SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

BOTOX® vacuum-dried injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BOTOX® (Botulinum toxin type A) is a sterile, vacuum-dried form of purified Botulinum toxin type A, produced from a culture of *Clostridium botulinum.* The crystalline complex is re-dissolved in a solution containing saline and albumin and sterile filtered (0,2 microns) prior to vacuum-drying.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Vacuum-dried injection

Clear glass vial containing a small white vacuum-dried powder cake.

Reconstituted BOTOX® should be clear, colourless and free of particulate matter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BOTOX® is indicated for the treatment and/or management of:

Neurologic disorders

- Focal spasticity associated with dynamic equinus foot deformity due to spasticity in paediatric cerebral palsy patients, two years of age or older by specialists trained in the procedure.
- Focal spasticity of the wrist and hand in adult post-stroke patients.

- Selected cases of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders (hemifacial spasm), in patients 12 years of age and older.

  The efficacy of BOTOX® in deviations over 50 prism diopters, in restrictive strabismus, in Duane's syndrome with lateral rectus weakness and in secondary strabismus caused by prior surgical over-recession of the antagonist is doubtful. BOTOX® is ineffective in chronic paralytic strabismus.
- The reduction of the signs and symptoms of cervical dystonia (spasmodic torticollis) in adults.
- 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.

Bladder disorders

- Idiopathic overactive bladder with symptoms of urinary incontinence (defined as three or more episodes of urinary incontinence per 3 days), urgency and urinary frequency in adult female patients who have an inadequate response to anticholinergic medicines), or who are intolerant of anticholinergic medication. Efficacy and safety have not been demonstrated for more than 2 treatment cycles. Efficacy has not been demonstrated in males with idiopathic overactive bladder (see section 4.4).
- Urinary incontinence due to neurogenic detrusor overactivity caused by spinal cord injury (SCI) or multiple sclerosis (MS) in adult patients who are willing and able to perform clean intermittent self-catheterisation, if required.

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.

- Moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in people less than or equal to 65 years of age. Efficacy beyond 4 treatments has not been demonstrated.
- Moderate to severe lateral canthal lines (crow's feet lines) seen at maximum smile. Efficacy beyond 4 treatments has not been demonstrated.
- Moderate to severe forehead lines seen at maximum eyebrow elevation.

4.2 Posology and method of administration

Posology

Please note that dosage and directions for use is specific to each individual indication.

BOTOX® should be administered only by a suitably qualified and registered medical practitioner.

BOTOX® is for single patient use only.

FOR INTRADERMAL, INTRADETRUSOR OR INTRAMUSCULAR USE

Once opened and reconstituted in the vial, use within twenty four hours and discard remaining solution, as the product and diluent do not contain a preservative. Reconstituted BOTOX® should not be frozen. When BOTOX® is diluted for urinary incontinence in a syringe, it should be used immediately.

Optimum dose levels and number of injection sites per muscle have not been established. Individual treatment regimens should therefore be drawn up by the medical practitioner. Optimum dose levels should be determined by titration.

Special populations

Elderly

With the exception of overactive bladder, clinical studies of BOTOX® did not identify differences in responses between the elderly and younger patients. The lowest effective dose with the longest clinically indicated interval between injections is recommended for elderly patients. Older people with significant medical history and concomitant medications should not be treated (for overactive bladder, see section 5.1 and section 4.8).

Paediatric population

The safety and efficacy of BOTOX® in the treatment of individual indications have not been established in children and adolescents under the ages listed in Table 1. No data are available.

Table 1: Paediatric use

Focal spasticity associated with paediatric cerebral palsy	2 years
Upper limb spasticity associated with stroke	18 years
Strabismus, blepharospasm and hemifacial spasm	12 years
Cervical dystonia	16 years
Chronic migraine	18 years
Overactive bladder and neurogenic detrusor overactivity	18 years
Primary hyperhidrosis of the axillae	18 years
Glabellar lines, crow's feet lines and forehead lines	18 years

The safety and efficacy of BOTOX® in indications other than those described for the paediatric population in Table 1 have not been established. Post-marketing reports of distant spread of toxin have been reported in paediatric patients with comorbidities, predominantly with cerebral palsy (see section 4.8).

There have been spontaneous reports of death sometimes associated with aspiration pneumonia in children with severe cerebral palsy after treatment with BOTOX®, including

following off-label use (e.g. neck area). Extreme caution should be exercised when treating paediatric patients who have significant neurologic debility, dysphagia, or have a recent history of aspiration pneumonia or lung disease. BOTOX® should not be used in patients with poor underlying health status.

Dilution technique

The following information is important:

If different vial sizes of BOTOX® are being used as 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 non-preserved sodium chloride 9 mg/ml (0,9 %) solution for injection. The appropriate amount of diluent (see Table 2) should be drawn up into a syringe.

Since BOTOX® is denatured by bubbling or similar violent agitation; inject the diluent into the vial gently. Discard the vial if a vacuum does not pull the diluent into the vial. Record the date and the time of reconstitution on the space on the label. BOTOX® should be administered within 24 hours after reconstitution. During this time period, reconstituted BOTOX® should be stored in a refrigerator (2 ° to 8 °C). Reconstituted BOTOX® should be clear, colourless and free of particulate matter. Parenteral products should be inspected visually for particulate matter and discolouration prior to administration and whenever the solution and the container permit.

Table 2: Dilution table for BOTOX® 50, 100 and 200 Unit vials for all indications except bladder disorders

Resulting dose (Units per 0,1 ml)	50 Unit vial	100 Unit vial	200 Unit vial
	Amount of diluent (sodium chloride 9 mg/ml (0,9 %) solution for injection) added in a 50 Unit vial	**Amount of diluent (sodium chloride 9 mg/ml (0,9 %) solution for injection) added in a 100 Unit vial**	**Amount of diluent (sodium chloride 9 mg/ml (0,9 %) solution for injection) added in a 200 Unit vial**
20 Units	0,25 ml	0,5 ml	1 ml
10 Units	0,5 ml	1 ml	2 ml
5 Units	1 ml	2 ml	4 ml
4 Units	1,25 ml	2,5 ml	5 ml
2,5 Units	2 ml	4 ml	8 ml
1,25 Units	4 ml	8 ml	N/A

Note: These dilutions are calculated for an injection volume of 0,1 ml. A decrease or increase in the BOTOX® dose is also possible by administering a smaller or larger injection volume - from 0,05 ml (50 % decrease in dose) to 0,15 ml (50 % increase in dose).

An injection of BOTOX® is prepared by drawing into a sterile 1,0 ml syringe an amount of the properly diluted toxin (see Table 2) slightly greater than the intended dose. Air bubbles in the syringe barrel are expelled and the syringe is attached to the electro-myographic injection needle, preferably a 27 gauge needle. Injection volume in excess of the intended dose is expelled through the needle into an appropriate waste container to assure patency of the needle and to confirm that there is no syringe-needle leakage. A new, sterile needle and syringe should be used to enter the vial on each occasion for dilution or removal of BOTOX®.

Overactive bladder - dilution instructions

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

Dilution instructions using a 100 Unit vial

- Reconstitute a 100 Unit vial of BOTOX® with 10 ml of 0,9 % non-preserved saline solution and mix gently.
- Draw the 10 ml from the vial into a 10 ml syringe.

Dilution instructions using two 50 Unit vials

- Reconstitute two 50 Unit vials of BOTOX® each with 5 ml of 0,9 % non-preserved saline solution and mix the vials gently.
- Draw the 5 ml from each of the vials into a single 10 ml syringe.

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

Urinary incontinence due to neurogenic detrusor overactivity - dilution instructions

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

Dilution instructions using two 100 Unit vials

- Reconstitute two 100 Unit vials of BOTOX®, each with 6 ml of 0,9 % non-preserved saline solution and mix the vials gently.
- Draw 4 ml from each vial into each of two 10 ml syringes. Draw the remaining 2 ml from each vial into a third 10 ml syringe.

- Complete the reconstitution by adding 6 ml of 0,9 % non-preserved saline solution into each of the 10 ml syringes, and mix gently.

Dilution instructions using a 200 Unit vial

- Reconstitute a 200 Unit vial of BOTOX® with 6 ml of 0,9 % non-preserved saline solution and mix the vial gently.
- Draw 2 ml from the vial into each of three 10 ml syringes.
- Complete the reconstitution by adding 8 ml of 0,9 % non-preserved saline solution into each of the 10 ml syringes, and mix gently.

Dilution instructions using four 50 Unit vials

- Reconstitute four 50 Unit vials of BOTOX, each with 3 ml of 0,9 % non-preserved saline solution and mix the vials gently.
- Draw 3 ml from the first vial and 1 ml from the second vial into one 10 ml syringe.
- Draw 3 ml from the third vial and 1 ml from the fourth vial into a second 10 ml syringe.
- Draw the remaining 2 ml from the second and fourth vials into a third 10 ml syringe.
- Complete the reconstitution by adding 6 ml of 0,9 % non-preserved saline solution into each of the three 10 ml syringes, and mix gently.

This will result in three 10 ml syringes each containing 10 ml (~67 Units in each), for a total of 200 Units of reconstituted BOTOX®. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

Method of administration

Neurologic disorders

Focal spasticity associated with paediatric cerebral palsy

Recommended needle: Sterile 23 - 26 gauge / 0,60 - 0,45 mm needle

Administration guidance: To be administered as a divided dose through single injections into the medial and lateral heads of the affected gastrocnemius muscle.

Recommended dose: Hemiplegia: The initial recommended dose is 4 Units/kg body weight in the affected limb.

Diplegia: The initial recommended dose is 6 Units/kg body weight divided between the affected limbs.

Maximum total dose: 200 Units

Additional information: Clinical improvement generally occurs within the first two weeks after injection. Repeat doses should be administered when the clinical effect of a previous injection diminishes but not more frequently than every three months. It may be possible to adapt the dosage regimen to obtain an interval of at least six months between treatment sessions.

Focal upper limb spasticity associated with stroke

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.

Recommended dose: 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.

Table 3: In controlled clinical trials the following doses were administered

Muscle	**Total Dose**
Flexor digitorum profundus	50 Units
Flexor digitorum sublimis	50 Units
Flexor carpi radialis	50 Units
Flexor carpi ulnaris	50 Units
Adductor pollicis	20 Units
Flexor pollicis longus	20 Units

Maximum total dose: It is recommended that the dose at any treatment session does not exceed 240 Units divided among selected muscles. Re-injections should not occur before 12 weeks.

Additional information: Improvement in muscle tone occurs within two weeks with the peak effect generally seen within four to six weeks. If it is deemed appropriate by the treating practitioner, repeat doses may be administered, when the effect of a previous injection has diminished. Consistent response to re-injection has been

observed with up to 5 successive treatments. 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.

Strabismus

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

Administration guidance: To prepare the eye for BOTOX® injection, it is recommended that several drops of a local anaesthetic and an ocular decongestant be given several minutes prior to injection.

Recommended dose: The volume of BOTOX® injected for treatment of strabismus should be between 0,05 ml to 0,15 ml per muscle.

Initial doses: (Use the lower listed doses for treatment of small deviations. Use the larger doses only for large deviations.)

- For vertical muscles, and for horizontal strabismus of less than 20 prism diopters: 1,25 Units to 2,5 Units in any one muscle.
- For horizontal strabismus of 20 prism diopters to 50 prism diopters: 2,5 Units to 5,0 Units in any one muscle.
- For persistent VI nerve palsy of one month or longer duration: 1,25 Units to 2,5 Units in the medial rectus muscle.

Subsequent doses for residual or recurrent strabismus:

- It is recommended that patients be re-examined 7 to 14 days after each injection to assess the effect of that dose.
- Patients experiencing adequate paralysis of the target muscle that require subsequent injections should receive a dose comparable to the initial dose.
- Subsequent doses for patients experiencing incomplete paralysis of the target muscle may be increased up to twice the size of the previously administered dose.
- Subsequent injections should not be administered until the effects of the previous dose have dissipated as evidenced by substantial function in the injected and adjacent muscles.

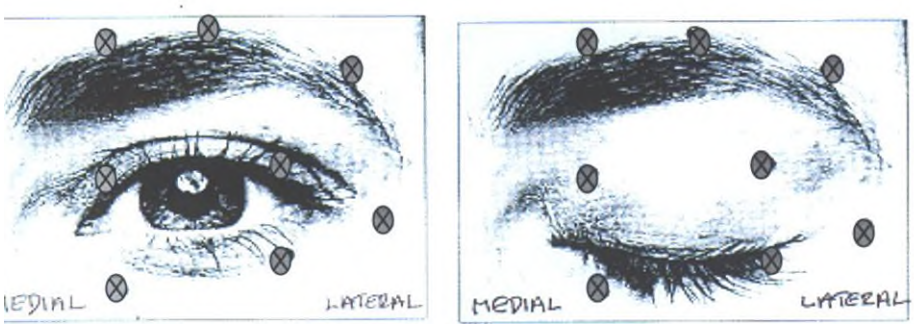
Maximum total dose: The maximum recommended dose as a single injection for any one muscle is 25 Units. The cumulative dose of BOTOX® for treatment of strabismus in a two month period should generally not exceed 200 Units.

Additional information: The initial listed doses of the diluted BOTOX® typically create paralysis of injected muscles beginning one to two days after injection and increasing in intensity during the first week. The paralysis lasts for 2 to 6 weeks and gradually resolves over a similar time period. Overcorrections lasting over 6 months have been rare. About one half of patients will require subsequent doses because of inadequate paralytic response of the muscle to the initial dose or because of mechanical factors such as large deviations or restrictions, or because of the lack of binocular motor fusion to stabilise the alignment.

Blepharospasm and hemifacial spasm

Recommended needle:	Sterile, 27 - 30 gauge / 0,40 - 0,30 mm needle
Administration guidance:	Electromyographic guidance is not necessary
Recommended dose:	For blepharospasm, the initial recommended dose is 1,25 to 2,5 Units (0,05 ml to 0,1 ml volume at each site) injected into the medial and lateral orbicularis oculi of the upper lid and the lateral orbicularis oculi of the lower lid. Additional sites in the brow area, the lateral orbicularis and in the upper facial area may also be injected if spasms here interfere with vision.
Maximum total dose:	The initial dose should not exceed 25 Units per eye. In the management of blepharospasm total dosage 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:

Figure 1



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

Cervical dystonia

Recommended needle: Appropriately sized needle (usually 25 - 30 gauge / 0,50 - 0,30 mm)

Administration guidance: The treatment of cervical dystonia may include, but is not limited to, injection of BOTOX® into the sternocleidomastoid, levator scapulae,

scalene, splenius capitis, semispinalis, longissimus and/or the trapezius muscle(s). This list is not exhaustive as any of the muscles responsible for controlling head position may be involved and therefore require treatment.

The muscle mass and the degree of hypertrophy 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 by an experienced medical practitioner.

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 controlled clinical trials, doses have ranged from 95 to 360 Units (with an approximate mean of 240 Units). Initial dosing in a treatment-naïve patient should begin at the lowest recommended dose. No more than 50 Units should be given at any one site. Limiting the total dose injected into the sternocleidomastoid muscles to 100 Units or less may decrease the occurrence of dysphagia. 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 sitting should not be exceeded. The maximum cumulative dose for cervical dystonia should not generally exceed 360 Units in a 3 month interval. 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 32 weeks) with a typical duration of approximately 12 to 16 weeks.

Chronic migraine

Recommended needle: Sterile 30-gauge, 0,5 inch needle

Administration guidance: BOTOX® should only be administered by medical practitioners who are adequately trained to do so, following diagnosis of chronic migraine by a specialist in this field, preferably a neurologist.

Injections should be divided across 7 specific head/neck muscle areas as specified in Table 4 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 Table 4 below.

The following diagrams indicate the injection sites:

Figure 2: Recommended injection sites for minimum 155 Unit dose for chronic migraine

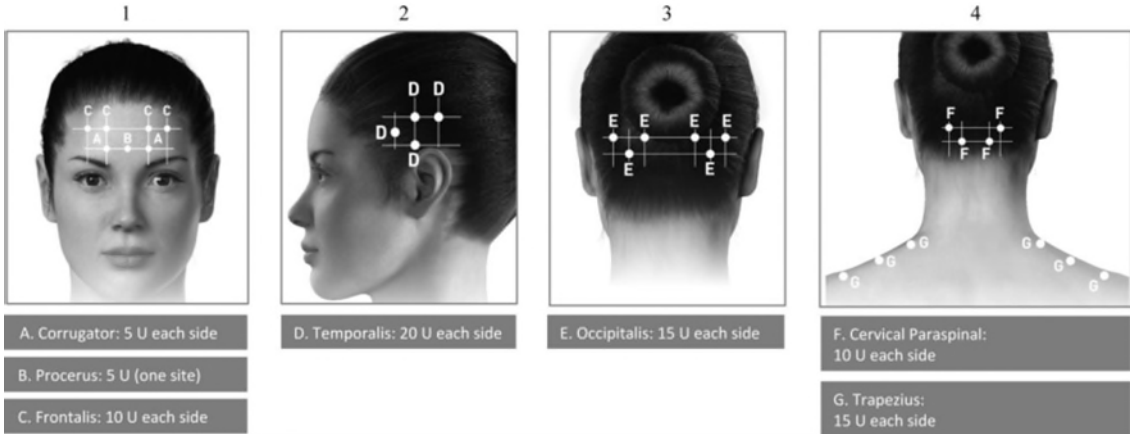
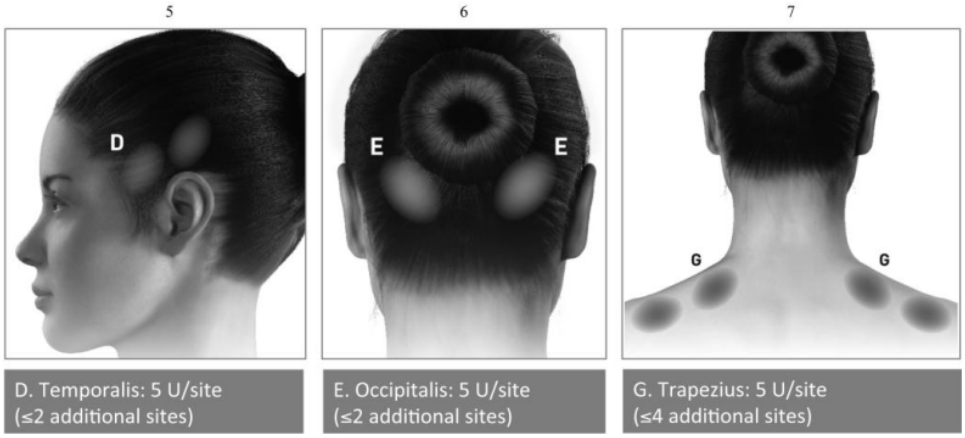


Figure 3: Recommended muscle groups for optional additional injections for chronic migraine



Recommended dose: 155 Units to 195 Units administered intramuscularly as 0,1 ml (5 Units) injections to 31 and up to 39 sites.

Table 4: BOTOX® Dosing by Muscle for Chronic Migraine

	Recommended Dose	
Head/Neck Area	**Total Dosage**	**Number of Sites[a]**
Frontalis[b]	20 Units	4 sites
Corrugator[b]	10 Units	2 sites
Procerus	5 Units	1 site
Occipitalis[b]	30 Units up to 40 Units	Occipitalis[b] up to 8 sites
Temporalis[b]	40 Units up to 50 Units	Temporalis[b] up to 10 sites
Trapezius[b]	30 Units up to 50 Units	Trapezius[b] up to 10 sites
Cervical Paraspinal Muscle Group[b]	20 Units	4 sites
Total Dose Range	**155 Units to 195 Units**	**31 to 39 sites**

[a]1 IM injection site = 0,1 ml = 5 Units BOTOX®

[b]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 medical

practitioners 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.

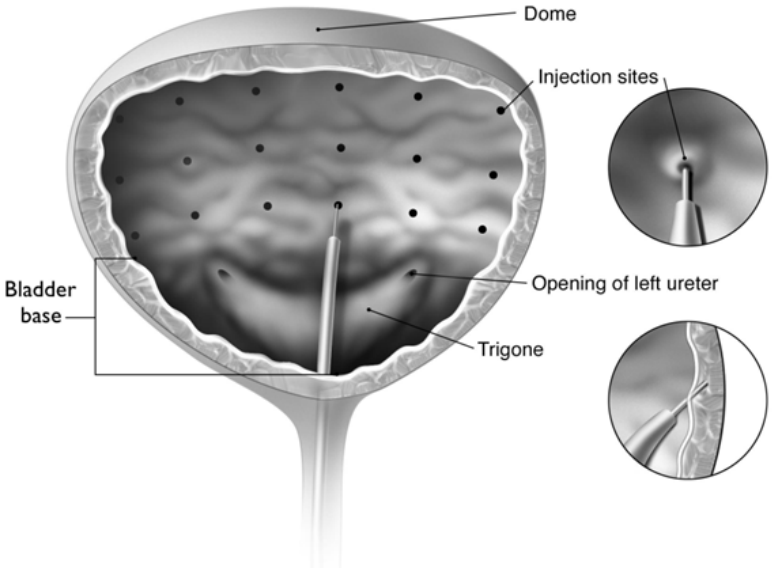
Administration guidance: Prior to injection an intravesical instillation of diluted local anaesthetic, with or without sedation, may be used, per local site practice. If a local anaesthetic instillation is performed, the bladder should be drained and irrigated with sterile saline before the next steps 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 saline 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 4). For the final injection, approximately 1 ml of sterile normal saline should be injected so the full dose is delivered. After the injections are given, the saline used for bladder wall visualisation should not be drained so that patients can demonstrate their ability to void prior to leaving the clinic. The patient should be observed for at least 30 minutes post-

injection and until a spontaneous void has occurred.

Figure 4



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]), but no sooner than 3 months from the prior bladder injection.

For geriatric use, the lowest effective dose with the longest clinically indicated interval between injections is recommended. Older people with significant medical history and concomitant medications should be treated with caution.

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 local anaesthetic (with or without sedation) or general anaesthesia may be used, per local site practice. If a local anaesthetic instillation is performed, the bladder should be drained and rinsed with sterile saline before injection.

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 saline 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 4). For the final injection, approximately 1 ml of sterile normal saline should be injected so the full dose is delivered. After the injections are given, the saline used for bladder wall visualisation should be drained. The patient should be observed for at least 30 minutes post-injection.

Recommended dose: The recommended total 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), but no sooner than 3 months from the prior bladder injection.

Skin and skin appendage disorders

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® are injected intradermally, evenly distributed in multiple sites approximately 1 to 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.

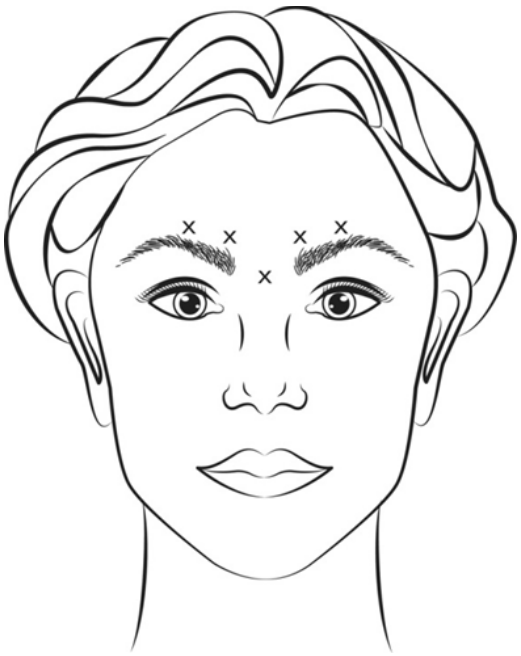
Additional information: Clinical improvement generally occurs within the first week after injection. Repeat injection of BOTOX® can be administered when the clinical effect of a previous injection diminishes and the treating practitioner deems it necessary.

Glabellar lines (50 Units per vial)

Recommended needle: 30 gauge / 0,30 mm needle

Recommended dose: 0,1 ml (4 Units) should be administered in each of five sites, two in each corrugator muscle and one in the procerus muscle for a total dose of 20 Units. Efficacy for more than 4 treatments has not been demonstrated.

Figure 5



Additional information: The needle should be oriented superiorly and medially during the injection. In order to reduce the risk of eyelid ptosis, the maximum dose of 4 Units for each injection site as well as the number of injection sites should not be exceeded. In addition, injection near the levator palpebrae superioris should be avoided, particularly in patients with larger brow-depressor complexes. Medial corrugator injections should be placed at least 1 cm above the bony supraorbital ridge.

Crow's feet lines

Recommended needle: Sterile 30 gauge needle

Recommended dose: 0,1 ml (4 Units) is administered in each of the 3 injection sites per side (total of 6 injection sites) in the lateral orbicularis oculi muscle, for a total dose of 24 Units in a total volume of 0,6 ml (12 Units per side). Efficacy for more than 4 treatments has not been established.

Injections should be given with the needle tip bevel up and oriented away from the eye. The first injection (A) should be made approximately 1,5 to 2,0 cm temporal to the lateral canthus and just temporal to the orbital rim. If the lines in the crow's feet region are above and below the lateral canthus, inject as shown in Figure 6. Alternatively, if the lines in the crow's feet region are primarily below the lateral canthus, inject as shown in Figure 7.

Figure 6

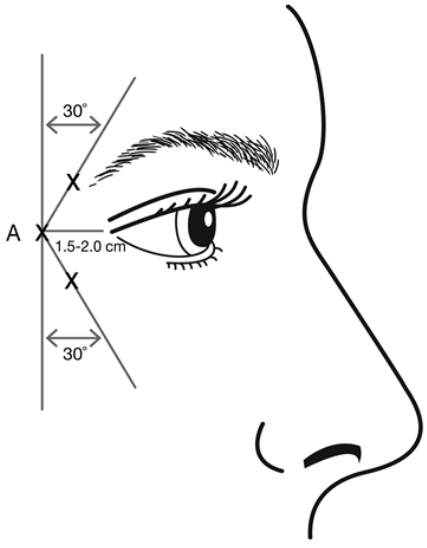
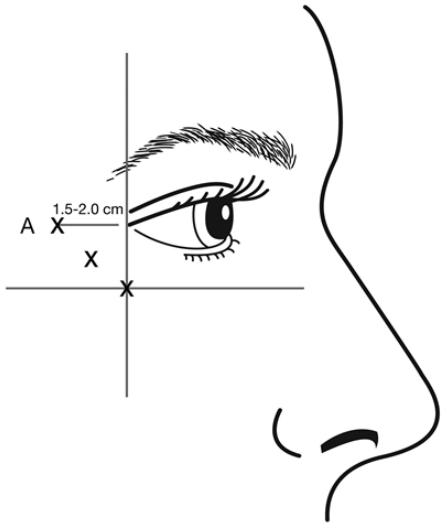


Figure 7



For simultaneous treatment with glabellar lines seen at maximum frown, the dose is 24 Units for crow's feet lines seen at maximum

smile and 20 Units for glabellar lines (see Method

of Administration for Glabellar lines, and Figure 5), for a total dose of 44 Units in a total volume of 1,1 ml.

Additional information: In order to reduce the risk of eyelid ptosis, the maximum dose of 4 Units for each injection site as well as the number of injection sites should not be exceeded. In addition, injections should be made temporal to the orbital rim, thereby maintaining a safe distance from the muscle controlling eyelid elevation.

Improvement of severity of crow's feet lines seen at maximum smile, when assessed by the investigator, occurred within one week of treatment. The effect was demonstrated for a median of 4 months after injection.

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

Forehead lines

Recommended needle: 30 gauge / 0,30 mm needle

Recommended dose: 0,1 ml (4 Units) should be administered in each of five injection sites, in the frontalis muscle, for a total dose of 20 Units.

To identify the location of the appropriate injection sites in the frontalis muscle, the overall relationship between the size of the subject's forehead, and the distribution of frontalis muscle activity

should be assessed.

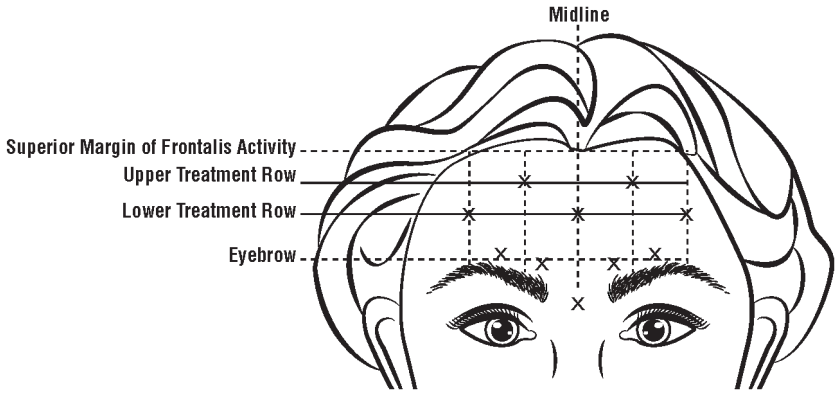
The following horizontal treatment rows should be located by light palpation of the forehead at rest and maximum eyebrow elevation:

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

The 5 injections should be placed at the intersection of the horizontal treatment rows with the following vertical landmarks:

- On the lower treatment row at the midline of the face, and 0,5 – 1,5 cm medial to the palpated temporal fusion line (temporal crest); repeat for the other side.
- On the upper treatment row, midway between the lateral and medial sites on the lower treatment row; repeat for the other side.

Figure 8



The total dose for treatment of forehead lines (20 Units) in conjunction with glabellar lines (20 Units) is 40 Units/1,0 ml.

For simultaneous treatment of forehead lines with glabellar lines and crow's feet lines, the total dose is 64 Units. This is comprised of 20 Units for forehead lines, 20 Units for glabellar lines (see Administration Instructions for Glabellar Lines, and Figure 5), and 24 Units for crow's feet lines (see Crow's Feet Lines Administration, and Figures 6 and 7).

Additional information: Improvement of severity of forehead lines seen at maximum eyebrow elevation occurred within one week of treatment. The effect was demonstrated for approximately 4 months after injection. Treatment intervals should not be more frequent than every 3 months.

All indications

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

considered:

- Clinical verification of the action of the toxin in the injected muscle(s), which may include electromyographic examination by an experienced electromyographer;
- Analysis of the potential causes of lack of effect, e.g. inappropriate selection of muscles to be injected, insufficient dose, poor injection technique, fixed contracture, relative weakness of antagonist muscles, and/or formation of toxin-neutralising antibodies;
- Re-evaluation of the appropriateness of treatment with botulinum toxin type A.

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

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

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

4.3 Contraindications

BOTOX® is contraindicated:

- in individuals with known hypersensitivity to botulinum toxin type A or any ingredient in the formulation;
- in the presence of infection or inflammation at the proposed injection site(s); or
- when excessive weakness or atrophy is present in the target muscle.

BOTOX® should not be used for treatment of patients with amyotrophic lateral sclerosis or disorders that produce peripheral neuromuscular dysfunction, or when there are

neuromuscular junctional disorders e.g. myasthenia gravis or Eaton Lambert Syndrome.

BOTOX® for management of bladder disorders is contraindicated:

- in patients who have 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 or able to initiate self-catheterisation post-treatment if required.

4.4 Special warnings and precautions for use

Medical practitioners wishing to inject BOTOX® should ensure that they are adequately trained to do so and have access to adequate resuscitating facilities.

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

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 medicine contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially “sodium free”.

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

Post-marketing safety data from BOTOX® suggest that botulinum toxin effects may, in some

cases, be observed beyond the site of local injection. These effects have been reported hours to weeks after injection, and may include muscular weakness, ptosis, diplopia, blurred vision, facial weakness, swallowing and speech disorders, constipation, aspiration pneumonia, difficulty in breathing and respiratory depression. The risk of symptoms is probably greatest in children treated for spasticity, but symptoms can also occur in patients who have underlying conditions and comorbidities that would predispose them to these symptoms, including children and adults treated for spasticity and other conditions.

Patients treated with BOTOX® may also experience exaggerated muscle weakness.

Older and debilitated patients should be treated with caution.

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).

Individuals with peripheral motor neuropathic diseases (e.g. amyotrophic lateral sclerosis or motor neuropathy) or neuromuscular junctional disorders (e.g. myasthenia gravis or Lambert-Eaton syndrome) should not receive BOTOX®. Patients with known or unrecognised neuromuscular junctional disorders are at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of BOTOX® (see section 4.3). There have been cases of administration of botulinum toxin to patients with known or unrecognised neuromuscular junction disorders where the patients have shown extreme sensitivity to the systemic effects of typical clinical doses. In some of these cases, dysphagia has lasted several months and required placement of a gastric feeding tube. When exposed to very high doses, patients with neurologic disorders, e.g. paediatric cerebral palsy or adult

spasticity, may also be at increased risk of clinically significant systemic effects.

Swallowing and breathing difficulties can be life threatening and death has been reported. Caution should be exercised when treating patients who have neurological debility or dysphagia or have a recent history of aspiration pneumonia or lung disease.

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

Sedentary patients should be cautioned to resume activity slowly and carefully following administration of BOTOX®.

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

Pneumothorax associated with injection procedure has been reported following the administration of BOTOX® near the thorax. Caution is warranted when injecting in proximity to the lung, particularly the apices.

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

Epinephrine (adrenaline) and other precautions as necessary should be available should an anaphylactic reaction occur. In the treatment of some indications with BOTOX®, there have been reports of death, sometimes associated with dysphagia, pneumonia and/or other

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

BOTOX® should be given only by medical practitioners with appropriate qualifications, and expertise in the treatment and the use of the required equipment.

Serious and/or immediate hypersensitivity reactions, such as anaphylaxis, and serum sickness have been reported, as well as other manifestations of hypersensitivity including urticaria, soft tissue oedema, and dyspnoea. If such a reaction occurs, further injection should be discontinued and appropriate medical therapy immediately instituted. Anaphylaxis and death have been reported after being injected with BOTOX® diluted with 5 ml of 1 % lidocaine (lignocaine).

Localised pain, inflammation, paraesthesia, hypoaesthesia, tenderness, swelling/oedema, erythema, localised infection, bleeding and/or bruising have been associated with the injection of BOTOX®. Needle-related pain and/or anxiety have resulted in vasovagal responses, including transient symptomatic hypotension and syncope.

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

There have been reports of adverse events involving the cardiovascular system, including dysrhythmia and myocardial infarction, some with fatal outcomes.

New onset or recurrent seizures have been reported. The majority were in patients who are predisposed to experiencing these events. 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. The critical factors for neutralising antibody formation have not been characterised. The results from some studies suggest that BOTOX® injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation (see section 4.2).

Clinical fluctuations during the repeated use of BOTOX® (as with 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.

BOTOX® contains human albumin. In spite of effective donor screening and product manufacturing processes, this still carries a risk for transmission of viral diseases. There is also a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD). No cases of transmission of viral diseases or CJD have ever been identified for albumin.

The safe and effective use of BOTOX® depends upon proper storage of the product, selection of the correct dose and proper reconstitution and administration techniques. Medical practitioners administering BOTOX® must understand the relevant neuromuscular anatomy and any alterations to the anatomy due to prior surgical procedures and standard electromyographic techniques.

Traceability

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

Neurologic disorders

Focal spasticity associated with paediatric cerebral palsy patients and spasticity of the hand and wrist in adult post-stroke patients

BOTOX® is a treatment of focal spasticity that has only been studied in association with usual

standard of care regimens, and is not intended as a replacement for these treatment modalities. BOTOX® is not effective in improving range of motion at a joint affected by a fixed contracture.

There have been reports of death (sometimes associated with aspiration pneumonia) and of possible distant spread of toxin in children with comorbidities, predominantly cerebral palsy, after treatment with BOTOX® (see section 4.2, Paediatric Population).

Strabismus

BOTOX® is ineffective in chronic paralytic strabismus except to reduce antagonist contracture in conjunction with surgical repair. The efficacy of BOTOX® in deviations over 50 prism diopters, in restrictive strabismus, in Duane's syndrome with lateral rectus weakness, and in secondary strabismus caused by prior surgical over-recession of the antagonist has not been demonstrated.

During the administration of BOTOX® for the treatment of strabismus, retrobulbar haemorrhages sufficient to compromise retinal circulation have occurred from needle penetration into the orbit. It is recommended that appropriate instruments to decompress the orbit be accessible. Ocular (globe) penetrations by needles have also occurred. An ophthalmoscope to diagnose this condition should be available. Inducing paralysis in one or more extraocular muscles may produce spatial disorientation, double vision, or past-pointing. Covering the affected eye may alleviate these symptoms.

Blepharospasm and hemifacial spasm

Reduced blinking from BOTOX® injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defect and corneal ulceration, especially in patients with VII nerve disorders. Corneal perforation in an aphakic eye requiring corneal grafting has occurred because of this effect. Careful testing of corneal sensation in eyes previously operated upon, avoidance of injection into the lower lid area to avoid ectropion, and vigorous treatment of any epithelial defect

should be employed. This may require protective eye drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.

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

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

Patients should be warned about possible disturbance of vision following injection of BOTOX®.

Cervical dystonia

Dysphagia is a commonly reported adverse event following treatment of cervical dystonia patients with BOTOX® (see section 4.8). Patients with cervical dystonia should be informed of the possibility of experiencing dysphagia which may be mild, but could be severe. Dysphagia may persist for two to three weeks after injection, but has been reported to last up to five months post-injection. Consequent to the dysphagia there is the potential for aspiration, dyspnoea and occasionally the need for tube feeding. 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 require bilateral injections into the sternocleidomastoid muscle, have been reported to be at greater risk of dysphagia. Dysphagia is attributable to the localised diffusion of the toxin to the oesophageal musculature.

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

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

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

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) has not been studied.

Bladder disorders

Due to the risk of urinary retention, only patients who are willing and able to initiate catheterisation post-treatment, if required, should be considered for treatment. 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 medical practitioner if they experience difficulties in voiding as catheterisation may be required.

Overactive bladder

Only a limited number of males were studied in the two phase 3 clinical studies and the results were not statistically significant for patients administered with BOTOX® compared to placebo. Men with signs and symptoms of urinary obstruction should not be treated with BOTOX®.

Urinary incontinence due to neurogenic detrusor overactivity

In patients with neurogenic detrusor overactivity, autonomic dysreflexia associated with cystoscopy could occur, which may require prompt medical therapy.

Skin and skin appendage disorders

Primary hyperhidrosis of the axillae

Exclude potential causes of secondary hyperhidrosis (e.g. hyperthyroidism or phaeochromocytoma). This will avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of underlying disease.

Glabellar lines, crow's feet lines and forehead lines

Reduced blinking from BOTOX® injection of the orbicularis oculi muscle can lead to corneal exposure, persistent epithelial defects and corneal ulceration, especially in patients with VII nerve disorders. Caution should be used when BOTOX® treatment is used in patients who have an inflammatory skin problem at the injection site, marked facial asymmetry, ptosis, excessive dermatochalasis (excess skin in the upper and lower eyelids), deep dermal scarring, thick sebaceous skin, or the inability to substantially lessen glabellar lines by physically spreading them apart. Injection intervals of BOTOX® should be no more frequent than every three months and should be performed using the lowest effective dose.

Care should be taken to ensure that BOTOX® is not injected into a blood vessel when it is injected in the glabellar lines, in the crow's feet lines or in the forehead lines (see section 4.2).

There is a risk of eyelid ptosis following treatment (see section 4.8). Refer to section 4.2 for administration instructions on how to minimise the risk.

4.5 Interaction with other medicines and other forms of interaction

The effect of botulinum toxin type A may be potentiated by aminoglycoside antibiotics or any

other medicinal products that interfere with neuromuscular transmission (e.g. neuromuscular blocking agents). Caution should be exercised when BOTOX® is used in patients receiving aminoglycosides (e.g. streptomycin, tobramycin, neomycin, gentamycin, netilmycin, kanamycin, amikacin), tetracyclines, lincomycin, or any other medicine that interferes with neuromuscular transmission (e.g. neuromuscular blocking agents, both depolarising and non-depolarising, lincosamides, polymyxins, quinidine, magnesium sulfate, and anticholinesterases). (See section 4.8.)

No tests have been carried out to establish the possibility of clinical interaction with other medicinal product.

The effect of administering different botulinum neurotoxin serotypes at the same time or within several months of each other is unknown. Excessive weakness may be exacerbated by administration of another dose of BOTOX® prior to the resolution of the effects of a previously administered BOTOX®.

4.6 Fertility, pregnancy and lactation

Pregnancy

BOTOX® should not be used during pregnancy.

Safety of BOTOX® when administered during pregnancy has not been established.

Breastfeeding

BOTOX® should not be used during lactation.

Safety of BOTOX® when administered during lactation has not been established. No information is available on the passage of the toxin into breast milk.

Fertility

There is no fertility data available.

4.7 Effects on ability to drive and use machines

BOTOX® may cause asthenia, muscle weakness, dizziness and visual disturbance, which could make driving or using machines dangerous.

4.8 Undesirable effects

General

Patients can be expected to experience an adverse reaction after treatment with BOTOX® at the rates of 35 % for blepharospasm, 28 % with cervical dystonia, 17 % for paediatric cerebral palsy, 11 % for hyperhidrosis of the axillae, 16 % with focal spasticity of the upper limb associated with stroke In clinical trials for overactive bladder the incidence was 26 % with the first treatment and 22 % with the second treatment. In clinical trials for urinary incontinence due to neurogenic detrusor overactivity, the incidence of adverse reactions was 32 % with the first treatment and declined to 18 % with a second treatment. In clinical trials for chronic migraine, the incidence was 26 % with the first treatment and declined to 11 % with the second treatment.

In controlled clinical trials for glabellar lines, adverse events considered by the investigators to be related to BOTOX® were reported in 23,5 % (placebo: 19,2 %) of patients. In treatment cycle 1 of the pivotal controlled clinical trials for crow's feet lines seen at maximum smile, such events were reported in 7,6 % (24 Units for crow's feet lines alone) and 6,2 % (44 Units : 24 Units for crow's feet lines administered simultaneously with 20 Units for glabellar lines) of patients compared to 4,5 % for placebo. Adverse reactions may be related to the treatment, injection technique or both.

In treatment cycle 1 of clinical trials for forehead lines seen at maximum eyebrow elevation, adverse events considered by the investigators to be related to BOTOX were reported in 20,6 % of patients treated with 40 Units (20 Units to the frontalis with 20 Units to the glabellar complex), and 14,3 % of patients treated with 64 Units (20 Units to the frontalis with 20 Units to

the glabellar complex and 24 Units to the lateral canthal lines areas), compared to 8,9 % of patients that received placebo.

Adverse reactions usually occur within the first few days following injection and may have duration of several months or, in some cases, longer.

Local muscle weakness represents the expected pharmacological action of botulinum toxin in muscle tissue. However, weakness of adjacent and/or distant muscles has also occurred due to spread of toxin.

Localised pain, inflammation, paraesthesia, hypoaesthesia, tenderness, swelling/oedema, erythema, localised infection, bleeding and/or bruising may be associated with the injection. Fever and flu-like symptoms have also been reported after injections with botulinum toxin. Needle-related pain and/or anxiety have resulted in vasovagal responses, including transient symptomatic hypotension and syncope.

Adverse reactions – frequency by indication

For each indication the frequency of adverse reactions arising from clinical experience is given as follows: Very common (≥ 1/10); Common (≥ 1/100, <1/10); Uncommon (≥ 1/1 000, <1/100); Rare (≥ 1/10 000, <1/1 000); Very rare (<1/10 000).

Below are lists of side effects which vary depending on the part of the body where BOTOX® is injected.

Neurologic disorders

Focal spasticity associated with paediatric cerebral palsy

System Organ Class	Preferred Term	Frequency

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

Focal upper limb spasticity associated with stroke

System Organ Class	**Preferred Term**	**Frequency**
Psychiatric disorders	Depression, insomnia	Uncommon
Nervous system disorders	Hypertonia	Common
	Hypoaesthesia, headache, paraesthesia, incoordination, amnesia	Uncommon
Ear and labyrinth disorders	Vertigo	Uncommon
Vascular disorders	Orthostatic hypotension	Uncommon
Gastrointestinal disorders	Nausea, oral paraesthesia	Uncommon
Skin and subcutaneous tissue disorders	Ecchymosis, purpura	Common
	Dermatitis, pruritus, rash	Uncommon
Musculoskeletal and connective	Pain in extremity, muscle weakness	Common

tissue disorders	Arthralgia, bursitis	Uncommon
General disorders and administration site conditions	Injection site pain, pyrexia, influenza-like illness, injection site haemorrhage, injection site irritation	Common
	Asthenia, pain, injection site hypersensitivity, malaise, peripheral oedema	Uncommon

Strabismus

System Organ Class	**Preferred Term**	**Frequency**
Eye disorders	Eyelid ptosis, eye movement disorder	Very common
	Ocular retrobulbar haemorrhages, eye penetration, Holmes-Adie pupil	Uncommon
	Vitreous haemorrhage	Rare

Blepharospasm and hemifacial spasm

System Organ Class	**Preferred Term**	**Frequency**
Nervous system disorders	Dizziness, facial paresis, facial palsy	Uncommon
Eye disorders	Eyelid ptosis	Very common
	Punctuate keratitis, lagophthalmos, dry eye, photophobia, eye irritation, increased lacrimation	Common
	Keratitis, ectropion, diplopia, entropion, visual disturbance, blurred vision	Uncommon
	Eyelid oedema	Rare
	Ulcerative keratitis, corneal epithelium	Very rare

	defect, corneal perforation	
Skin and subcutaneous tissue disorder	Ecchymosis	Common
	Rash/dermatitis	Uncommon
General disorders and administration site conditions	Irritation, face oedema	Common
	Fatigue	Uncommon

Cervical dystonia

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

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	Pruritus, 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
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

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. During the complete treatment cycle, urinary tract infections and urinary retention were reported in 25,5 % and 5,8 %, respectively, for patients treated with BOTOX®.

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 older people in both the placebo and BOTOX® groups compared to the younger patients.

In patients 65 years and older, urinary tract infection was reported in 33,1 % and 15,2 % in patients treated with BOTOX® and placebo respectively. In patients less than 65 years of age, urinary tract infection was reported in 21,2 % and 6,6 % in patients treated with BOTOX® and placebo respectively. In patients 65 years and older, urinary retention was reported in 8,4 % and 0,4 % in patients treated with BOTOX® and placebo respectively. In patients less than 65 years of age, urinary retention was reported in 6,1 % and 0,6 % in patients treated with BOTOX® and placebo respectively.

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

Urinary incontinence due to neurogenic detrusor overactivity

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

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

* Procedure-related adverse reactions

In clinical trials urinary tract infection was reported in 49,2 % of patients treated with 200 Units of 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 of 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 was observed in the overall safety profile with repeat dosing.

No difference on the multiple sclerosis (MS) exacerbation annualised rate (i.e. number of MS exacerbation events per patient-year) was observed (BOTOX® = 0,23; placebo = 0,20) in the

MS patients enrolled in the pivotal studies.

Skin and skin appendage disorders

Primary hyperhidrosis of the axillae

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

Note: Increase in non-axillary sweating was reported in 4,5 % of patients within one month after injection and showed no pattern with respect to anatomical sites affected. Resolution was seen in approximately 30 % of the patients within four months.

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.

Glabellar lines

The following adverse drug reactions were reported in the double-blind, placebo-controlled clinical studies following injection of BOTOX 20 Units for glabellar lines alone:

System Organ Class	**Preferred Term**	**Frequency**
Infections and infestations	Infection	Uncommon
Psychiatric disorders	Anxiety	Uncommon
Nervous system disorders	Headache, paraesthesia	Common
	Dizziness	Uncommon
Eye disorders	Eyelid ptosis	Common
	Blepharitis, eye pain, visual disturbance (includes blurred vision)	Uncommon
Gastrointestinal disorders	Nausea	Common
	Oral dryness	Uncommon
Skin and subcutaneous tissue disorders	Erythema, skin tightness	Common
	Oedema (face, eyelid, periorbital), photosensitivity reaction, pruritus, dry skin	Uncommon
Musculoskeletal and connective tissue disorders	Localised muscle weakness	Common
	Muscle twitching	Uncommon
General disorders and administration site conditions	Facial pain, injection site oedema, ecchymosis, injection site pain, injection site irritation	Common
	Flu syndrome, asthenia, fever	Uncommon

Crow's feet lines (with or without glabellar lines)

The following adverse reactions were reported in the double-blind, placebo-controlled clinical studies following injection of BOTOX® for crow's feet lines with or without glabellar lines.

System Organ Class	Preferred Term	Frequency
Eye disorders	Eyelid oedema	Common
General disorders and administration site conditions	Injection site haemorrhage*	Common
	Injection site haematoma*	Common
	Injection site pain*	Uncommon
	Injection site paraesthesia	Uncommon

* Procedure-related adverse reactions

Forehead lines and glabellar lines with or without crow's feet lines

The following adverse drug reactions were reported in double-blind, placebo-controlled clinical studies following injection of BOTOX for simultaneous treatment of forehead lines and glabellar lines with or without crow's feet lines:

System Organ Class	Preferred Term	Frequency
Nervous System Disorders	Headache	Common
Eye Disorders	Eyelid Ptosis[1]	Common
Skin and subcutaneous tissue disorders	Skin tightness	Common
	Brow Ptosis[2]	Uncommon
General disorders and administration site conditions	Injection site bruising*	Common
	Injection site haematoma*	Common
	Injection site pain*	Uncommon

[1]*The median time to onset of eyelid ptosis was 9 days following treatment*

[2]*The median time to onset of brow ptosis was 5 days following treatment*

*****procedure-related adverse reactions*

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

Post-marketing experience

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

Serious and/or immediate hypersensitivity reactions such as anaphylaxis and serum sickness have been reported, as well as other manifestations of hypersensitivity including urticaria, soft tissue oedema, and dyspnoea. One fatal case of anaphylaxis has been reported in which the patient died after being injected with BOTOX® diluted with 5 ml of 1 % lidocaine (lignocaine). The causal role of BOTOX®, lidocaine, or both cannot be reliably determined.

There have also been reports of adverse events involving the cardiovascular system, including dysrythmia and myocardial infarction, some with fatal outcomes following BOTOX® treatment. Some of these patients had risk factors including cardiovascular disease.

A case of peripheral neuropathy has been reported in a large adult male after receiving four sets of BOTOX® injections, totalling 1 800 Units (for neck and back spasm, and severe pain) over an 11 week period.

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

Eyelid oedema has been reported following periocular BOTOX® injection.

The following list includes adverse reactions or other medically relevant adverse events that have been reported since BOTOX® has been marketed, regardless of indication:

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

You can also report side effects to AbbVie (Pty) Ltd by sending an e-mail to MEAPV@abbvie.com

4.9 Overdose

Signs and symptoms of overdose are likely not to be apparent immediately post-injection. Overdose may produce local, or distant, generalised and profound neuromuscular paralysis.

Should accidental injection or oral ingestion occur or overdose be suspected, the patient should be medically monitored for up to several weeks for progressive signs or symptoms of systemic muscular weakness which could be local, or distant from the site of injection which may include ptosis, diplopia, dysphagia, dysarthria, 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 may be necessary 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

Pharmacological classification: A. 30.4 Biologicals. Other.

BOTOX® (botulinum toxin type A) blocks neuromuscular conduction by inhibiting the release of acetylcholine. When injected intramuscularly at therapeutic doses, BOTOX® produces a localised chemical denervation effect resulting in temporary muscle paralysis.

Recovery after intramuscular injection takes place usually within 12 weeks of injection. After intradermal injection, where the target is the eccrine sweat glands the effect lasted for about 4 to 7 months after the first injection in patients treated with 50 Units per axilla.

When injected into extraocular eye muscle, the medicine induces a period of paralysis lasting from 2 to 20 weeks.

5.2 Pharmacokinetic properties

The molecular weight is about 150 000 Daltons, and the molecule is constructed of a heavy chain protein, about 100 000 Daltons, and a lighter chain protein, about 50 000 Daltons, held together by one or more disulphide bonds.

Specific receptors on the terminal non-myelinated portion of the motor nerves are sites of attachment of the heavy chain. This is then internalised, and it appears that the light and heavy chain separate, the light chain acting to interfere with calcium metabolism essential to the impulse triggered release of transmitter, acetylcholine. While some minimal transport of the botulinum molecule within the nerve terminal has been shown, widespread transport of it up through the cell body and transneuronally does not occur, as with tetanus.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Human albumin and sodium chloride.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store the vacuum-dried product in a refrigerator between 2 °C to 8 °C, or in a freezer at or below -5 °C. Administer BOTOX® within twenty-four (24) hours after the vial is removed from the freezer and reconstituted. During these twenty-four (24) hours, reconstituted BOTOX® should be stored in a refrigerator (2 °C to 8 °C). Reconstituted BOTOX® should be clear, colourless and free of particulate matter.

Since the product does not contain a preservative, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at +2 °C to +8 °C. Do not freeze the reconstituted vial.

6.5 Nature and contents of container

BOTOX® (botulinum toxin type A) is available in three vial sizes: 50 Units, 100 Units or 200 Units. The clear glass vials are sealed with rubber closures and aluminium seals.

In order to verify receipt of actual BOTOX® product from Allergan, look for a tamper-evident seal that contains a translucent silver Allergan logo on the top and bottom flaps of the BOTOX® cartons, and a holographic film on the vial label. In order to see this film, examine the vial under

a desk lamp or fluorescent light source. Rotating the vial back and forth between your fingers, look for horizontal lines of rainbow colour on the label and confirm that the name “Allergan” appears within the rainbow lines.

Do not use the product and contact your local Allergan office for additional information if:

- The horizontal lines of rainbow colour or the word “Allergan” are not present on the vial label
- The tamper-evident seal is not intact and present on both ends of the carton
- The translucent silver Allergan logo on the seal is not clearly visible or has a black circle with a diagonal line through it (i.e., prohibition sign)

Additionally, Allergan has created detachable stickers on the BOTOX® vial label, which include the lot number and expiry date of the product you have received. These stickers can be peeled off and placed in your patient’s clinical file for traceability purposes. Note that once you remove the sticker off the BOTOX® vial label, the word “USED” will show, which is to provide you with further assurance that you are using an authentic BOTOX® product manufactured by Allergan.

6.6 Special precautions for disposal and other handling

All vials, including expired vials, or equipment used with the medicine should be disposed of carefully as is done with all medical waste. In cases when deactivation of the toxin is desired (e.g., spills), the use of dilute hypochlorite solution (0,5 % or 1 %) for five minutes is recommended prior to disposal as medical waste.

7. HOLDER OF CERTIFICATE OF REGISTRATION

AbbVie (Pty) Ltd

Building 7, Waterfall Corporate Campus

74 Waterfall Drive

Waterfall City

Midrand

1685

South Africa

8. REGISTRATION NUMBER

27/30.4/0164

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

5 February 1993

10. DATE OF REVISION OF TEXT

21 April 2023

CCDS v20.0, EU SmPC 25/08/2021