50 Units, and BOTOX 100 Units, respectively. Prior to treatment administration, patients received anaesthesia based on local site practice. All patients received general anaesthesia or conscious sedation.

Primary and Secondary Endpoint Results at Baseline and Change from Baseline in a Double-Blind, Parallel-Group Clinical Study

	BOTOX 100 Units N=20	**BOTOX 50 Units N=17**	**BOTOX 25 Units N=18**	**p-value BOTOX 100 vs. 25 Units**	**p-value BOTOX 50 vs. 25 Units**
Daily frequency of daytime urinary incontinence episodes[a] Mean Baseline Mean Change* at Week 12** (95% CI)	3.6 -2.3 (-3.8, -0.9)	3.5 -1.0 (-2.6, 0.7)	5.3 -1.4 (-3.0, 0.2)	0.3802	0.7330
Proportion of Patients with at Least 50% Reduction from Baseline in Daily Frequency of Daytime UI Episodes[b]**(%)** Week 12[c] (95% CI)	80.0 (56.3, 94.3)	47.1 (23.0, 72.2)	50.0 (26.0, 74.0)	0.0472	0.9924
Positive treatment response ("greatly improved" or "improved")[b]**(%)** Week 12[c] (95% CI)	68.4 (43.5, 87.4)	70.6 (44.0, 89.7)	52.9 (27.8, 77.0)	0.6092	0.4824
Daily Frequency of Daytime Micturition Episodes[b] Baseline Mean Mean Change* at Week 12** (95% CI)	8.1 -1.0 (-3.0, 1.0)	8.5 0.3 (-1.7, 2.4)	11.2 -1.8 (-3.9, 0.2)	0.5743	0.1451
Daily Frequency of Daytime Urgency Episodes[b] Baseline Mean Mean Change* at Week 12** (95% CI)	4.4 -2.2 (-4.1, -0.3)	5.4 -1.8 (-3.8, 0.2)	7.5 -1.9 (-3.9, 0.2)	0.8206	0.9604

CI = Confidence Interval

* Least squares (LS) mean change from baseline, treatment difference, 95% CI and P-value are based on an ANCOVA model with baseline value as covariate and treatment group as factor. Last observation carried forward values were used to analyse the primary efficacy variable.

** Primary timepoint

a. Primary variable.
b. Secondary variable.
c. P-values are obtained from Cochran–Mantel–Haenszel test, stratified by baseline daytime urinary urgency incontinence episodes (≤ 6 or > 6). Exact (Clopper-Pearson) 95% CI is constructed using the binomial distribution.

In the 55 paediatric patients who had a negative baseline result for binding antibodies or neutralising antibodies and had at least one evaluable post-baseline value from one randomised double-blind study, no patients developed neutralising antibodies after receiving 25 Units to 100 Units of BOTOX.

Adult urinary incontinence due to neurogenic detrusor overactivity

Pivotal Phase 3 Clinical Trials
Two double-blind, placebo-controlled, randomised phase 3 clinical studies were conducted in a total of 691 patients with spinal cord injury or multiple sclerosis, who were not adequately managed with at least one anticholinergic agent and were either spontaneously voiding or using catheterisation. These patients were randomised to receive either 200 Units of BOTOX (n=227), 300 Units of BOTOX (n=223), or placebo (n=241).

Primary and Secondary Endpoints at Baseline and Change from Baseline in Pooled Pivotal Studies

	BOTOX 200 Units (N=227)	**Placebo (N=241)**	**P-value**
Weekly Frequency of Urinary Incontinence			
Mean Baseline	32.4	31.5	
Mean Change† at Week 2	-16.8	-9.1	<0.001
Mean Change† at Week 6[a]	-20.0	-10.5	<0.001
Mean Change† at Week 12	-19.8	-9.3	<0.001
Maximum Cystometric Capacity (ml)			
Mean Baseline	250.2	253.5	
Mean Change† at Week 6[b]	+140.4	+6.9	<0.001
Maximum Detrusor Pressure during 1st Involuntary Detrusor Contraction (cmH20)			
Mean Baseline	51.5	47.3	
Mean Change† at Week 6[b]	-27.1	-0.4	<0.001
Incontinence Quality of Life Total Score[c,d]			
Mean Baseline	35.4	35.3	
Mean Change† at Week 6[b]	+23.6	+8.9	<0.001
Mean Change† at Week 12	+26.9	+7.1	<0.001
Percentage of patients achieving full continence at Week 6 (dry patients over a 7-day diary)	37%	9%	
Percentage of patients achieving reduction from baseline in urinary incontinence episodes at Week 6			
at least 75%	63%	24%	
at least 50%	76%	39%	

† LS mean changes are presented
[a] Primary endpoint
[b] Secondary endpoints
[c] I-QOL total score scale ranges from 0 (maximum problem) to 100 (no problem at all).
[d] In the pivotal studies, the pre-specified minimally important difference (MID) for I-QOL total score was 8 points based on MID estimates of 4-11 points reported in neurogenic detrusor overactivity patients.

The median duration of response, based on time to qualification for re-treatment (time to < 50% reduction in incontinence episodes), was 42 weeks in the 200 Unit dose group. The median interval between the first and second administrations was 42 weeks in patients with spinal cord injury and 45 weeks in patients with multiple sclerosis. The median duration of response, based on time to qualification for re-treatment (at least 1 urinary incontinence episode in a 3 day diary), in patients who continued into the open label extension study and received treatments with only BOTOX 200 Units (N=174), was 264 days (~38 weeks).

For all efficacy endpoints in the pivotal phase 3 studies, patients experienced consistent response with re-treatment (n=116).

None of the 475 patients with analysed serum specimens developed neutralising antibodies after 1-2 treatments. In patients with analysed specimens in the drug development program (including the open-label extension study), neutralising antibodies developed in 3 of 300 patients (1.0%) after receiving only BOTOX 200 Unit doses and 5 of 258 patients (1.9%) after receiving at least one 300 Unit dose. Four of these eight patients continued to experience clinical benefit. Compared to the overall BOTOX treated population, patients who developed neutralising antibodies generally had shorter duration of response and consequently received treatments more frequently (see section 4.4).

In the multiple sclerosis (MS) patients enrolled in the pivotal studies, the MS exacerbation annualised rate (i.e. number of MS exacerbation events per patient year) was 0.23 in the 200 Unit dose group and 0.20 in the placebo group. With repeated BOTOX treatments, including data from a long-term study, the MS exacerbation annualised rate was 0.19 during each of the first two BOTOX treatment cycles.

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

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

Results from the post-approval study are presented below:

Primary and Secondary Endpoints at Baseline and Change from Baseline in Post-Approval Study of BOTOX 100 Units in MS patients not catheterising at baseline

	BOTOX 100 Units (N=66)	**Placebo (N=78)**	**p-values**
Daily Frequency of Urinary Incontinence*			
Mean Baseline	4.2	4.3	
Mean Change at Week 2	-2.9	-1.2	p<0.001
Mean Change at Week 6[a]	**-3.3**	**-1.1**	**p<0.001**
Mean Change at Week 12	-2.8	-1.1	p<0.001

Maximum Cystometric Capacity (mL)			
Mean Baseline	246.4	245.7	
Mean Change at Week 6[b]	**+127.2**	**-1.8**	**p<0.001**
Maximum Detrusor Pressure during 1st Involuntary Detrusor Contraction (cmH_2O)			
Mean Baseline	35.9	36.1	
Mean Change at Week 6[b]	**-19.6**	**+3.7**	**p=0.007**
Incontinence Quality of Life Total Score[c,d]			
Mean Baseline	32.4	34.2	
Mean Change at Week 6[b]	**+40.4**	**+9.9**	**p<0.001**
Mean Change at Week 12	+38.8	+7.6	p<0.001

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

[a] Primary endpoint

[b] Secondary endpoints

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

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

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

Paediatric neurogenic detrusor overactivity

One double-blind, parallel-group, randomised, multi-centre clinical study (191622-120) was conducted in patients 5 to 17 years of age with urinary incontinence due to detrusor overactivity associated with a neurologic condition and using clean intermittent catheterisation. A total of 113 patients (including 99 with spinal dysraphism such as spina bifida, 13 with spinal cord injury and 1 with transverse myelitis) who had an inadequate response to or were intolerant of at least one anticholinergic medication. The median age was 11 years and 42.5% were female. These patients were randomised to 50 Units, 100 Units or 200 Units, not to exceed 6 Units/kg bodyweight. Patients receiving less than the randomised dose due to this maximum were assigned to the nearest dose group for analysis: N= 38, 45 and 30 for BOTOX 50 Units, BOTOX 100 Units, and BOTOX 200 Units, respectively. Prior to treatment administration, patients received anaesthesia based on age and local site practice. One hundred and nine patients (97.3%) received general anaesthesia or conscious sedation and 3 patients (2.7%) received local anaesthesia.

The study results demonstrated within group improvements in the primary efficacy variable of change from baseline in daytime urinary incontinence episodes (normalised to 12 hours) at the primary efficacy time point (Week 6) for all 3 BOTOX treatment groups. Additional benefits were seen with BOTOX 200 Units for measures related to reducing maximum bladder pressure when compared to 50 Units. The decrease in maximum detrusor pressure (MDP) during the storage phase, defined as the highest value in the Pdet channel during the storage phase [i.e., the greater of the following: the maximum Pdet during the highest amplitude IDC, the maximum Pdet during a terminal detrusor contraction, the Pdet at the end of filling, or the highest Pdet at any other time during the storage phase] for BOTOX 200 Units at Week 6 was greater than the decrease observed for 50 Units.

Summary of results in the paediatric study

	BOTOX 200 Units (N=30)	**BOTOX 100 Units (N=45)**	**BOTOX 50 Units (N=38)**
Daily Frequency of Daytime Urinary Incontinence Episodes[a]			
Mean Baseline (SD)	3.7 (5.1)	3.0 (1.1)	2.8 (1.0)
Mean Change* at Week 2 (95% CI)	-1.1 (-1.7, -0.6)	-1.0 (-1.4, -0.6)	-1.2 (-1.6, -0.7)
Mean Change* at Week 6** (95% CI)	-1.3 (-1.8, -0.9)	-1.3 (-1.7, -0.9)	-1.3 (-1.7, -0.9)
Mean Change* at week 12 (95% CI)	-0.9 (-1.5, -0.4)	-1.4 (-1.8, -1.0)	-1.2 (-1.6, -0.7)
Urine volume at the first morning catheterisation (mL)[b]			
Mean Baseline (SD)	187.7 (135.7)	164.2 (114.5)	203.5 (167.5)
Mean Change* at Week 2 (95% CI)	63.2 (27.9, 98.6)	29.4 (2.5, 56.3)	31.6 (3.3, 60.0)
Mean Change* at Week 6** (95% CI)	87.5 (52.1, 122.8)	34.9 (7.9, 61.9)	21.9 (-7.2, 51.1)
Mean Change* at Week 12 (95% CI)	45.2 (10.0, 80.5)	55.8 (28.5, 83.0)	12.9 (-17.1, 42.9)
Maximum Detrusor Pressure during the storage phase (cmH2O)b			
Mean Baseline (SD)	56.7 (33.9)	56.5 (26.9)	58.2 (29.5)
Mean Change* at Week 6** (95% CI)	-27.3 (-36.4, -18.2)	-20.1 (-27.3, -12.9)	-12.9 (-20.4, -5.3)

CI = Confidence Interval
*Least Squares (LS) mean change and 95% CI are based on ANCOVA model with baseline value as covariate, and treatment group, age (< 12 years or ≥ 12 years), baseline daytime urinary incontinence episodes (≤ 6 or > 6), and anticholinergic therapy (yes/no) at baseline as factors.
** Primary timepoint
[a] Primary endpoint
[b] Secondary endpoint

The median duration of response in this study, based on patient request for re-treatment was 214 (31 weeks), 169 (24 weeks), and 207 days (30 weeks) for BOTOX 50 Units, BOTOX 100 Units, and BOTOX 200 Units, respectively.

Out of 99 paediatric patients who had a negative baseline result for antibodies and had at least one evaluable post-baseline value, none developed neutralising antibodies after receiving up to 4 treatments of 50 to 200 Units of BOTOX.

SKIN AND SKIN APPENDAGE DISORDERS

Glabellar lines

537 patients with moderate to severe glabellar lines between the eyebrows seen at maximum frown have been included in clinical studies.

BOTOX injections significantly reduced the severity of glabellar lines seen at maximum frown for up to 4 months, as measured by the investigator assessment of glabellar line severity at maximum frown and by subject's global assessment of change in appearance of his/her glabellar lines seen at maximum frown. Improvement generally occurred within one week of treatment. None of the clinical endpoints included an objective evaluation of the psychological impact. Thirty days after injection, 80% (325/405) of BOTOX-treated patients were considered by investigators as treatment responders (none or mild severity at maximum frown), compared to 3% (4/132) of placebo-treated patients. At this same timepoint, 89% (362/405) of BOTOX-treated patients felt they had a moderate or better improvement, compared to 7% (9/132) of placebo-treated patients.

BOTOX injections also significantly reduced the severity of glabellar lines at rest. Of the 537 patients enrolled, 39% (210/537) had moderate to severe glabellar lines at rest (15% had no lines at rest). Of these, 74% (119/161) of BOTOX-treated patients were considered treatment responders (none or mild severity) thirty days after injection, compared with 20% (10/49) of placebo-treated patients.

There is limited phase 3 clinical data with BOTOX in patients older than 65 years. Only 6.0% (32/537) of subjects were >65 years old and efficacy results obtained were lower in this population.

Crow's feet lines

1362 patients with moderate to severe crow's feet lines seen at maximum smile, either alone (n=445, Study 191622-098) or also with moderate to severe glabellar lines seen at maximum frown (n=917, Study 191622-099), were enrolled.

BOTOX injections significantly reduced the severity of crow's feet lines seen at maximum smile compared to placebo at all timepoints ($p < 0.001$) for up to 5 months (median 4 months). Improvement assessed by the investigator occurred within one week of treatment. This was measured by the proportion of patients achieving a crow's feet lines severity rating of none or mild at maximum smile in both pivotal studies; until day 150 (end of study) in Study 191622-098 and day 120 (end of first treatment cycle) in Study 191622-099. For both investigator and subject assessments, the proportion of subjects achieving none or mild crow's feet lines severity seen at maximum smile was greater in patients with moderate crow's feet lines seen at maximum smile at baseline, compared to patients with severe crow's feet lines seen at maximum smile at baseline. Table 1 summarises results at day 30, the timepoint of the primary efficacy endpoint.

In Study 191622-104 (extension to Study 191622-099), 101 patients previously randomised to placebo were enrolled to receive their first treatment at the 44 Units dose. Patients treated with BOTOX had a statistically significant benefit in the primary efficacy endpoint compared to placebo at day 30 following their first active treatment. The response rate was similar to the 44 Units group at day 30 following first treatment in Study 191622-099. A total of 123 patients received 4 cycles of 44 Units BOTOX for combined crow's feet and glabellar lines treatment.

Day 30: Investigator and Patient Assessment of Crow's Feet Lines Seen at Maximum Smile - Responder Rates (% of Patients Achieving Crow's Feet Lines Severity Rating of None or Mild)

Clinical Study	Dose	BOTOX	Placebo	BOTOX	Placebo
		Investigator Assessment		Patient Assessment	
191622-098	24 Units (crow's feet lines)	66.7%* (148/222)	6.7% (15/223)	58.1%* (129/222)	5.4% (12/223)
191622-099	24 Units (crow's feet lines)	54.9%* (168/306)	3.3% (10/306)	45.8%* (140/306)	3.3% (10/306)
	44 Units (24 Units crow's feet lines; 20 Units glabellar lines)	59.0%* (180/305)	3.3% (10/306)	48.5%* (148/305)	3.3% (10/306)

*$p < 0.001$ (BOTOX vs placebo)

Improvements from baseline in subject-assessment of the appearance of crow's feet lines seen at maximum smile were seen for BOTOX (24 Units and 44 Units) compared to placebo, at day 30 and at all timepoints following each treatment cycle in both pivotal studies ($p<0.001$).

Treatment with BOTOX 24 Units also significantly reduced the severity of crow's feet lines at rest. Of the 528 patients treated, 63% (330/528) had moderate to severe crow's feet lines at rest at baseline. Of these, 58% (192/330) of BOTOX-treated patients were considered treatment responders (none or mild severity) thirty days after injection, compared with 11% (39/352) of placebo-treated patients.

Improvements in subject's self-assessment of age and attractiveness were also seen for BOTOX (24 Units and 44 Units) compared to placebo using the Facial Line Outcomes (FLO-11) questionnaire, at the primary timepoint of day 30 ($p<0.001$) and at all subsequent timepoints in both pivotal studies.

In the pivotal studies, 3.9% (53/1362) of patients were older than 65 years of age. Patients in this age group had a treatment response as assessed by the investigator, of 36% (at day 30) for BOTOX (24 Units and 44 Units). When analysed by age groups of ≤50 years and >50 years, both populations demonstrated statistically significant improvements compared to placebo. Treatment response for BOTOX 24 Units, as assessed by the investigator, was lower in the group of subjects >50 years of age than those ≤50 years of age (42.0% and 71.2%, respectively).

Overall BOTOX treatment response for crow's feet lines seen at maximum smile is lower (60%) than that observed with treatment for glabellar lines seen at maximum frown (80%).

916 patients (517 patients at 24 Units and 399 patients at 44 Units) treated with BOTOX had specimens analysed for antibody formation. No patients developed the presence of neutralising antibodies.

Forehead Lines

Forehead lines were treated in conjunction with glabellar lines to minimise the potential of brow ptosis. 822 patients with moderate to severe forehead lines and glabellar lines seen at maximum contraction, either alone (N=254, Study 191622-142) or also with moderate to severe crow's feet lines seen at maximum smile (N=568, Study 191622-143), were enrolled and included for analyses of all primary and secondary efficacy endpoints.

For both investigator and patient assessments, the proportion of patients achieving none or mild forehead lines seen at maximum eyebrow elevation following BOTOX injections was greater than patients treated with placebo at day 30. This primary endpoint along with additional endpoints are provided in the table below.

Day 30 (primary timepoint): Investigator and Patient Assessment of Forehead Lines and Upper Facial Lines at Maximum Contraction and Rest

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

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

BOTOX injections significantly reduced the severity of forehead lines seen at maximum eyebrow elevation compared to placebo for up to 6 months ($p < 0.05$): This was measured by the proportion of patients achieving a forehead lines severity rating of none or mild in both pivotal studies; until day 150 in Study 191622-142 (21.6% with BOTOX treatment compared to 0% with placebo) and day 180 in Study 191622-143 (6.8% with BOTOX treatment compared to 0% with placebo).

When all 3 areas were treated simultaneously in Study 191622-143 (BOTOX 64 U group), BOTOX injections significantly reduced the severity of glabellar lines for up to 6 months (5.5% with BOTOX treatment compared to 0% with placebo), lateral canthal lines for up to 6 months (3.4% with BOTOX treatment compared to 0% with placebo) and forehead lines for up to 6 months (9.4% with BOTOX treatment compared to 0% with placebo).
A total of 116 and 150 patients received 3 cycles over 1 year of BOTOX 40 Units and 64, respectively. The response rate for forehead lines improvement was similar across all treatment cycles.

Using the Facial Lines Satisfaction Questionnaire (FLSQ), 78.1% of patients in Study 191622-142 and 62.7% in Study 191622-143 reported improvements in appearance-related and emotional impacts (as defined by items pertaining to feeling older,

negative self-esteem, looking tired, feeling unhappy, looking angry) with BOTOX 40 Units treatment compared to patients treated with placebo 19.0% in Study 191622-142 and 18.9% in Study 191622-143 at day 30 ($p < 0.0001$ in both studies).

On the same questionnaire, 90.2% of patients in Study 191622-142 and 79.2% (40 Units), or 86.4% (64 Units) in Study 191622-143 reported they were "very satisfied"/ "mostly satisfied" with BOTOX 40 Units or 64 Units compared to patients treated with placebo (1.7%, 3.6% in Study 191622-142 and Study 191622-143, respectively), at the primary timepoint of day 60 using the FLSQ ($p < 0.0001$ in both studies). The pivotal studies, 3.7% of patients were older than 65 years of age. Responder rates in this BOTOX-treated subgroup were similar to those in the overall population, but statistical significance was not reached due to the small number of patients.

Platysma Prominence

A total of 748 subjects with moderate to severe platysma prominence at maximum contraction, who were psychologically impacted by their platysma prominence, were included in the clinical studies (N=367, Study M21-309; N=381, Study M21-310).

Improvements in platysma prominence severity at maximum contraction were greater for BOTOX compared to placebo at Day 14 ($p<0.0001$) and at all subsequent timepoints through Day 120 (end of study) in both Study M21-309 and Study M21-310. This was measured by the proportion of subjects achieving a $\geq$ 2-grade improvement from baseline based on investigator and subject assessments (table below).

Investigator and Subject Assessment of Platysma Prominence at Maximum Contraction - Responder Rates (% of Subjects Achieving $\geq$ 2-Grade Improvement from Baseline at Day 14)

Clinical Study	BOTOX 26, 31, or 36 Units	Placebo	BOTOX 26, 31, or 36 Units	Placebo
	Investigator Assessment		Subject Assessment	
M21-309	43.8%* (79/181)	3.9% (7/186)	45.6%* (83/181)	3.9% (7/186)
M21-310	41.0%* (76/186)	2.2% (4/195)	40.8%* (76/186)	3.9% (8/195)

*$p < 0.0001$ (BOTOX vs placebo)

Including Study M21-309 with its open-label extension study of BOTOX for platysma prominence, a total of 261 subjects, who were psychologically impacted by their platysma prominence, received up to 4 treatments over 1 year. The response rates for platysma prominence improvement were similar across all treatment cycles.

Using Appearance of Neck and Lower Face Questionnaire (ANLFQ): Satisfaction (Follow-up) Item 5, 63.6% (115/181) of subjects in Study M21-309 and 61.2% (114/186) in Study M21-310 reported being "*Satisfied*" or "*Very satisfied*" with BOTOX treatment compared to subjects treated with placebo (11.7% [22/186] and 11.8% [23/195], respectively) at Day 14 ($p < 0.0001$ in both studies).

Using Bother Assessment Scale-Platysma Prominence (BAS-PP) Item 2 (jawline), 51.5% (93/181) of subjects in Study M21-309 and 49.4% (92/186) in Study M21-310

reported being "*Not at all bothered*" or "*A little bothered*" by the appearance of their jawline after BOTOX treatment compared to subjects treated with placebo (11.3% [21/186] and 20.6% [40/195], respectively) at Day 14 ($p < 0.0001$ in both studies).

Using BAS-PP Item 1 (vertical neck bands), 50.6% (92/181) of subjects in Study M21-309 and 47.8% (89/186) in Study M21-310 reported being "*Not at all bothered*" or "*A little bothered*" by the appearance of their vertical neck bands after BOTOX treatment compared to subjects treated with placebo (5.4% [10/186] and 11.9% [23/195], respectively) at Day 14 ($p < 0.0001$ in both studies).

Based on change in ANLFQ: Impacts summary score from baseline, BOTOX group demonstrated a greater improvement in psychosocial impact related to platysma prominence at Day 14 compared to placebo, which was maintained at Days 30, 60, and 90 in both studies (table below).

Studies M21-309 and M21-310: Results for ANLFQ: Impacts*

Secondary Efficacy Endpoints	**Study M21-309**		**Study M21-310**	
	BOTOX 26, 31, or 36 Units (N = 181)	**Placebo (N = 186)**	**BOTOX 26, 31, or 36 Units (N = 186)**	**Placebo (N = 195)**
Change from baseline on the ANLFQ: Impacts summary score at Day 14, mean (SE)	-7.8 (0.43)	-2.1 (0.44)	-7.7 (0.51)	-3.0 (0.50)
Change from baseline on the ANLFQ: Impacts summary score at Day 30, mean (SE)	-8.4 (0.44)	-2.8 (0.45)	-8.8 (0.55)	-3.9 (0.54)
Change from baseline on the ANLFQ: Impacts summary score at Day 60, mean (SE)	-7.7 (0.43)	-2.7 (0.43)	-8.2 (0.56)	-3.5 (0.56)
Change from baseline on the ANLFQ: Impacts summary score at Day 90, mean (SE)	-6.3 (0.44)	-2.4 (0.45)	-7.4 (0.50)	-3.5 (0.50)

* For ANLFQ: Impacts, greater negative change in scores indicates greater improvement in psychosocial impact from the appearance of the neck and lower face; p<0.0001 BOTOX vs. placebo for all listed timepoints in both studies.

In M21-309 and M21-310 studies, 3.2% (24/748) of subjects were 65 years of age or older. For these subjects, investigator-assessed improvements at Day 14 were 22.2% (2/9) for BOTOX compared to 0% (0/15) for placebo. Subject-assessed improvements at Day 14 were 33.3% (3/9) for BOTOX compared to 0% (0/15) for placebo. Responder rates in this subgroup were lower than those in the overall population.

5.2 Pharmacokinetic properties

a) General characteristics of the active substance:
Classical absorption, distribution, biotransformation and elimination studies on the active substance have not been performed due to the extreme toxicity of botulinum toxin type A.

b) Characteristics in patients:
Human ADME studies have not been performed due to the nature of the product. It is believed that little systemic distribution of therapeutic doses of BOTOX occurs. BOTOX is probably metabolised by proteases and the molecular components recycled through normal metabolic pathways.

5.3 Preclinical safety data

Non-clinical data based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity reveal no special hazard for humans other than exaggerated pharmacological effects predictable at high doses, given the neurotoxic nature of BOTOX. Carcinogenicity studies have not been conducted.

Acute toxicity
In monkeys receiving a single intramuscular (i.m.) injection of BOTOX, the No Observed Effect Level (NOEL) ranged from 4 to 24 Units/kg. The i.m. LD_{50} was reported to be 39 Units/kg.

Toxicity on repeated injection
In three different studies (six months in rats; 20 weeks in juvenile monkeys; 1 year in monkeys) where the animals received i.m. injections, the NOEL was at the following respective BOTOX dosage levels: < 4 Units/kg, 8 Units/kg and 4 Units/kg. The main systemic effect was a transient decrease in body weight gain.

In a study in which juvenile rats received intramuscular injection of BOTOX every other week from postnatal day 21 for 3 months at the doses of 8, 16, or 24 units/kg, changes in bone size/geometry associated with decreased bone density and bone mass secondary to the limb disuse, lack of muscle contraction and decrease in body weight gain observed. The changes were less severe at the lowest dose tested, with signs of reversibility at all dose levels. The no-observed adverse effect dose in juvenile animals (8 Units/kg) is similar to the maximum adult dose (400 Units) and lower than the maximum paediatric dose (340 Units) on a body weight (kg) basis.

There was no indication of a cumulative effect in the animal studies when BOTOX was given at dosage intervals of 1 month or greater.

Decrease in bodyweight was observed following a single intradetrusor injection of <10 Units/kg BOTOX in rats. To simulate inadvertent injection, a single dose of BOTOX (~7 Units/kg) was administered into the prostatic urethra and proximal rectum, the seminal vesicle and urinary bladder wall, or the uterus of monkeys (~3 Units/kg) without adverse clinical effects. However, bladder stones have been observed in monkeys given a single dose of BOTOX to the prostatic urethra and proximal rectum, and in a repeated dose intraprostatic study. Due to anatomical differences the clinical relevance of these findings is unknown. In a 9 month repeat dose intradetrusor study (4 injections), eyelid ptosis was observed at 24 Units/kg, and mortality was observed at doses ≥24 Units/kg. No adverse effects were observed in monkeys at 12 Units/kg, which corresponds to a 3-fold greater exposure than the recommended clinical dose of 200 Units for urinary incontinence due to neurogenic detrusor overactivity (based on a 50 kg person).

Local toxicity

BOTOX was shown not to cause ocular or dermal irritation, or give rise to toxicity when injected into the vitreous body in rabbits.

Allergic or inflammatory reactions in the area of the injection sites are rarely observed after BOTOX administration. However, formation of haematoma may occur.

Reproduction toxicology

Teratogenic effects

When pregnant mice and rats were injected intramuscularly during the period of organogenesis, the developmental NOEL of BOTOX was at 4 Units/kg. Reductions in ossification were observed at 8 and 16 Units/kg (mice) and reduced ossification of the hyoid bone at 16 Units/kg (rats). Reduced foetal body weights were observed at 8 and 16 Units/kg (rats).

In a range-finding study in rabbits, daily injections at dosages of 0.5 Units/kg/day (days 6 to 18 of gestation), and 4 and 6 Units/kg (administered on days 6 and 13 of gestation), caused death and abortions among surviving dams. External malformations were observed in one foetus each in the 0.125

Units/kg/day and the 2 Units/kg dosage groups. The rabbit appears to be a very sensitive species to BOTOX treatment.

Impairment of fertility and reproduction
The reproductive NOEL following i.m. injection of BOTOX was 4 Units/kg in male rats and 8 Units/kg in female rats. Higher dosages were associated with dose-dependent reductions in fertility. Provided impregnation occurred, there were no adverse effects on the numbers or viability of the embryos sired or conceived by treated male or female rats.

Pre- and post-natal developmental effects
In female rats, the reproductive NOEL was 16 Units/kg. The developmental NOEL was 4 Units/kg.

Antigenicity
BOTOX showed antigenicity in mice only in the presence of adjuvant. BOTOX was found to be slightly antigenic in the guinea pig.

Blood compatibility
No haemolysis was detected up to 100 Units/ml of BOTOX in normal human blood.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Human albumin
Sodium chloride

6.2 Incompatibilities

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

6.3 Shelf life

3 years.

After reconstitution, stability has been demonstrated for 24 hours at 2°C – 8°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C (see also section 6.6).

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C), or store in a freezer (-5°C to -20°C).

For storage conditions of the reconstituted medicinal product see section 6.3.

6.5 Nature and contents of container

Clear glass vial, with rubber stopper and tamper-proof aluminium seal, containing white powder for solution for injection.

Pack size:

- Carton comprising one 50 Allergan Unit vial and package leaflet.
- Packs containing one, two, three or six cartons.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Reconstitution

BOTOX is reconstituted prior to use with sterile unpreserved normal saline (0.9% sodium chloride for injection). It is good practice to perform vial reconstitution and syringe preparation over plastic-lined paper towels to catch any spillage. An appropriate amount of diluent (see dilution table below) is drawn up into a syringe. The exposed portion of the rubber septum of the vial is cleaned with alcohol (70%) prior to insertion of the needle. Since BOTOX is denatured by bubbling or similar violent agitation, the diluent should be injected gently into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Reconstituted BOTOX is a clear colourless to slightly yellow solution free of particulate matter. When reconstituted, BOTOX may be stored in a refrigerator (2-8°C) for up to 24 hours prior to use. After this period used or unused vials should be discarded.

Each vial is for single use only.

Care should be taken to use the correct diluent volume for the presentation chosen to prevent accidental overdose. If different vial sizes of BOTOX are being used as part of one injection procedure, care should be taken to use the correct amount of diluent when reconstituting a particular number of units per 0.1 ml. The amount of diluent varies between BOTOX 50 Allergan Units, BOTOX 100 Allergan Units and BOTOX 200 Allergan Units. Each syringe should be labelled accordingly.

Dilution table for **BOTOX 50**, 100 and 200 **Allergan Units** vial size **for all** indications except bladder disorders:

	50 Unit vial	100 Unit vial	200 Unit vial
Resulting dose (Units per 0.1 ml)	**Amount of diluent (sterile unpreserved normal saline (0.9% sodium chloride for injection)) added in a 50 Unit vial**	Amount of diluent (sterile unpreserved normal saline (0.9% sodium chloride for injection)) added in a 100 Unit vial	Amount of diluent (sterile unpreserved normal saline (0.9% sodium chloride for injection)) added in a 200 Unit vial
20 Units	**0.25 ml**	0.5 ml	1 ml
10 Units	**0.5 ml**	1 ml	2 ml
5 Units	**1 ml**	2 ml	4 ml
4 Units	**1.25 ml**	2.5 ml	5 ml
2.5 Units	**2 ml**	4 ml	8 ml
1.25 Units	**4 ml**	8 ml	N/A

Overactive bladder:

It is recommended that a 100 Unit or two 50 Unit vials are used for convenience of reconstitution.

Dilution instructions using two 50 Unit vials:

- **Reconstitute two 50 Unit vials of BOTOX each with 5 ml of sterile unpreserved normal saline (0.9% sodium chloride for injection) and mix the vials gently.**
- **Draw the 5 ml from each of the vials into a single 10 ml syringe.**

This will result in a 10 ml syringe containing a total of 100 Units of reconstituted BOTOX. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

Dilution instructions using a 100 Unit vial:

- Reconstitute a 100 Unit vial of BOTOX with 10 ml of sterile unpreserved normal saline (0.9% sodium chloride for injection) and mix gently.
- Draw the 10 ml from the vial into a 10 ml syringe.

This will result in a 10 ml syringe containing a total of 100 Units of reconstituted BOTOX. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

Dilution instructions using a 200 Unit vial:

- Reconstitute a 200 Unit vial of BOTOX with 8 ml of sterile unpreserved normal saline (0.9% sodium chloride for injection) and mix gently.
- Draw 4 ml from the vial into a 10 ml syringe.
- Complete the reconstitution by adding 6 ml of sterile unpreserved normal saline (0.9% sodium chloride for injection) into the 10 ml syringe and mix gently.

This will result in a 10 ml syringe containing a total of 100 Units of reconstituted BOTOX. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

This product is for single use only and any unused reconstituted product should be disposed of.

Urinary incontinence due to neurogenic detrusor overactivity:

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

Dilution instructions using four 50 Unit vials:

- **Reconstitute four 50 Unit vials of BOTOX, each with 3 ml of sterile unpreserved normal saline (0.9% sodium chloride for injection) and mix the vials gently.**
- **Draw 3 ml from the first vial and 1 ml from the second vial into one 10 ml syringe.**
- **Draw 3 ml from the third vial and 1 ml from the fourth vial into a second 10 ml syringe.**
- **Draw the remaining 2 ml from the second and fourth vials into a third 10 ml syringe.**
- **Complete the reconstitution by adding 6 ml of sterile unpreserved normal saline (0.9% sodium chloride for injection) into each of the three 10 ml syringes, and mix gently.**

This will result in three 10 ml syringes containing a total of 200 Units of reconstituted BOTOX. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

Dilution instructions using two 100 Unit vials:

- Reconstitute two 100 Unit vials of BOTOX, each with 6 ml of sterile unpreserved normal saline (0.9% sodium chloride for injection) 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 sterile unpreserved normal saline (0.9% sodium chloride for injection) into each of the 10 ml syringes, and mix gently.

This will result in three 10 ml syringes containing a total of 200 Units of reconstituted BOTOX. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

Dilution instructions using a 200 Unit vial:

- Reconstitute a 200 Unit vial of BOTOX with 6 ml of sterile unpreserved normal saline (0.9% sodium chloride for injection) and mix the vials gently.
- Draw 2 ml from the vial into each of three 10 ml syringes.
- Complete the reconstitution by adding 8 ml of sterile unpreserved normal saline (0.9% sodium chloride for injection) into each of the 10 ml syringes, and mix gently.

This will result in three 10 ml syringes containing a total of 200 Units of reconstituted BOTOX. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

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

Disposal

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

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

AbbVie Ltd.
Maidenhead
SL6 4UB
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 41042/0059

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/09/2007

10 DATE OF REVISION OF THE TEXT

14/05/2025