Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

BOTOX 100 Allergan Units powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

botulinum toxin* type A, 100 Allergan Units/vial.
* from *Clostridium botulinum*
Botulinum toxin units are not interchangeable from one product to another.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection.
White powder.
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

Neurological disorders:

BOTOX is indicated for the symptomatic treatment of:

- **Focal spasticity** of the ankle and foot in ambulant **paediatric cerebral palsy** patients, two years of age or older as an adjunct to rehabilitative therapy.
- **Focal spasticity** of the wrist and hand in **adult post-stroke** patients.
- **Focal spasticity** of the ankle and foot in **adult post-stroke** patients (see section 4.4)
- **Blepharospasm, hemifacial spasm** and associated focal dystonias.
- **Cervical dystonia** (spasmodic torticollis).
- Symptom relief in adults fulfilling criteria for **chronic migraine** (headaches on ≥15 days per month of which at least 8 days with migraine) in patients who have responded inadequately or are intolerant of prophylactic migraine medications (see section 4.4).

BOTOX is indicated for the management of:

Bladder disorders:

- **Idiopathic overactive bladder** with symptoms of urinary incontinence, urgency and frequency in adult patients who have an inadequate response to, or are intolerant of, anticholinergic medication.
- Urinary incontinence in adults with **neurogenic detrusor overactivity** resulting from neurogenic bladder due to stable sub-cervical spinal cord injury, or multiple sclerosis.

Skin and skin appendage disorders:

- Persistent severe primary **hyperhidrosis of the axillae**, which interferes with the activities of daily living and is resistant to topical treatment.

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.

Chronic migraine should be diagnosed by, and BOTOX should be exclusively administered under the supervision of neurologists who are experts in the treatment of chronic migraine.

Elderly patients
No specific dose adjustment is required for use in the elderly. Initial dosing should begin at the lowest recommended dose for the specific indication. For repeat injections the lowest effective dose with the longest clinically indicated interval between injections is recommended. Elderly patients with significant medical history and concomitant medications should be treated with caution. There are limited clinical data in patients older than 65 years treated for post-stroke spasticity of the upper and lower limb with BOTOX. See sections 4.4, 4.8 and 5.1 for further information.

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 physicians who are experienced in the assessment and treatment of paediatric focal spasticity and as part of a structured programme 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.

• Blepharospasm/Hemifacial spasm	12 years (see section 4.4 and 4.8)
• Cervical dystonia	12 years (see section 4.4 and 4.8)
• Focal spasticity in paediatric patients	2 years (see section 4.2, 4.4 and 4.8)
• Primary hyperhidrosis of the axillae	12 years (limited experience in adolescents between 12 and 17 years, see section 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)

The following information is important:

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.

BOTOX must only be reconstituted with sterile unpreserved 0.9% sodium chloride solution for injection. The appropriate amount of diluent should be drawn up into a syringe. See dilution tables in section 6.6.

This product is for single use only and any unused solution should be discarded.

For instructions on use, handling and disposal of vials please refer to section 6.6.

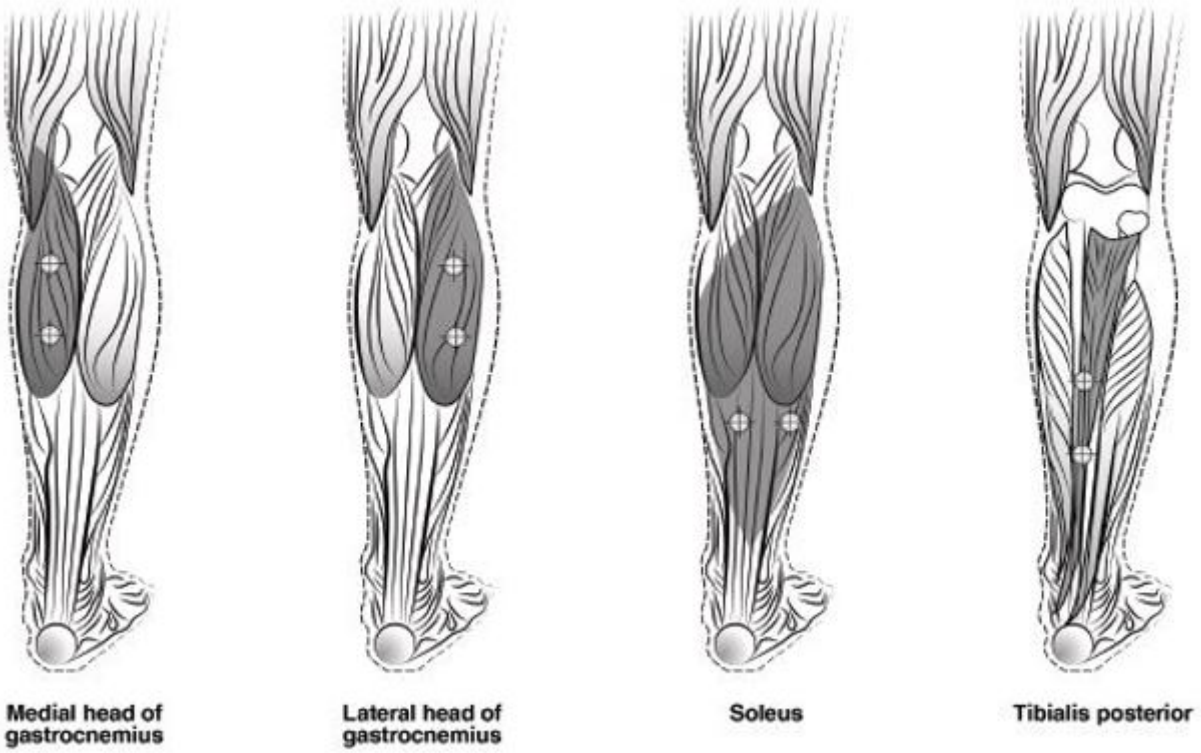
Method of administration
Refer to specific guidance for each indication described below.
BOTOX should only be given by physicians with appropriate qualifications, and expertise in the treatment and the use of the required equipment.
Generally valid optimum dose levels and number of injection sites per muscle have not been established for all indications. In these cases, individual treatment regimens should therefore be drawn up by the physician. Optimum dose levels should be determined by titration but the recommended maximum dose should not be exceeded.

NEUROLOGICAL DISORDERS:
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 (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, as 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 treating 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**
Mandatory Ankle Muscles			
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

* did not exceed a total dose of 150 Units
** did not exceed a total dose of 300 Units

Maximum total 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 physician, 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, the total dose should not exceed the lower of 10 Units/kg body weight or 340 Units, in a 12 week interval.

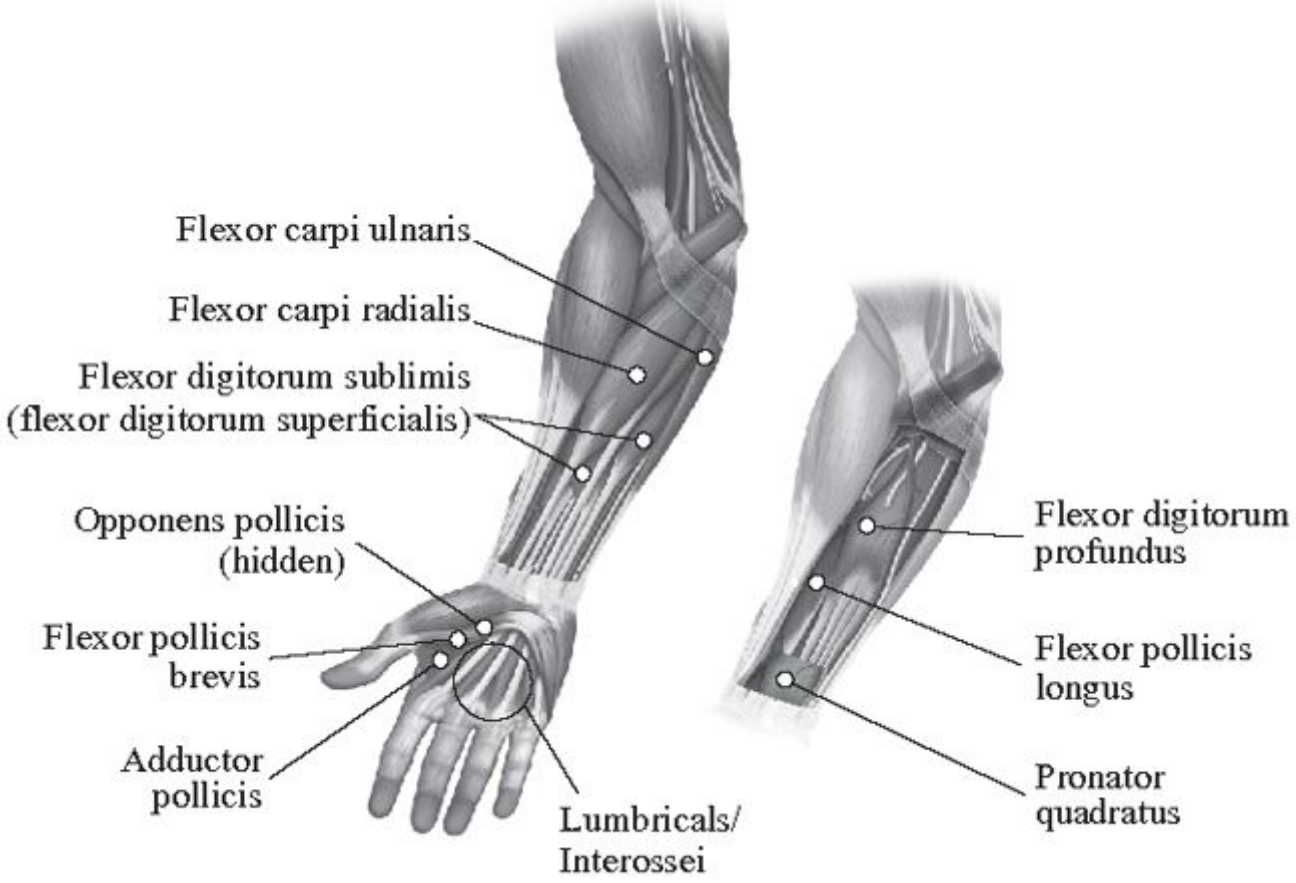
Additional information: Treatment with BOTOX is not intended to substitute for usual standard of care rehabilitation regimens. Clinical improvement generally occurs within the first two weeks after injection. Repeat treatment should be administered when the clinical effect of a previous injection diminishes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

Focal upper limb spasticity associated with stroke 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 electromyographic guidance or nerve stimulation or ultrasound techniques may be useful. 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 240 Units divided among the affected muscles as listed in the following table. The maximum dose at one treatment is 240 Units.

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

Muscle	**Recommended Dose; Number of Sites**
Forearm Pronator quadratus	 10 – 50 Units; 1 site
Wrist Flexor carpi radialis Flexor carpi ulnaris	 15 – 60 Units; 1-2 sites 10 – 50 Units; 1-2 sites
Fingers/Hand Flexor digitorum profundus Flexor digitorum sublimis/superficialis Lumbricals* Interossei*	 15 – 50 Units; 1-2 sites 15 – 50 Units; 1-2 sites 5 – 10 Units; 1 site 5 – 10 Units; 1 site
Thumb Adductor pollicis Flexor pollicis longus Flexor pollicis brevis Opponens pollicis	 20 Units; 1-2 sites 20 Units; 1-2 sites 5 – 25 Units; 1 site 5 – 25 Units; 1 site

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

Additional information: In controlled clinical trials patients were followed for 12 weeks after single treatment. Improvement in muscle tone occurred within two weeks with the peak effect generally seen within four to six weeks. In an open label continuation study, most of the patients were re-injected after an interval of 12 to 16 weeks, when the effect on muscle tone had diminished. These patients received up to four injections with a maximum cumulative dose of 960 Units over 54 weeks. If it

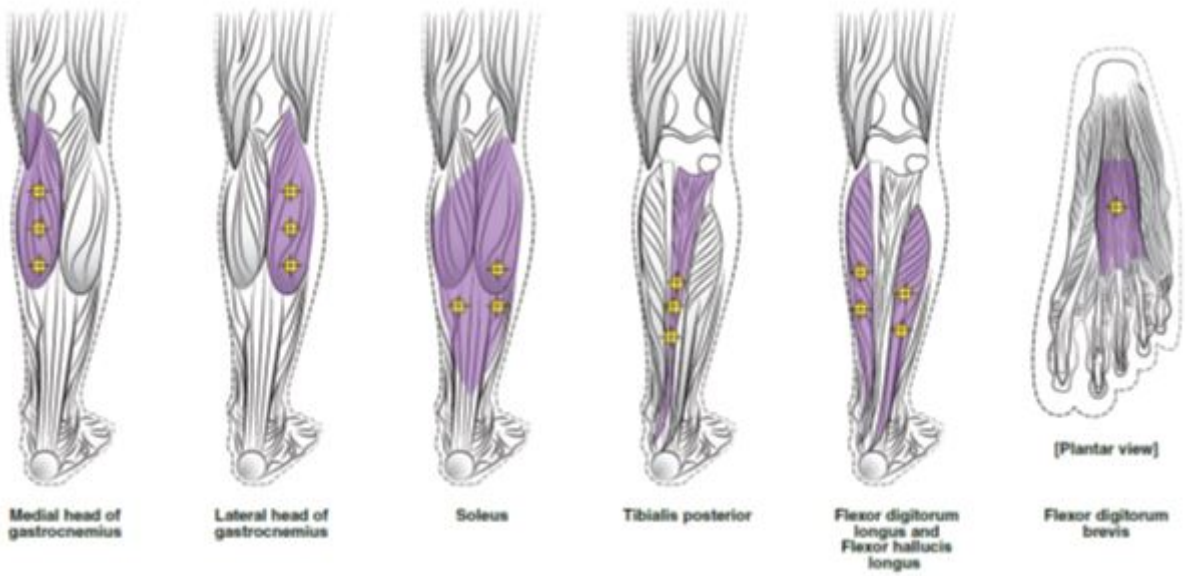
is deemed appropriate by the treating physician, repeat doses may be administered, when the effect of a previous injection has diminished, no sooner than 12 weeks after the previous injection. The degree and pattern of muscle spasticity at the time of re-injection may necessitate alterations in the dose of BOTOX and muscles to be injected. The lowest effective dose should be used.

Focal lower limb spasticity associated with stroke 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 electromyographic guidance or nerve stimulation techniques may be useful. 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 lower limb spasticity:



Recommended dose: The recommended dose for treating adult lower limb spasticity involving the ankle and foot is 300 Units to 400 Units divided among up to 6 muscles, as listed in the following table. The maximum recommended dose at one treatment is 400 Units.

BOTOX Dosing by Muscle for Adult Lower Limb Spasticity:

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

Additional information: If it is deemed appropriate by the treating physician, 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

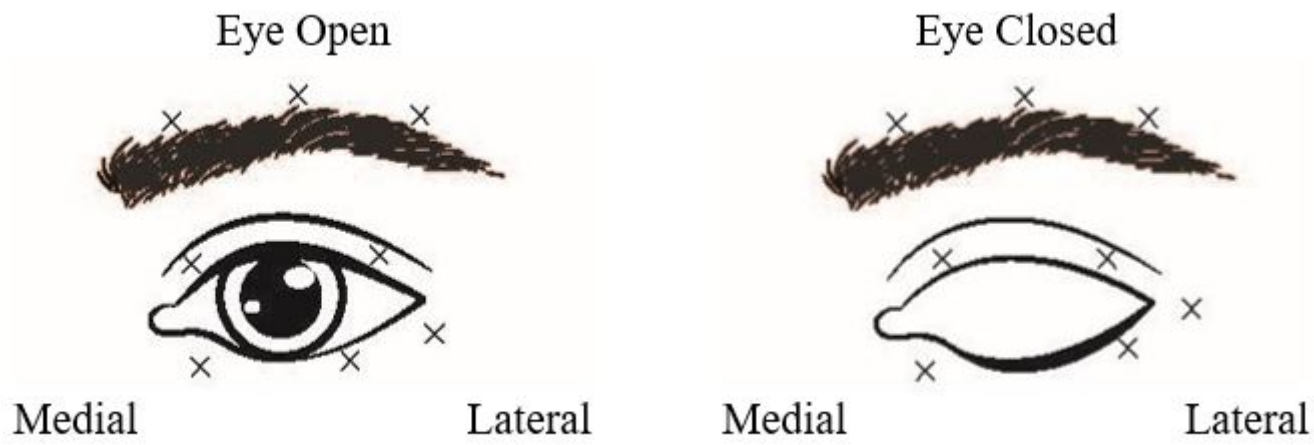
Recommended needle: Sterile, 27-30 gauge/0.40–0.30 mm needle.

Administration guidance: Electromyographic guidance is not necessary.

Recommended dose: The initial recommended dose is 1.25-2.5 Units 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.

Maximum total dose: The initial dose should not exceed 25 Units per eye. In the management of blepharospasm total dosing should not exceed 100 Units 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. The following diagrams indicate the possible injection sites:



In general, the initial effect of the injections is seen within three days and reaches a peak at one to two weeks post-treatment. Each treatment lasts approximately three months, following which the procedure can be repeated as needed. At repeat treatment sessions, the dose may be increased up to two-fold if the response from the initial treatment is considered insufficient. However, there appears to be little benefit obtainable from injecting more than 5 Units per site. Normally no additional benefit is conferred by treating more frequently than every three months.

Patients with hemifacial spasm or VIIth nerve disorders should be treated as for unilateral blepharospasm, with other affected facial muscles (e.g. zygomaticus major, orbicularis oris) being injected as needed.
Cervical dystonia

Recommended needle: Appropriately sized needle (usually 25-30 gauge/0.50–0.30 mm).

Administration guidance: In clinical trials the treatment of cervical dystonia has typically included injection of BOTOXinto 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 or atrophy 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.

Recommended dose: No more than 200 Units total should be injected for the first course of therapy, with adjustments made in subsequent courses dependent on the initial response.

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, the doses have ranged from 95 to 360 Units (with an approximate mean of 240 Units). As with any drug treatment, initial dosing in a naïve patient should begin at the lowest effective dose. No more than 50 Units should be given at any one site. No more than 100 Units should be given to the sternomastoid. To minimise the incidence of dysphagia, the sternomastoid should not be injected bilaterally.

Maximum total dose: A total dose of 300 Units at any one session should not be exceeded. The optimal number of injection sites is dependent upon the size of the muscle. Treatment intervals of less than 10 weeks are not recommended.

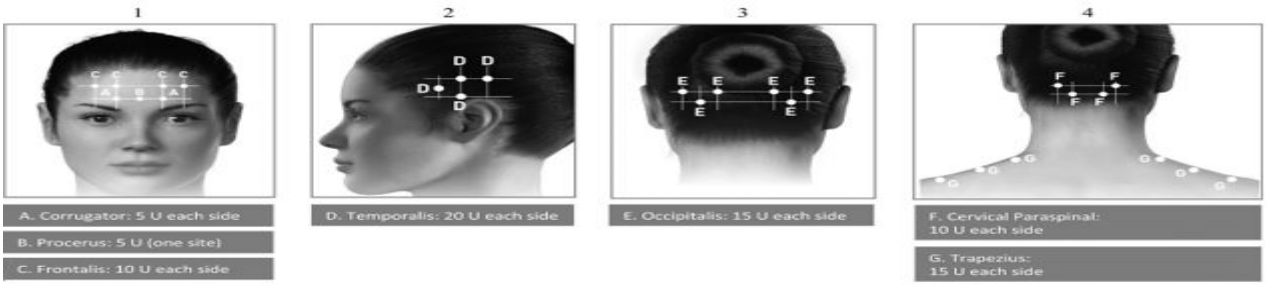
Additional information: Clinical improvement generally occurs within the first two weeks after injection. The maximum clinical benefit generally occurs approximately six weeks post-injection. The duration of beneficial effect reported in clinical trials showed substantial variation (from 2 to 33 weeks) with a typical duration of approximately 12 weeks.

Chronic Migraine

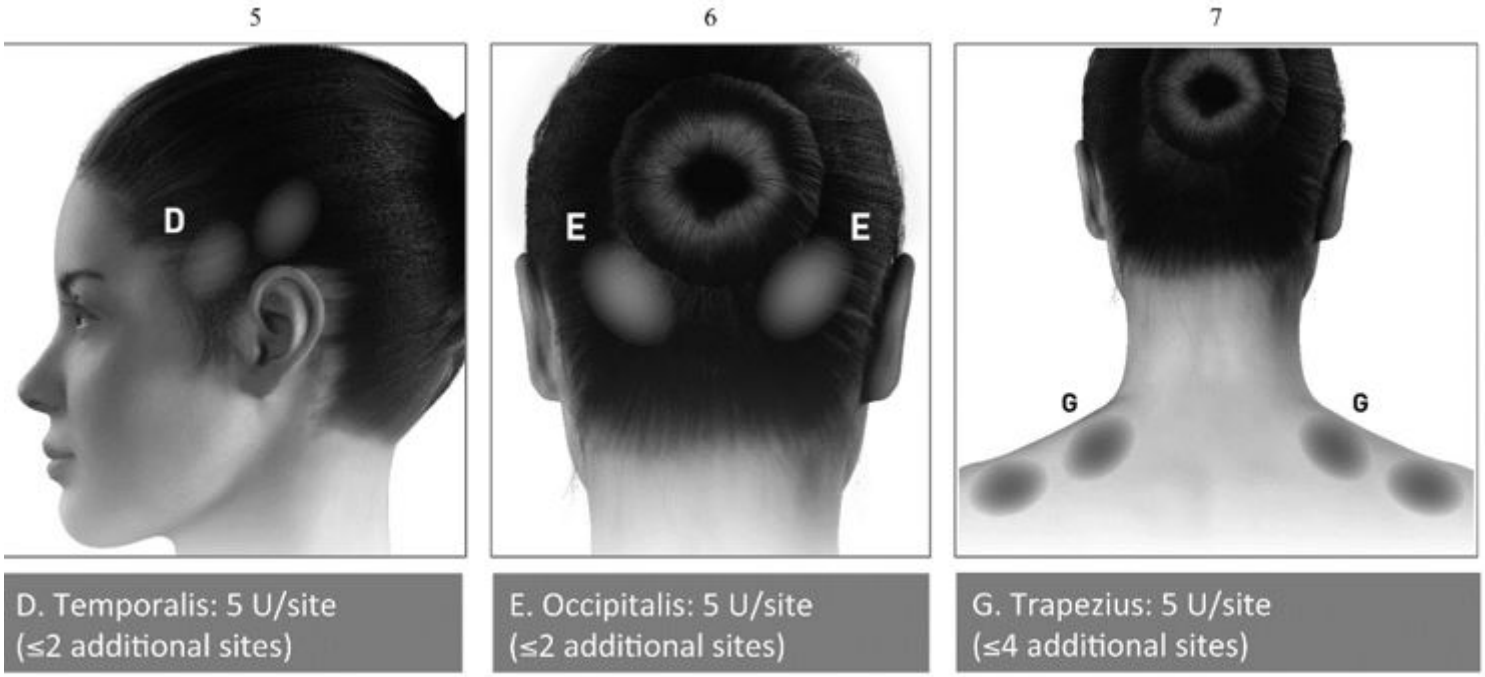
Recommended needle: Sterile 30-gauge, 0.5 inch needle

Administration guidance: Injections should be divided across 7 specific head/neck muscle areas as specified in the table below. A 1-inch needle may be needed in the neck region for patients with extremely thick neck muscles. With the exception of the procerus muscle, which should be injected at 1 site (midline), all muscles should be injected bilaterally with half the number of injections sites administered to the left, and half to the right side of the head and neck. If there is a predominant pain location(s), additional injections to one or both sides may be administered in up to 3 specific muscle groups (occipitalis, temporalis, and trapezius), up to the maximum dose per muscle as indicated in the table below.

The following diagrams indicate the injection sites:



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.

BOTOX Dosing By Muscle for Chronic Migraine:

	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 retreatment schedule is every 12 weeks.

BLADDER DISORDERS:
Patients should not have a urinary tract infection at the time of treatment.
Prophylactic antibiotics should be administered 1-3 days pre-treatment, on the treatment day, and 1-3 days post-treatment.

It is recommended that patients discontinue anti-platelet therapy at least 3 days before the injection procedure. Patients on anti-coagulant therapy need to be managed appropriately to decrease the risk of bleeding.

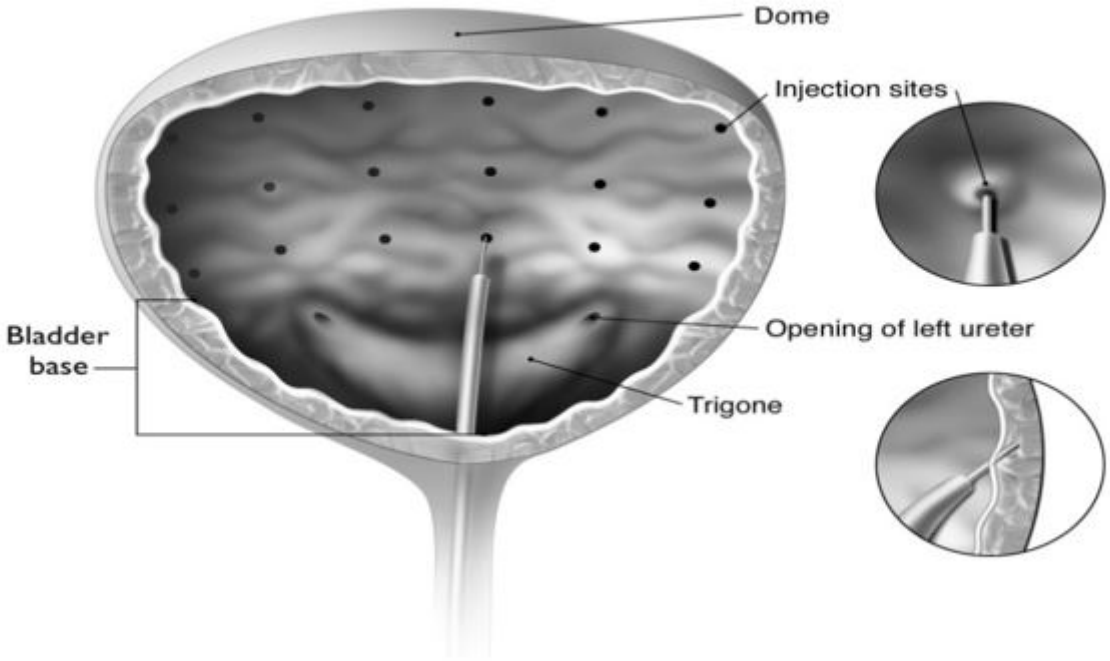
For the management of urinary incontinence, BOTOX should be administered by physicians who are experienced in the assessment and treatment of bladder dysfunction (e.g, urologists and urogynaecologists).
Overactive bladder

Recommended needle: A flexible or rigid cystoscope can be used. The injection needle should be filled (primed) with approximately 1 ml of the reconstituted BOTOX prior to the start of the injections (depending on the needle length) to remove any air.

Administration guidance: Prior to injection an intravesical instillation of diluted local anaesthetic, with or without sedation, may be used, as per local site practice. If a local anaesthetic instillation is performed, the bladder should be drained and irrigated with sterile sodium chloride solution before the next steps of the procedure.

Reconstituted BOTOX (100 Units/10 ml) is injected into the detrusor muscle via a flexible or rigid cystoscope, avoiding the trigone and base. The bladder should be instilled with enough sodium chloride solution to achieve adequate visualisation for the injections, 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 0.9% sodium chloride solution for injection should be injected so the full dose is delivered. After the injections are given, the sodium chloride solution used for bladder wall visualisation should not be drained so that patients can demonstrate their ability to void prior to leaving the clinic. The patient should be observed for at least 30 minutes post-injection and until a spontaneous void has occurred.



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

Additional information: Clinical improvement may occur within 2 weeks. Patients should be considered for reinjection when the clinical effect of the previous injection has diminished (median duration in phase 3 clinical studies was 166 days [~24 weeks] based on patient request for re-treatment), but no sooner than 3 months from the prior bladder injection.

Urinary incontinence due to neurogenic detrusor overactivity

Recommended needle: A flexible or rigid cystoscope can be used. The injection needle should be filled (primed) with approximately 1 ml prior to the start of the injections (depending on the needle length) to remove any air.

Administration guidance: Prior to injection, either an intravesical instillation of diluted anaesthetic (with or without sedation) or general anaesthesia may be used, as per local site practice. If a local anaesthetic instillation is performed, the bladder should be drained and rinsed with sterile sodium chloride solution before the next steps of the injection procedure.

Reconstituted BOTOX (200 Units/30 ml) is injected into the detrusor muscle via a flexible or rigid cystoscope, avoiding the trigone and base. The bladder should be instilled with enough sodium chloride solution to achieve adequate visualisation for the injections, 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 0.9% sodium chloride solution for injection should be injected so the full dose is delivered. After the injections are given, the sodium chloride solution used for bladder wall visualisation should be drained. The patient should be observed for at least 30 minutes post-injection.

Recommended dose: The recommended dose is 200 Units of BOTOX, as 1 ml (~6.7 Units) injections across 30 sites in the detrusor.

Additional information: Clinical improvement generally occurs within 2 weeks. Patients should be considered for reinjection when the clinical effect of the previous injection has diminished (median duration in phase 3 clinical studies was 256-295 days (~36-42 weeks) for BOTOX 200 Units) based on patient request for re-treatment, but no sooner than 3 months from the prior bladder injection.

SKIN AND SKIN APPENDAGE DISORDER:

Primary hyperhidrosis of the axillae

Recommended needle: Sterile 30-gauge needle.

Administration guidance: The hyperhidrotic area may be defined by using standard staining techniques, e.g. Minor´s iodine-starch test.

Recommended dose: 50 Units of BOTOX is injected intradermally, evenly distributed in multiple sites approximately 1-2 cm apart within the hyperhidrotic area of each axilla.

Maximum total dose: Doses other than 50 Units per axilla cannot be recommended. Injections should not be repeated more frequently than every 16 weeks (see section 5.1).

Additional information: Clinical improvement generally occurs within the first week after injection. Repeat injection of BOTOX can be administered when the clinical effect of a previous injection diminishes and the treating physician deems it necessary.

ALL INDICATIONS:

In the event 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.

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

4.3 Contraindications

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

BOTOX for management of bladder disorders is also contraindicated:
- in patients who have a urinary tract infection at the time of treatment;
- in patients with acute urinary retention at the time of treatment, who are not routinely catheterising;
- in patients who are not willing and/or able to initiate catheterisation post-treatment if required.

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, that is to say essentially 'sodium free'.

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

Adverse reactions 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.

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 anatomical structures must be avoided.

Pneumothorax associated with the injection procedure has been reported following the administration of BOTOX near the thorax. Caution is warranted when injecting in proximity to the lung (particularly the apices) or other vulnerable anatomical 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 withperipheral motor neuropathic diseases (e.g.amyotrophic lateral sclerosis or motor neuropathy).

There have also 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 cardiovascular disease.

New onset or recurrent seizures have been reported, typically in adult and paediatric patients, who are predisposed to experiencing these events. The exact relationship of these events to the 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 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. 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 neurological 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.

NEUROLOGICAL DISORDERS:

Focal spasticity of the ankle and foot associated with paediatric cerebral palsy and focal spasticity of the ankle, foot, wrist and hand in adult post-stroke patients
BOTOX is a treatment of focal spasticity thathas only been studied in association with usual standard of care regimens, and is not intended as a replacement for these treatment modalities. BOTOX is not likely to be effective in improving range of motion at a joint affected by a fixed contracture.

BOTOX should not be used for the treatment of focal spasticity of upper limb (hand and wrist) and lower limb (ankle and foot) in adult post-stroke patients if muscle tone reduction is not expected to result in improved function (e.g. improvement in walking), or improved symptoms (e.g. reduction in pain), or to facilitate care. For lower limb spasticity, improvement in active function may be limited if BOTOX treatment is initiated longer than 2 years post-stroke or in patients with less severe ankle spasticity (Modified Ashworth Scale (MAS) < 3).

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

- BOTOX should be used with caution for the treatment of focal spasticity of the upper limb (wrist and hand) and lower limb (ankle and foot) in elderly post-stroke patients with significant co-morbidity and treatment should only be initiated if the benefit of treatment is considered to outweigh the potential risk.
- BOTOX should only be used for the treatment of post-stroke upper and /or lower limb spasticity following evaluation by health care professionals experienced in the management of the rehabilitation of post-stroke patients.

There have been post-marketingreports 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 population".

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 may occur 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
Safety and efficacy have not been established in prophylaxis of headaches in patients with episodic migraine (headaches on < 15 days per month) or chronic tension type headache. Safety and efficacy of BOTOX in patients with medication overuse headache (secondary headache disorder) have not been studied.

BLADDER DISORDERS:
Appropriate medical caution should be exercised when performing a cystoscopy.

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

Overactive bladder
Men with overactive bladder and signs or symptoms of urinary obstruction should not be treated with BOTOX.

Urinary incontinence due to neurogenic detrusor overactivity
Autonomic dysreflexia associated with the procedure can occur. Prompt medical attention may be required.

SKIN AND SKIN APPENDAGE DISORDER:

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.

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.

Paediatric Population

No interaction studies have been performed in children.

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 riskfor humans is unknown. BOTOX should not be used during pregnancy and in women of childbearing potential not using contraception unless clearly necessary.

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, BOTOXmay cause asthenia, muscle weakness, dizziness and visual disturbance, which could affect driving and using machines.

4.8 Undesirable effects

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, 16% with focal spasticity of the upper limb associated with stroke and 15% with focal spasticity of the lower limb associated with stroke. In clinical trials for overactive bladder the incidence was 26% with the first treatment and 22% with a second treatment. In clinical trials for neurogenic detrusor overactivity in adults, the incidence was 32% with the first treatment and declined to 18% with a second treatment. For paediatric neurogenic detrusor overactivity the incidence was 6.2% with the first treatment. In clinical trials for chronic migraine, the incidence was 26% with the first treatment and declined to 11% with a second treatment.

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.

The adverse reactions are classified into the following categories, depending on how often they occur: 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), or not known (cannot be estimated from the available data).

Below are lists of adverse reactions which vary depending on the part of the body where BOTOX is injected.

NEUROLOGICAL DISORDERS:
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
Injury, poisoning and procedural complications	Ligament sprain, skin abrasion	Common
General disorders and administration site conditions	Gait disturbance, injection site pain	Common

Focal upper limb spasticity associated with stroke in adults

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, oedema peripheral	Common

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

Focal lower limb spasticity associated with stroke in adults

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	Oedema peripheral	Common
Injury, poisoning and procedural complications	Fall	Common

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

Blepharospasm, hemifacial spasm and associated dystonias

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, vision blurred	Uncommon
	Eyelid oedema	Rare
	Ulcerative keratitis, 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 tract 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, 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
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
Gastrointestinal disorders	Dysphagia	Uncommon

The discontinuation rate due to adverse events in these phase 3 trials was 3.8% for BOTOX vs. 1.2% for placebo.

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 that occurred with a common frequency were dysuria and haematuria.

Clean intermittent catheterisation was initiated in 6.5% of patients following treatment with BOTOX 100 Units versus 0.4% in the placebo group.

Of 1242 patients in the placebo-controlled clinical studies, 41.4% of patients (n = 514) were ≥ 65 years of age and 14.7% (n = 182) 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], dysuria*[a,b], bladder diverticulum[a]	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*
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 clinical trials urinary tract infection was reported in 49.2% of patients treated with 200 Units BOTOX and in 35.7% of patients treated with placebo (53.0% of multiple sclerosis patients treated with 200 Units vs. 29.3% with placebo; 45.4% of spinal cord injury patients treated with 200 Units vs. 41.7% with placebo). Urinary retention was reported in 17.2% of patients treated with 200 Units BOTOX and in 2.9% of patients treated with placebo (28.8% of multiple sclerosis patients treated with 200 Units vs. 4.5% with placebo; 5.4% of spinal cord injury patients treated with 200 Units vs. 1.4% with placebo).

No change in the type of adverse reactions was observed with repeat dosing.

No difference on the multiple sclerosis (MS) exacerbation annualised rate (i.e. number of MS exacerbation events per patient-year) was observed (BOTOX=0.23, placebo=0.20) in the MS patients enrolled in the pivotal studies, nor in the post-approval study of BOTOX 100 Units in MS patients not catheterising at baseline (BOTOX=0, placebo=0.07).

In the pivotal studies, among patients who were not catheterising at baseline prior to treatment, catheterisation was initiated in 38.9% following treatment with BOTOX 200 Units versus 17.3% on placebo.

In the post-approval study of BOTOX 100 Units in MS patients not catheterising at baseline, 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, Bladder pain*	Common

** procedure-related adverse reaction*

No change in the type of adverse reactions was observed with repeat dosing.

See sections 4.2 and 5.1.

SKIN AND SKIN APPENDAGE DISORDER:

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), skin odour abnormal, 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,	Common

	asthenia, injection site reactions	

In the management of primary axillary hyperhidrosis, 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).

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), strabismus, vision blurred, visual disturbance, dry eye (associated with periocular injections), 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, 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:

HPRA Pharmacovigilance
Website: www.hpra.ie

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, that 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

Pharmacotherapeutic group: Other muscle relaxants, peripherally acting agents
ATC code: M03A X01

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

Pharmacodynamic effect
After injection, there is an initial rapid high-affinity binding of toxin to specific cell surface receptors. This is followed by transfer of the toxin across the plasma membrane by receptor-mediated endocytosis. Finally, the toxin is released into the cytosol. This latter process is accompanied by progressive inhibition of acetylcholine release; clinical signs are manifested within 2-3 days, with peak effect seen within 5-6 weeks of injection. 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 an average of 7.5 months after the first injection in patients treated with 50 Units per axilla. However, in 27.5 % of patients the duration of effect was 1 year or greater. Recovery of sympathetic nerve endings that innervate sweat glands after intradermal injection with BOTOX has not been studied.

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

Clinical efficacy and safety

NEUROLOGICAL 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 were evaluated in a randomised, multi-centre, double-blind, placebo-controlled study. The study randomised 235 paediatric patients (77 BOTOX 6 Units/kg, 78 BOTOX 3 Units/kg and 80 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 week 8 and 12. 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 the lower limb was also treated 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 (mITT Population)

	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 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).

mITT = modified intent-to-treat; included all randomised participants with a valid MAS baseline score of the principal muscle group and at least one postbaseline measurement at weeks 2, 4, or 6 for the MAS of the principal muscle group and the CGI by Physician. The mITT population was analysed according to randomisation assignment, regardless of treatment actually received.

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 were evaluated in, a randomised, multi-centre, double-blind, placebo-controlled study. The study randomised 384 paediatric patients (128 BOTOX 8 Units/kg, 126 BOTOX 4 Units/kg and 130 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) Score 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 up to 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 (mITT Population)

	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] TheEVG 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).

mITT = modified intent-to-treat; included all randomised participants with a valid MAS baseline ankle score with knee extended and ≥1 postbaseline measurement at weeks 2, 4, or 6 for the MAS ankle score with knee extended and the CGI by Physician. The mITT population was analysed according to randomisation assignment, regardless of treatment actually received.

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 associated with stroke in adults

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

This study randomised 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 was 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. Use of an EMG/nerve stimulator was recommended to assist in proper muscle localisation for injection. Patients were followed for 12 weeks.

The primary efficacy endpoint was wrist flexors muscle tone at week 6, as measured by the Ashworth score. Key secondary endpoints included Physician Global Assessment, finger flexors muscle tone, and thumb flexors tone at Week 6. Study 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

	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]	-1.66*	-0.48

* Significantly different from placebo ($p\leq0.05$)

[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.

Focal lower limb spasticity associated with stroke in adults
The efficacy and safety of BOTOX for the treatment of lower limb spasticity were evaluated in a randomised, multi-centre, double-blind, placebo-controlled study which randomised 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 between-group differences for BOTOX over placebo were demonstrated for the primary efficacy measures of MAS and key secondary measure of CGI and are presented in table below. 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, likely due to small patient numbers.

Primary and Key Secondary Efficacy Endpoints (ITT Population)

	BOTOX® 300 to 400 Units (ITT) (N=233)	**Placebo (N=235)**
Mean Changes from Baseline in Ankle Plantar Flexors in MAS Score		
Week 4 and 6 Average	-0.8*	-0.6
Mean Clinical Global Impression Score by Investigator		
Week 4 and 6 Average	0.9*	0.7
Mean Change in Toe Flexors in MAS Score		
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**	**≥65 years N=64**
Week 4 and 6 Average	-0.7	-0.7

*Significantly different from placebo ($p<0.05$)
ITT – intent-to-treat

Another double-blind, placebo-controlled, randomised, multi-centre, Phase 3 clinical study was conducted in adult post-stroke patients with lower limb spasticity affecting the ankle. A total of 120 patients were randomised to receive either BOTOX (n=58) (total dose of 300 Units) or placebo (n=62). This study was conducted exclusively in Japanese patients with Modified Ashworth Scale (MAS) ≥ 3 who were on average 6.5 years post-stroke.

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 than in placebo treated patients at these visits.

BOTOX treatment was also associated with significant improvement in the investigator's clinical global impression (CGI) of functional disability (secondary endpoint, no multiplicity adjustment) compared to placebo. There was no clinically meaningful improvement in function as measured by the Physician's Rating Scale (PRS) and speed of gait.

Results from the phase 3 study are presented below.

Primary and Key Secondary Efficacy Endpoints

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

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

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

A consistent response was observed with re-treatment.

Chronic migraine

BOTOX blocks the release of neurotransmitters associated with the genesis of pain. The mechanism of action of BOTOX for symptom relief in chronic migraine is not fully established. Pre-clinical and clinical pharmacodynamic studies suggest that BOTOX suppresses peripheral sensitisation, thereby possibly also inhibiting central sensitisation.

The main results achieved from the pooled efficacy analysisafter two BOTOX treatments administered at a 12-week interval from two phase 3 clinical trials in chronic migraine patients, who during a 28-day baseline period had at least 4 episodes and ≥ 15 headache days (with at least 4 hours of continuous headache), with at least 50% of headache days being migraine/probable migraine days, 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	p<0.001
Frequency of moderate/severe headache days	-7.7	-5.8	p<0.001
Frequency of migraine/probable migraine days	-8.2	-6.2	p<0.001
% patients with 50% reduction in headache days	47%	35%	p<0.001
Total cumulative hours of headache on headache days	-120	-80	p<0.001
Frequency of headache episodes	-5.2	-4.9	p=0.009
Total Headache Impact Test (HIT-6) scores	-4.8	-2.4	p<0.001

Although the studies were not powered to show differences in subgroups, the treatment effect appeared smaller in the subgroup of male patients (N=188) and non-Caucasians (N= 137) than in the whole study population.

BLADDER DISORDERS

Adult overactive bladder

Two double-blind, placebo-controlled, randomised, multi-centre, 24 week Phase 3 clinical studies were conducted in patients with overactive bladder with symptoms of urinary incontinence, urgency and frequency. A total of 1105 patients, whose symptoms had not been adequately managed with at least one anticholinergic therapy (inadequate response or intolerable adverse reactions), were randomised to receive either 100 Units of BOTOX (n=557), or placebo (n=548).

In both studies, significant improvements compared to placebo in the change from baseline in daily frequency of urinary incontinence episodes were observed for BOTOX (100 Units) at the primary time point of week 12 (baseline was 5.49 for BOTOX and 5.39 for placebo), including the proportion of dry patients. Using the Treatment Benefit Scale, the proportion of patients reporting a positive treatment response (their condition had been 'greatly improved' or 'improved') was significantly greater in the BOTOX group compared to the placebo group in both studies. Significant improvements compared to placebo were also observed for the daily frequency of micturition, urgency and nocturia episodes. Volume voided per micturition was also significantly higher. Significant improvements were observed in all OAB symptoms from week 2.

BOTOX treatment was associated with significant improvements over placebo in health-related quality of life as measured by the Incontinence Quality of Life (I-QOL) questionnaire (including avoidance and limiting behaviour, psychosocial impact and

social embarrassment), and the King's Health Questionnaire (KHQ) (including incontinence impact, role limitations, social limitations, physical limitations, personal relationships, emotions, sleep/energy and severity/coping measures).
No overall difference in effectiveness following BOTOX treatment was observed between patients ≥65 years compared to <65 years.

Results from the pooled pivotal studies are presented below:

Primary and Secondary Efficacy Endpoints at Baseline and Change from Baseline in the 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	-2.85	-1.21	< 0.001
Mean Change at Week 6	-3.11	-1.22	< 0.001
Mean Change at Week 12[a]	**-2.80**	**-0.95**	**< 0.001**
Proportion with Positive Treatment Response using Treatment Benefit Scale (%)			
Week 2	64.4	34.7	< 0.001
Week 6	68.1	32.8	< 0.001
Week 12[a]	**61.8**	**28.0**	**< 0.001**
Daily Frequency of Micturition Episodes			
Mean Baseline	11.99	11.48	
Mean Change at Week 2	-1.53	-0.78	< 0.001
Mean Change at Week 6	-2.18	-0.97	< 0.001
Mean Change at Week 12[b]	**-2.35**	**-0.87**	**< 0.001**
Daily Frequency of Urgency Episodes			
Mean Baseline	8.82	8.31	
Mean Change at Week 2	-2.89	-1.35	< 0.001
Mean Change at Week 6	-3.56	-1.40	< 0.001
Mean Change at Week 12[b]	**-3.30**	**-1.23**	**< 0.001**
Incontinence Quality of Life Total Score			
Mean Baseline	34.1	34.7	
Mean Change at Week 12[bc]	**+22.5**	**+6.6**	**< 0.001**
King's Health Questionnaire: Role Limitation			
Mean Baseline	65.4	61.2	
Mean Change at Week 12[bc]	**-25.4**	**-3.7**	**< 0.001**
King's Health Questionnaire: Social Limitation			
Mean Baseline	44.8	42.4	
Mean Change at Week 12[bc]	**-16.8**	**-2.5**	**< 0.001**

* Percentage of patients who were dry (without incontinence) at week 12 was 27.1% for the Botox group and 8.4% for the placebo group. The proportions achieving at least a 75% and 50% reduction from baseline in urinary incontinence episodes were 46.0% and 60.5% in the Botox group compared to 17.7% and 31.0% in the placebo group, respectively.
[a] Co-primary endpoints
[b] Secondary endpoints
[c] Pre-defined minimally important change from baseline was +10 points for I-QOL and -5 points for KHQ

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).

Although only a limited number of patients aged <40 years (n=88, 8.0%), non-Caucasians (n=101, 9.1%) and males (n=135, 12.2%) were studied in the two Phase 3 clinical studies, data in these subgroups were supportive of a positive treatment effect. A higher incidence of the adverse events of urinary retention, residual urine volume, and pollakiuria was observed in males compared to females. Results for the co-primary endpoints in males are presented below:

Co-primary Efficacy Endpoints at Baseline and Change from Baseline in Male Patients (Pooled Pivotal Studies):

	Botox 100 Units (N=61)	Placebo (N=74)	p-value
Daily Frequency of Urinary Incontinence Episodes			
Mean Baseline	5.61	4.33	
Mean Change at Week 12	-1.86	-1.23	0.612
Proportion with Positive Treatment Response using Treatment Benefit Scale (%)			
Week 12	40.7	25.4	0.060

A total of 839 patients were evaluated in a long-term open-label extension study (n=758 females, n=81 males). For all efficacy endpoints, patients experienced consistent response with re-treatments. In the subset of 345 patients (n=316 females, n=29 males), who had reached week 12 of treatment cycle 3, the mean reductions in daily frequency of urinary incontinence were -3.07, -3.49, and -3.49 episodes at week 12 after the first, second, and third BOTOX 100 Unit treatments, respectively. The corresponding proportions of patients with a positive treatment response on the Treatment Benefit Scale were 63.6%, 76.9%, and 77.3%, respectively.

In the pivotal studies, none of the 615 patients with analysed specimens developed neutralising antibodies. 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

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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	8.1	8.5	11.2	0.5743	0.1451
Mean Change* at Week 12** (95% CI)	-1.0 (-3.0, 1.0)	0.3 (-1.7, 2.4)	-1.8 (-3.9, 0.2)		
Daily Frequency of Daytime Urgency Episodes[b] Baseline Mean	4.4	5.4	7.5	0.8206	0.9604
Mean Change* at Week 12** (95% CI)	-2.2 (-4.1, -0.3)	-1.8 (-3.8, 0.2)	-1.9 (-3.9, 0.2)		

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

In both phase 3 studies, significant improvements compared to placebo in the primary efficacy variable of change from baseline in weekly frequency of incontinence episodes were observed favouring BOTOX (200 Units and 300 Units) at the primary efficacy time point at week 6, including the percentage of dry patients. Significant improvements in urodynamic parameters including increase in maximum cystometric capacity and decreases in peak detrusor pressure during the first involuntary detrusor contraction were observed. Significant improvements, compared with placebo, in patient reported incontinence specific health-related quality of life scores as measured by the I-QOL (including avoidance limiting behaviour, psychosocial impacts and social embarrassment) were also observed. No additional benefit of BOTOX 300 Units over 200 Units was demonstrated and a more favourable safety profile was observed with BOTOX 200 Units.

Results from the pooled pivotal studies are presented below:

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	-17.7	-9.0	p<0.001
Mean Change at Week 6[a]	**-21.3**	**-10.5**	**p<0.001**
Mean Change at Week 12	-20.6	-9.9	p<0.001
Maximum Cystometric Capacity (ml)			

Mean Baseline	250.2	253.5	**p<0.001**
Mean Change at Week 6[b]	**+153.6**	**+11.9**	
Maximum Detrusor Pressure during 1st Involuntary Detrusor Contraction (cmH_20)			
Mean Baseline	51.5	47.3	
Mean Change at Week 6[b]	**-32.4**	**+1.1**	**p<0.001**
Incontinence Quality of Life Total Score[c,d]			
Mean Baseline	35.37	35.32	
Mean Change at Week 6[b]	**+25.89**	**+11. 15**	**p<0.001**
Mean Change at Week 12	+28.89	+8.86	p<0.001

* Percentage of dry patients (without incontinence) throughout week 6 was 37% for the 200 Unit BOTOX group and 9% for placebo. The proportions achieving at least a 75% reduction from baseline, in incontinence episodes, were 63% and 24% respectively. The proportions achieving at least a 50% reduction from baseline were 76% and 39% respectively.

[a] Primary endpoint

[b] Secondary endpoints

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

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

The median duration of response in the two pivotal studies, based on patient request for re-treatment, was 256-295 days (36-42 weeks) for the 200 Unit dose group compared to 92 days (13 weeks) with placebo. The median duration of response, based on patient request for re-treatment, in patients who continued into the open label extension study and received treatments with only BOTOX200 Units (N=174), was 253 days (~36 weeks).

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

In the pivotal studies, none of the 475 neurogenic detrusor overactivity patients with analysed specimens developed neutralising antibodies. In patients with analysed specimens in the drug development programme (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).

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 impacts 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. These patients were randomised to 50 Units, 100 Units or 200 Units, not to exceed 6 Units/kg body weight. Patients receiving less than the randomised dose due to the 6 Units/kg maximum were assigned to the nearest dose group for analysis; N= 38, N=45 and N=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 (required for patients < 12 years) and 3 patients (2.7%) received local anaesthesia (allowed only for patients ≥ 12 years).

Baseline and Change from Baseline in Daily Daytime Frequency of Urinary Incontinence Episodes, Urine Volume at First Morning Catheterisation and Maximum Detrusor Pressure during the Storage Phase (cmH_2O) in a Double-Blind, Parallel-Group Clinical Study

	BOTOX 200 Units (N=30)	**BOTOX 100 Units (N=45)**	**BOTOX 50 Units (N=38)**	**p-value * BOTOX 200 vs. 50 Units**	**p-value * BOTOX 100 vs. 50 Units**
Daily Frequency of Daytime Urinary Incontinence Episodes[a]					
Mean Baseline (SD)	3.7 (5.06)	3.0 (1.07)	2.8 (1.04)		
Mean Change* at Week 2	-1.1	-1.0	-1.2		
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)	0.9123	0.9949
Mean Change* at week 12	-0.9	-1.4	-1.2		
Urine volume at the first morning catheterisation (mL)[b]					
Mean Baseline (SD)	187.7 (135.70)	164.2 (114.48)	203.5 (167.48)		

Mean Change* at Week 2	63.2	29.4	31.6		
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)	0.0055	0.5117
Mean Change* at Week 12	45.2	55.8	12.9		
Maximum Detrusor Pressure during the storage phase (cmH2O)b					
Mean Baseline (SD)	56.7 (33.89)	56.5 (26.86)	58.2 (29.45)		
Mean Change* at Week 6** (95% CI)	-27.3 (-36.4, -18.2)	-20.1 (-27.3, -12.8)	-12.9 (-20.4, -5.3)	0.0157	0.1737

CI = Confidence Interval

*Least Squares (LS) mean change and 95% CI and p-values 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 214.0 (31 weeks), 169.0 (24 weeks), and 207 days (30 weeks) for BOTOX 50 Units, BOTOX 100 Units, and BOTOX 200 Units, respectively.

In 99 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 and one double-blind extension study, no patients developed neutralising antibodies after receiving 50 Units to 200 Units of BOTOX.

SKIN AND SKIN APPENDAGE DISORDERS

Primary hyperhidrosis of the axillae

A double-blind, multi-centre clinical study was conducted in patients presenting with persistent bilateral primary axillary hyperhidrosis defined as baseline gravimetric measurement of at least 50 mg spontaneous sweat production in each axilla over 5 minutes at room temperature, at rest. Three hundred and twenty patients were randomised to receive either 50 Units of BOTOX (n=242) or placebo (n=78). Treatment responders were defined as subjects showing at least a 50% reduction from baseline in axillary sweating. At the primary endpoint, week 4 post-injection, the response rate in the BOTOX group was 93.8% compared with 35.9% in the placebo group (p< 0.001). The incidence of responders among BOTOX treated patients continued to be significantly higher (p<0.001) than placebo treated patients at all post-treatment time points for up to 16 weeks.

A follow up open-label study enrolled 207 eligible patients who received up to 3 BOTOX treatments. Overall, 174 patients completed the full 16-month duration of the 2 studies combined (4 month double-blind and 12 month open-label continuation). Incidence of clinical response at week 16 following the first (n=287), second (n=123) and third (n=30) treatments was 85.0%, 86.2% and 80% respectively. The mean duration of effect based on the combined single-dose and open-label continuation trial was 7.5 months following the first treatment, however for 27.5% of patients the duration of effect was 1 year or greater.

There is limited clinical trial experience of the use of BOTOX in primary axillary hyperhidrosis in children 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 conclusively established.

5.2 Pharmacokinetic properties

General characteristics of the active substance:

Distribution studies in rats indicate slow muscular diffusion of ^{125}I-botulinum neurotoxin A complex in the gastrocnemius muscle after injection, followed by rapid systemic metabolism and urinary excretion. The amount of radiolabelled material in the muscle declined at a half-life of approximately 10 hours. At the injection site the radioactivity was bound to large protein molecules, whereas in the plasma it was bound to small molecules, suggesting rapid systemic metabolism of the substrate. Within 24 hours of dosing, 60% of the radioactivity was excreted in the urine. Toxin is probably metabolised by proteases and the molecular components recycled through normal metabolic pathways.

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

Characteristics in patients:
It is believed that little systemic distribution of therapeutic doses of BOTOX occurs. Clinical studies using single fibre electromyographic techniques have shown increased electrophysiologic neuromuscular activity in muscles distant to the injection site, unaccompanied by any clinical signs or symptoms.

5.3 Preclinical safety data

Reproductive studies
When pregnant mice, rats and rabbits were given intramuscular injections of BOTOX during the period of organogenesis, the developmental No Observed Adverse Effect Level (NOAEL) was 4, 1 and 0.125 Units/kg, respectively. Higher doses were associated with reductions in foetal body weights and/or delayed ossification and in rabbits abortions were noted.

Fertility and reproduction
The reproductive NOAEL 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.

Other studies
In addition to the reproductive toxicology, the following preclinical safety studies of BOTOX have been performed: Acute toxicity, toxicity on repeated injection, local tolerance, mutagenicity, antigenicity, human blood compatibility. These studies revealed no special hazard for humans at clinically relevant dose levels.

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.

No systemic toxicity was observed following a single intradetrusor injection of <50 Units/kg BOTOX in rats. To simulate inadvertent injection, a single dose of BOTOX (~7 Units/kg) was administered into the prostatic urethra and proximal rectum, the seminal vesicle and urinary bladder wall, or the uterus of monkeys (~3 Units/kg) without adverse clinical effects. In a 9-month repeat dose intradetrusor study (4 injections), ptosis was observed at 24 Units/kg, and mortality was observed at doses ≥24 Units/kg. Myofibre degeneration/regeneration was observed in skeletal muscle of animals dosed with 24 Units/kg and higher. These myopathic changes were considered secondary effects of systemic exposure. In addition, myofibre degeneration was observed in one animal dosed with 12 Units/kg. The lesion in this animal was minimal in severity and considered not to be associated with any clinical manifestations. It could not be determined with certainty if it was related to the BOTOX treatment. The dose of 12 Units/kg corresponds to a 3-fold greater exposure to BOTOX than the recommended clinical dose of 200 Units for urinary incontinence due to neurogenic detrusor overactivity (based on a 50 kg person).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Human albumin
Sodium chloride

6.2 Incompatibilities

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

6.3 Shelf life

3 years.

Potency studies have demonstrated that the product may be stored for up to 5 days at 2 – 8°C following reconstitution.

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 to 8°C, unless reconstitution/dilution (etc) has taken place in controlled and validated aseptic conditions.

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

Colourless Type I glass vial, of 10 ml nominal capacity, fitted with chlorobutyl rubber stopper and tamper-proof aluminium seal.

Each pack contains 1, 2, 3, 6 or 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

It is good practice to perform vial reconstitution and syringe preparation over plastic-lined paper towels to catch any spillage.

BOTOX must only be reconstituted with sterile unpreserved 0.9% sodium chloride for injection. The appropriate amount of diluent should be drawn up into a syringe. See below for dilution instructions.

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* added in a 50 Unit vial	**Amount of diluent* added in a 100 Unit vial**	Amount of diluent* 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
2.5 Units	2 ml	**4 ml**	8 ml
1.25 Units	4 ml	**8 ml**	N/A

* sterile unpreserved 0.9% sodium chloride solution for injection

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 0.9% sodium chloride solution for injection and mix the vials gently. • Draw the 5 ml from each of the vials into a single 10 ml syringe.
Dilution instructions using a 100 Unit vial	• **Reconstitute a 100 Unit vial of BOTOX with 10 ml of sterile unpreserved 0.9% sodium chloride solution for injection and mix gently.** • **Draw the 10 ml from the vial into a 10 ml syringe.**
Dilution instructions using a 200 Unit vial	• Reconstitute a 200 Unit vial of BOTOX with 8 ml of sterile unpreserved 0.9% sodium chloride solution 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 0.9% sodium chloride solution 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 sodium chloride solution.

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 0.9% sodium chloride solution 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 0.9% sodium chloride solution for injection into each of the three 10 ml syringes and mix gently.
Dilution instructions using two 100 Unit vials	• **Reconstitute two 100 Unit vials of BOTOX, each with 6 ml of sterile unpreserved 0.9% sodium chloride solution 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 0.9% sodium chloride solution for injection into each of the three 10 ml syringes, and mix gently.**
Dilution instructions using a 200 Unit vial	• Reconstitute a 200 Unit vial of BOTOX with 6 ml of sterile unpreserved 0.9% sodium chloride solution for injection and mix the vial gently. • Draw 2 ml from the vial into each of three 10 ml syringes. • Complete the reconstitution by adding 8 ml of sterile unpreserved 0.9% sodium chloride solution 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 sodium chloride solution.

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.

Since BOTOX is denatured by bubbling or similar vigorous agitation, the diluent should be gently injected into the vial. The vial should be discarded 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. The reconstituted solution should be visually inspected for clarity and absence of particles prior to use. When reconstituted in the vial, BOTOX may be stored in a refrigerator (2 - 8°C) for up to 24 hours prior to use. If BOTOX is further diluted for intradetrusor injection in a syringe, it should be used immediately. This product is for single use only and any unused solution should be discarded.

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

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

7 MARKETING AUTHORISATION HOLDER

AbbVie Limited
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