BOTOX® Purified Neurotoxin Complex

Botulinum Toxin Type A

PRESENTATION

BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex is a sterile, vacuum-dried purified Botulinum Toxin Type A, produced from a culture of the Hall strain of Clostridium botulinum grown in a medium containing casein hydrolysate, glucose and yeast extract, and intended for intramuscular and intradermal use. It is purified from the culture solution by a series of acid precipitations to a crystalline complex consisting of the haemagglutinin protein and the active high molecular weight toxin protein. The complex is dissolved in a solution containing sodium chloride and human albumin, and sterile filtered (0.2 microns) prior to filling and vacuum-drying. BOTOX® is to be reconstituted with sterile non-preserved saline prior to intramuscular/intradermal injection.

One Unit of BOTOX® corresponds to the calculated median intraperitoneal lethal dose (LD50) in mice. The method utilized for performing the assay is specific to Allergan's product, BOTOX®. Due to specific details of this assay such as the vehicle, dilution scheme and laboratory protocols for the various mouse LD50 assays, Units of biological activity of BOTOX® cannot be compared to nor converted into Units of any other botulinum toxin or any toxin assessed with any other specific assay method. Therefore, differences in species sensitivities to different botulinum neurotoxin serotypes precludes extrapolation of animal-dose activity relationships to human dose estimates. The specific activity of BOTOX® is approximately 20 Units/nanogram of neurotoxin protein complex.

Each vial of BOTOX® contains either 100 units (U) of Botulinum Toxin Type A, as a haemagglutinin complex, 0.5 mg of human albumin and 0.9 mg of sodium chloride or 50 U of Botulinum Toxin, Type A, 0.25 mg of human albumin and 0.45 mg of sodium chloride in a sterile, vacuum-dried preparation without a preservative.

USES

Actions

Therapeutic Class: Neuromuscular Blocking Agent

BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex blocks neuromuscular conduction by binding to receptor sites on motor nerve terminals, entering the nerve terminals and inhibiting the release of acetylcholine. When injected intramuscularly at therapeutic doses, BOTOX® produces a localized chemical denervation of the muscle, resulting in localized muscle paralysis. When the muscle is chemically denervated, it atrophies and may develop extrajunctional acetylcholine receptors. There is evidence that the nerve can sprout and reinnervate the muscle, with the weakness thus being reversible.

Blepharospasm

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

Strabismus

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

Cervical Dystonia (spasmodic torticollis)

When injected into neck muscles BOTOX® acts to provide relief from both objective signs and subjective symptoms of cervical dystonia (spasmodic torticollis). These improvements may include reduced pain/discomfort, reduced head rotation, reduced shoulder elevation, decreased size and strength of hypertrophic muscles and functional disability improvement. Based on the results of early publications in naïve patients, 40 to 58% of patients with cervical dystonia respond with a significant improvement in their symptoms after initial treatment with BOTOX®. Among patients who have previously benefited from BOTOX® injection for cervical dystonia, approximately 91% can expect improvement for any given treatment period based on patient withdrawal data in a recent trial.

Spasticity (due to juvenile cerebral palsy)

BOTOX® injections into the gastrocnemius produce an improvement in ankle position (reduction in equinus) and subsequently an improvement in gait pattern due to increased heel-to-floor contact. Neurophysiological studies of the M-response and H-reflex amplitudes supported the view that BOTOX® produces a partial but reversible denervation of the gastrocnemius muscle. No significant changes in electromyography were seen in placebo-treated patients.

Primary Hyperhidrosis of the axillae

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

In a double-blind placebo controlled clinical trial of 320 patients, the responder rate was 95% at week 1 and 93.8% at the primary endpoint of week 4, as assessed by the objective gravimetric evaluations.

The objective of treatment is to reduce sweating to a physiologically normal level which patients find tolerable. Anhydrosis is not the target.

Glabellar Lines

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

Crow's Feet

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

Forehead Lines

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

Focal Spasticity Associated with Stroke

The efficacy of BOTOX® used for the treatment of upper limb spasticity associated with stroke was evaluated in double-blind and open label studies in 339 unique patients. BOTOX® injected into upper limb muscles reduces the objective signs and subjective symptoms of spasticity. Improvements include reduction of muscle tone, increase in range of motion, and in some patients reduction of spasticity-related disability.

PHARMACOKINETICS

Pharmacokinetic studies in humans are not practicable with BOTOX®.

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

In vitro studies of isolated rat synaptosome fragments indicated that botulinum toxin has a high affinity for cholinergic terminals where it binds to the pre-synaptic membrane. Despite this high affinity to the nerve terminal, there is indirect evidence that radiolabelled toxin is transported in a retrograde fashion up the spinal cord. When high doses of radiolabelled toxin were injected into the gastrocnemius of cats, histological evidence of radioactivity was later detected in the spinal cord, ipsilateral to the injection site. It is not known whether the radioactivity was still bound to the botulinum toxin. These data may suggest that there is pre-synaptic uptake and retrograde axonal transport of the toxin from the injection site.

INDICATIONS

- BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex is indicated for the treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above.
- BOTOX® is indicated to reduce the subjective symptoms and objective signs of spasmodic torticollis (cervical dystonia) in adults.
- BOTOX® is also indicated for the treatment of dynamic equinus foot deformity due to spasticity in juvenile cerebral palsy patients two years of age or older.
- BOTOX® is indicated for the treatment of primary hyperhidrosis of the axilla.
- BOTOX® is indicated for temporary improvement in the appearance of upper facial rhytides (glabellar lines, crow's feet and forehead lines) in adults.
- BOTOX® is indicated in the management of focal spasticity, including the treatment of upper limb spasticity associated with stroke in adults.

DOSAGE AND ADMINISTRATION

Route of Administration

Intramuscular injection. Intradermal for hyperhidrosis. May be subcutaneous for blepharospasm. Reconstituted BOTOX® is injected with the purpose of reaching the motor endplate region of the muscle to be treated.

General

The use of one vial for more than one patient is not recommended because the product and diluent do not contain a preservative. Once opened and reconstituted, store in the refrigerator and use within 3 days. Discard any remaining solution. Do not freeze reconstituted BOTOX®.

In general, dosing of BOTOX® should be with the minimal effective dose. The dosing interval should not be more frequent than every two months.

Cervical Dystonia (spasmodic torticollis)

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

Multiple injection sites allow BOTOX® to have more uniform contact with the innervation areas of the dystonic muscle and are especially useful in larger muscles. The optimal number of injection sites is dependent upon the size of the muscle to be chemically denervated. The treatment of cervical dystonia typically may include, but is not limited to, injection of BOTOX® into the sternocleidomastoid, levator scapulae, scalene, splenius capitis, and/or the trapezius muscle(s).

A 25, 27 or 30 gauge needle may be used for superficial muscles, and a 22 gauge needle may be used for deeper musculature. For cervical dystonia, localization of the involved muscles with electromyographic guidance may be useful.

The table below is intended to give dosing guidelines for injection of BOTOX® in the treatment of cervical dystonia.

Dosage Guide

Classification of Cervical Dystonia	Muscle Groupings	Total Dosage; Number of Sites
Type I Head rotated toward side of shoulder elevation	Sternocleidomastoid Levator scapulae Scalene Splenius capitis Trapezius	50-100 U; at least 2 sites 50 U; 1-2 sites 25-50 U; 1-2 sites 25-75 U; 1-3 sites 25-100 U; 1-8 sites
Type II Head rotation only	Sternocleidomastoid	25-100 U; at least 2 sites if >25 U given
Type III Head tilted toward side of shoulder elevation	Sternocleidomastoid Levator scapulae Scalene Trapezius	25-100 U; at posterior border; at least 2 sites if >25 U given 25-100 U; at least 2 sites 25-75 U; at least 2 sites 25-100 U; 1-8 sites
Type IV Bilateral posterior cervical muscle spasm with elevation of the face	Splenius capitis and cervicis	50-200 U; 2-8 sites, treat bilaterally

This information is provided as guidance for the initial injection. The extent of muscle hypertrophy and the muscle groups involved in the dystonic posture may change with time necessitating alterations in the dose of toxin and muscles to be injected. The exact dosage and sites injected must be individualised for each patient.

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

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

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

** Limiting the dose injected into the sternocleidomastoid muscle to less than 100 U may decrease the occurrence of dysphagia. (See Precautions.)

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

In general, a total dose of 360 U every two months should not be exceeded for the treatment of cervical dystonia. The time-to-retreatment will vary between patients, however data from controlled clinical studies indicates that symptoms may start to re-emerge at approximately 8-10 weeks post-injection. Clinical improvement generally occurs within the first two weeks after injection. The maximum clinical benefit generally occurs approximately six weeks post-injection. The duration of therapeutic effect reported in the clinical trials showed substantial variation (from 2 to 32 weeks), with a typical duration of approximately 12 to 16 weeks, depending on the patient's individual disease and response.

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

Strabismus

BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex is intended for injection into extraocular muscles utilizing the electrical activity recorded from the tip of the injection needle as a guide to placement within the target muscle. Injection without surgical exposure or electromyographic guidance should not be attempted. Physicians should be familiar with electromyographic technique.

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

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

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

Strabismus dosage: The initial doses of the reconstituted BOTOX® (see Dilution Table below) 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 2-6 weeks and gradually resolves over a similar time period.

Overcorrections lasting over 6 months have been rare. About one half of patients will require subsequent doses because of inadequate paralytic response of the muscle to the initial dose because of mechanical factors such as large deviations or restrictions, or because of lack of binocular motor fusion to stabilize the alignment.

1. Initial doses in units (abbreviated as U).
   Use the lower listed doses for treatment of small deviations. Use the larger doses only for large deviations.
   - A. For vertical muscles and for horizontal Strabismus of less than 20 prism diopters: 1.25 U to 2.5 U in any one muscle.
   - B. For horizontal strabismus of 20 prism diopters to 50 prism diopters: 2.5 U to 5.0 U in any one muscle.
   - C. For persistent VII nerve palsy of one month or longer duration: 1.25 U to 2.5 U in the medial rectus muscle.
2. Subsequent doses for residual or recurrent strabismus.
   - A. It is recommended that patients be re-examined 7-14 days after each injection to assess the effect of that dose.
   - B. Patients experiencing adequate paralysis of the target muscle that require subsequent injections should receive a dose comparable to the initial dose.
   - C. Subsequent doses for patient experiencing incomplete paralysis of the target muscle maybe increased up to twice the size of the previously administered dose.
   - D. Subsequent injections should not be administered until the effects of the previous dose have dissipated as evidenced by substantial function in the injected and adjacent muscles.
   - E. The maximum recommended dose as a single injection for any one muscle is 25 U.

Blepharospasm

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

For blepharospasm, reconstituted BOTOX® (see Dilution Table) is injected using a sterile, 27-30 gauge needle with or without electromyographic guidance. 1.25 U to 2.5 U (0.05 mL to 0.1 mL volume at each site) injected into the medial and lateral pre-tarsal orbicularis oculi of the upper lid and into the lateral pre-tarsal orbicularis oculi of the lower lid is the initial recommended dose. Pretarsal injections are often appropriate and may vary based on the patient's presentation. In the upper lid, maximising the distance of the injection from the levator palpebrae superioris may reduce the complication of ptosis. Avoiding medial lower lid injections, and thereby reducing diffusion into the inferior oblique, may reduce the complication of diplopia.

In general, the initial effect of the injections is seen within three days and reaches a peak at one to two weeks post-treatment. Each treatment lasts approximately three months, following which the procedure can be repeated indefinitely.

At repeat treatment sessions, the dose may be increased up to two-fold if the response from the initial treatment is considered insufficient - usually defined as an effect that does not last longer than two months. However there appears to be little benefit obtainable from injecting more than 5.0 Units per site.

Some tolerance may be found when BOTOX® is used in treating blepharospasm if treatments are given any more frequently than every three months but it is rare to have the effect be permanent.

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

VII Nerve Disorders

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

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

Spasticity (due to juvenile cerebral palsy)

For the treatment of equinus foot deformity due to spasticity in juvenile cerebral palsy, diluted BOTOX® is injected using a sterile 27 gauge needle. The recommended total dose is 4 U/kg administered by injecting 2 cc of reconstituted BOTOX® into each of two sites in the medial and lateral heads of the gastrocnemius muscle of the affected lower limb(s).

Following initial injection to the gastrocnemius muscle, further involvement of the anterior or posterior tibialis may need to be considered for additional improvement in the foot position at heel strike and during standing.

Clinical 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 two months. The average duration of the therapeutic effect reported in an open-label clinical trial of 207 patients was 3.1 to 3.6 months. In this study, although the dose was 4 U/kg, the number of Units injected did not exceed 200 U in a 30 day period.

Primary Hyperhidrosis of the axillae

The hyperhidrotic area to be injected may be defined using standard staining techniques, e.g. Minor's iodine-starch test. BOTOX® is reconstituted with 0.9% non-preserved sterile saline (100U/4.0 mL). Using a 30 gauge needle, 50 U of BOTOX® (2.0 mL) is injected intradermally, to each axilla evenly distributed in multiple sites approximately 1-2 cm apart.

At week 1 BOTOX® treated patients demonstrated 95% treatment responder rate based on gravimetric assessment. At 16 weeks 82% of BOTOX® treated patients were responding to treatment. Approximately 40% of patients received only 1 treatment with BOTOX® and had duration of effect for over 1 year (median time 68 weeks). When patients received at least 2 consecutive treatments with BOTOX® the mean time to re-treatment following their first treatment was 33 weeks (range 15 to 51 weeks). Repeat injections for axillary hyperhidrosis should be administered when effects from previous injections subside but usually not more frequently than every two months.

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

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

Glabellar Lines

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

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

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

Improvement of severity of glabellar lines generally occurs one or two days after injection, increasing in intensity during the first week after treatment. The effect was demonstrated for up to 4 months.

Crow's Feet

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

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

Forehead Lines

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

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

Focal Spasticity Associated with Stroke

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. In clinical trials, the doses did not exceed 360 U divided among selected muscles (typically in the flexor muscles of the elbow, wrist and fingers) at any treatment session. Clinical improvement in muscle tone generally occurs within two weeks following treatment with the peak effect seen four to six weeks following treatment. In clinical studies, patients were reinjected at 12 to 16 week intervals. The degree of muscle spasticity at the time of reinjection may necessitate alterations in the dose of BOTOX® and muscles to be injected.

The table below is intended to give dosing guidelines for injection of BOTOX® in the treatment of upper limb spasticity associated with stroke.

Muscle	Total Dosage; Number of Sites
Biceps brachii	100 - 200 U; up to 4 sites
Flexor digitorum profundus	15 - 50 U; 1-2 sites
Flexor digitorum sublimis	15 - 50 U; 1-2 sites
Flexor carpi radialis	15 - 60 U; 1-2 sites
Flexor carpi ulnaris	10 - 50 U; 1-2 sites
Adductor Pollicis	20 U; 1-2 sites
Flexor Pollicis Longus	20 U; 1-2 sites

A 25, 27 or 30 gauge needle may be used for superficial muscles, and a 22-gauge needle may be used for deeper musculature. For focal spasticity, localization of the involved muscles with electromyographic guidance or nerve stimulation techniques may be useful.

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

Dilution Technique

To reconstitute vacuum-dried BOTOX® injection, use sterile normal saline without a preservative; 0.9% Sodium Chloride injection is the recommended diluent. Draw up the proper amount of diluent in the appropriate size syringe. Since BOTOX® is denatured by bubbling or similar violent agitation, inject the diluent into the vial gently. Discard the vial if a vacuum does not pull the diluent into the vial. Record the date and time of reconstitution on the space on the label. BOTOX® should be administered within 3 days after reconstitution.

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

Dilution Table

Diluent Added to 100 Units Vial (0.9% Sodium Chloride Only)	Resulting Dose Units per 0.1mL	Diluent Added to 50 Units Vial (0.9% Sodium Chloride Only)	Resulting Dose Units per 0.1mL
1.0 mL 2.0 mL 4.0 mL 8.0 mL	10.0 Units 5.0 Units 2.5 Units 1.25 Units	1.0 mL 2.0 mL 4.0 mL	5.0 Units 2.5 Units 1.25 Units

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

Lack of Response

There are several potential explanations for a diminished or absent response to an individual treatment with BOTOX®. These may include neutralising antibodies to botulinum toxin as well as inadequate dose selection, selection of inappropriate muscles for injection, muscles inaccessible to injection, underlying structural abnormalities such as muscle contractures or bone disorders, change in pattern of muscle involvement, patient perception of benefit compared with initial results, and inappropriate storage or reconstitution.

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

The critical factors for neutralising antibody production are the frequency and dose of injection. Some

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tolerance may be observed when BOTOX® is used in treating blepharospasm if treatments are given more frequently than every three months. To reduce the potential for neutralising antibodies, it is recommended that injection intervals should be no more frequent than every two months. The adult dose should not exceed 360 U in any two month period. The total dose of BOTOX® in any two month period should not exceed 4 U/kg when used in children for equinus foot deformity.

When patients do not respond to BOTOX® injections a suggested course of action is: 1) wait the usual treatment interval; 2) consider reasons for lack of response listed above; 3) test the patient's serum for neutralising antibody presence. More than one ineffective treatment course should occur before classification of a patient as a non-responder, because there are patients who continue to respond to therapy despite the presence of neutralising antibodies.

CHILDREN

Safety and effectiveness in children below the age of 12 has not been established for the indications of blepharospasm, strabismus, VII nerve disorder, cervical dystonia, glabellar lines or primary hyperhidrosis of the axillae, nor in children below 2 years of age for cerebral palsy.

ELDERLY

Refer Adult dosage.

CONTRAINDICATIONS

BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex, is contraindicated in individuals with known hypersensitivity to any ingredient in the formulation.

BOTOX® is contraindicated in patients with myasthenia gravis or Eaton Lambert Syndrome.

BOTOX® is contraindicated in the presence of infection at the proposed injection site(s).

WARNINGS AND PRECAUTIONS

General

Lack of Interchangeabilty between Botulinum Toxin Products
The potency Units of BOTOX® are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of BOTOX® cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method (see PRESENTATION).

Spread of Toxin Effect
Postmarketing safety data from BOTOX® and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The symptoms that are consistent with the mechanism of action of botulinum toxin have been reported hours to weeks after injection, and may include muscular weakness, ptosis, diplopia, blurred vision, facial weakness, swallowing and speech disorders, constipation, aspiration pneumonia, difficulty breathing and respiratory depression. The risk of symptoms is probably greatest in children treated for spasticity, but symptoms can also occur in patients who have underlying conditions that would predispose them to these symptoms including adults treated for spasticity and other conditions, and are treated with high doses. Swallowing and breathing difficulties can be life threatening and there have been reports of death in compromised patients, although a definitive causal association to BOTOX® has not been established.

No definitive serious adverse event reports of distant spread of toxin effect associated with dermatologic use of BOTOX® at the labeled dose of 20 Units (for glabellar lines) or 100 Units (for severe primary axillary hyperhidrosis) have been reported.

No definitive serious adverse event reports of distant spread of toxin effect associated with BOTOX® for blepharospasm at the recommended dose (30 Units and below) or for strabismus at the labeled doses have been reported. The recommended dosages and frequencies of administration for BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex should not be exceeded.

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BOTOX®

One case of peripheral neuropathy has been reported in an adult male weighing 126 kg who received a total cumulative dose of 1800 U of BOTOX® intramuscularly over an 11 week period. This exceeded the approved dose.

In clinical use, there have been reports of events such as generalised weakness and myalgia which may possibly have been related to systemic absorption and systemic effects of BOTOX®.

There have not been any reported instances of systemic toxicity resulting from accidental injection or oral ingestion of BOTOX®. However, should accidental injection or oral ingestion occur the person should be medically supervised for several days up to six weeks, on an office or outpatient basis for signs and symptoms of systemic weakness or muscle paralysis. The entire contents of a vial is below the estimated dose for systemic toxicity in humans weighing 6 kg or greater.

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

BOTOX® is not recommended for the treatment of patients with amyotropic lateral sclerosis or other disorders that produce a depletion of acetylcholine at the neuromuscular junction, as there is insufficient clinical experience of the safety of BOTOX® in these patients.

As with any treatment with the potential to allow previously sedentary patients to resume activities, the sedentary patient should be cautioned to resume activity gradually following the administration of BOTOX® injection.

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

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

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

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of viral diseases or CJD have ever been identified for albumin.

Strabismus

During the administration of BOTOX® for the treatment of strabismus, retrobulbar haemorrhages sufficient to compromise retinal circulation have occurred from needle penetrations into the orbit. It is recommended that appropriate instruments to decompress the orbit be accessible. Ocular (globe) penetrations by needles have also occurred. An ophthalmoscope to diagnose this condition should be available.

BOTOX® is ineffective in chronic paralytic strabismus except to reduce antagonist contracture in conjunction with surgical repair. The efficacy of BOTOX® in deviations over 50 prism diopters, in restrictive strabismus, in Duane's syndrome with lateral rectus weakness, and in secondary strabismus caused by prior surgical over-recession of the antagonist is doubtful. In order to enhance efficacy, multiple injections over time may be required.

Blepharospasm

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. One case of corneal perforation in an aphakic eye requiring corneal grafting has occurred because of this effect.

Careful testing of corneal sensation in eyes previously operated upon, avoidance of injection into the lower lid area to avoid ectropion and vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.

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

Cervical Dystonia (spasmodic torticollis)

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

Limiting the dose injected into the sternocleidomastoid muscle to less than 100 U may decrease the occurrence of dysphagia. Patients with smaller neck muscle mass, or patients who require bilateral injections into the sternocleidomastoid muscle, have been reported to be at greater risk of dysphagia. Dysphagia may be attributable to distribution of the pharmacological effect of BOTOX® injection resulting from spread of the toxin in the vicinity of the injection site.

Spasticity (due to juvenile cerebral palsy)

Although BOTOX® has not been studied in patients with fixed contracture at the ankle, it is not likely to be effective in the reduction of an equinus position in these patients.

Primary Hyperhidrosis of the axillae

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

Focal Spasticity Associated with Stroke

BOTOX® is a treatment of focal spasticity that has only been studied in association with usual standard of care regimens. BOTOX® is not likely to be effective in improving range of motion at a joint affected by a known fixed contracture.

Pregnancy

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

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

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

There are no adequate and well-controlled studies of the effects of BOTOX® in pregnant women, and its use in pregnancy should be avoided. If this drug is used during pregnancy, or if the patient becomes pregnant whilst taking this drug, the patient should be apprised of the potential risks, including abortion or fetal malformations.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals have not been performed to evaluate the carcinogenic potential of BOTOX® injection. BOTOX® is not structurally related to any known carcinogens. There has been no clinical evidence of cumulative adverse events following repeated injection of BOTOX®. BOTOX® was inactive in *in vitro* tests for gene mutation and in *in vitro* and *in vivo* tests for clastogenicity. Intramuscular BOTOX® doses of 4 U/kg (males) and 8 U/kg (females) did not affect rat fertility. Decreased fertility occurred with higher doses, but these also resulted in signs of toxicity.

Nursing Mothers

It is not known whether this medicine is excreted in human milk. Because many medicines are excreted in human milk, caution should be exercised when BOTOX® is administered to a nursing woman.

ADVERSE EFFECTS

In general, adverse events occur within the first week following injection of BOTOX® and are transient. As is expected for any intramuscular injection procedure, localized pain, tenderness and/or bruising may be associated with the injection. Local weakness represents the expected pharmacological action of botulinum toxin.

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

There have been rare spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin type A.

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

Strabismus

Inducing paralysis in one or more extraocular muscles may produce spatial disorientation, double vision, or past-pointing. Covering the affected eye may alleviate these symptoms. Extraocular muscles adjacent to the injection site are often affected, causing ptosis or vertical deviation, especially with higher doses of BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex. The incidence rates of these side effects in 2058 adults who received 3650 injections for horizontal strabismus are listed below:

Ptosis	15.7%
Vertical deviation	16.9%

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

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

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

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

Blepharospasm

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

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

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

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

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

Acute angle closure glaucoma has been reported very rarely following periorbital injections of botulinum toxin (see Warnings and Precautions).

VII Nerve Disorders (Hemifacial Spasm)

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

Cervical Dystonia (Spasmodic Torticollis)

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

SAFETY DATA FROM PLACEBO-CONTROLLED, DOUBLE-BLIND CLINICAL TRIALS *

Adverse Event	BOTOX® (N = 231)	Placebo (N = 224)
Pain†	32%	21%
Weakness, Focal	17%	4%
Dysphagia	13%	3%
Soreness	9%	3%
Malaise	6%	2%
Weakness, General	6%	1%
Upper Respiratory Infection	5%	3%
Nausea	5%	1%
Headache	5%	3%
Drowsiness	4%	1%
Stiffness	3%	0%
Dry mouth	3%	0.4%
Dizziness	3%	1%
Rhinitis	3%	0%
Hypertonia	2%	0%
Flu syndrome	3%	4%
Numbness	2%	1%
Diplopia	1%	0%
Fever	1%	0%
Ptosis	0.4%	0%
Dyspnea	0.4%	0%
Voice Alteration	0.4%	0%

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

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

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

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

Spasticity (due to juvenile cerebral palsy):

The safety of BOTOX® used for the treatment of dynamic equinus foot deformity due to spasticity in juvenile cerebral palsy patients was evaluated. As is expected for any intramuscular injection procedure, localised pain was associated with the injection in these patients. All treatment related adverse events were mild to moderate in severity.

The adverse events most frequently reported as related to treatment include falling, leg pain, leg (local) weakness and general weakness. The percentage of patients who experienced these events at least once during the study are summarised below:

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

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

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

Primary Hyperhidrosis of the axillae

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

Glabellar Lines

Safety of BOTOX® for the treatment of Glabellar lines was evaluated in two multicenter, double-blind, placebo-controlled, parallel group studies (N=535; 405 in the BOTOX®-treated group and 130 in the placebo-treated group). Most adverse events reported were of mild to moderate severity and all were transient. The most frequently reported treatment related adverse events were headache (9.4% in the BOTOX® group and 12.3% in the placebo group) and blepharoptosis (3.2% in the BOTOX® group and 0% in the placebo group). Blepharoptosis is consistent with the pharmacologic action of BOTOX® and may be injection technique related.

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

Crow's Feet

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

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

Forehead Lines

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

Focal Spasticity Associated with Stroke

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

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

The following events were reported as treatment related in less than 1% of patients and are listed in decreasing order of incidence: hypesthesia, arthralgia, asthenia, pain, bursitis, dermatitis, headache, injection site hypersensitivity, malaise, nausea, paresthesia, postural hypotension, pruritus, and rash.

Fever and flu syndrome were also reported in approximately 1% of patients.

INTERACTIONS

The effect of botulinum toxin may be potentiated by aminoglycoside antibiotics or any other medicines that interfere with neuromuscular transmission. Caution should be exercised when BOTOX® is used in patients taking any of these medicines. (See Warnings and Precautions)

OVERDOSAGE

Overdose of BOTOX® is a relative term and depends upon dose, site of injection, and underlying tissue properties. Local weakness is usually well tolerated and resolves spontaneously without intervention. However, dysphagia may result in loss of airway protection and aspiration pneumonia.

Patients with botulism may present with symptoms of ptosis, diplopia, swallowing and speech disorders, cranial nerve findings, generalized weakness, or paresis of the respiratory muscles. Should accidental injection or oral ingestion occur, the person should be medically supervised for several days up to six weeks on an office or outpatient basis for signs or symptoms of systemic weakness or muscle paralysis. The entire contents of a vial is below the estimated dose (from primate studies) for toxicity in humans weighing 6 kg or greater.

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

In the event of overdosage, additional information may be obtained by contacting the Poisons Information Centre.

PHARMACEUTICAL PRECAUTIONS

BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex is a sterile, vacuum-dried preparation. It is supplied in a clear glass vial with a rubber stopper and tamper-proof aluminium seal, containing a white powder for reconstitution. Each vial contains 50/100 U of vacuum-dried *Clostridium botulinum* Toxin type A. Refer to description for list of excipients.

Vials of BOTOX® have a holographic film on the vial label that contains the name "Allergan" within horizontal lines of rainbow color. In order to see the hologram, rotate the vial back and forth between your fingers under a desk lamp or fluorescent light source (Note the holographic film on the label is absent in the data/batch area). If you do not see the lines of rainbow color or the name "Allergan", do not use the product and contact Allergan for additional information.

STORE THE VACUUM-DRIED PRODUCT IN A REFRIGERATOR BETWEEN 2-8°C OR FREEZER BETWEEN -5°C TO -20°C. Administer BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex within 3 days after the vial is removed from the refrigerator and reconstituted. During these 3 days, reconstituted BOTOX® should be clear, colourless and free of particulate matter.

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

MEDICINE CLASSIFICATION

Prescription Medicine

PACKAGE QUANTITIES

Each vial contains 50/100 Units of Botulinum Toxin Type A, packaged individually.

ALLERGAN®

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

INSERT, BOTOX
500mm X 348mm
(FOLDED TO 63mm X 38mm)

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Part number:	**71580UT11A**
Drawing number:	**0196901**
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