ANNEX I

LIST OF THE NAME, PHARMACEUTICAL FORM, STRENGTH OF THE MEDICINAL PRODUCT, ROUTE OF ADMINISTRATION, APPLICANT MARKETING AUTHORISATION HOLDER, PACKAGING AND PACKAGE SIZE IN THE MEMBER STATES

Member State	Marketing Authorisation Holder	Applicant	Invented name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package-size
Austria	Allergan Pharmaceuticals Ireland	Allergan Pharmaceuticals Ireland	BOTOX	100 units	Powder for Solution for Injection	Intradermal use	Vial (glass)	1 vial
Belgium	Allergan Pharmaceuticals Ireland	Allergan Pharmaceuticals Ireland	BOTOX	100 units	Powder for Solution for Injection	Intradermal use	Vial (glass)	1 vial
Denmark	Allergan Pharmaceuticals Ireland	Allergan Pharmaceuticals Ireland	BOTOX	100 units	Powder for Solution for Injection	Intradermal use	Vial (glass)	1 vial
Finland	Allergan Pharmaceuticals Ireland	Allergan Pharmaceuticals Ireland	BOTOX	100 units	Powder for Solution for Injection	Intradermal use	Vial (glass)	1 vial
Greece	Allergan Pharmaceuticals Ireland	Allergan Pharmaceuticals Ireland	BOTOX	100 units	Powder for Solution for Injection	Intradermal use	Vial (glass)	1 vial
Germany	Allergan Pharmaceuticals Ireland	Allergan Pharmaceuticals Ireland	BOTOX	100 units	Powder for Solution for Injection	Intradermal use	Vial (glass)	1 vial
Ireland	Allergan Pharmaceuticals Ireland	Allergan Pharmaceuticals Ireland	BOTOX	100 units	Powder for Solution for Injection	Intradermal use	Vial (glass)	1 vial
Italy	Allergan Pharmaceuticals Ireland	Allergan Pharmaceuticals Ireland	BOTOX	100 units	Powder for Solution for Injection	Intradermal use	Vial (glass)	1 vial
Luxembourg	Allergan Pharmaceuticals Ireland	Allergan Pharmaceuticals Ireland	BOTOX	100 units	Powder for Solution for Injection	Intradermal use	Vial (glass)	1 vial
Portugal	Allergan Pharmaceuticals Ireland	Allergan Pharmaceuticals Ireland	BOTOX	100 units	Powder for Solution for Injection	Intradermal use	Vial (glass)	1 vial
Spain	Allergan Pharmaceuticals Ireland	Allergan Pharmaceuticals Ireland	BOTOX	100 units	Powder for Solution for Injection	Intradermal use	Vial (glass)	1 vial
Sweden	Allergan Pharmaceuticals Ireland	Allergan Pharmaceuticals Ireland	BOTOX	100 units	Powder for Solution for Injection	Intradermal use	Vial (glass)	1 vial

Member State	Marketing Authorisation Holder	Applicant	Invented name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package-size
Iceland	Allergan Pharmaceuticals Ireland	Allergan Pharmaceuticals Ireland	BOTOX	100 units	Powder for Solution for Injection	Intradermal use	Vial (glass)	1 vial
Norway	Allergan Pharmaceuticals Ireland	Allergan Pharmaceuticals Ireland	BOTOX	100 units	Powder for Solution for Injection	Intradermal use	Vial (glass)	1 vial

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF BOTOX

- Safety and efficacy issues

The pivotal trial plus its open extension demonstrates that Botox in the 50U/axial dose is efficacious in the symptomatic treatment of primary axilar hyperhidrosis. It is acknowledge that the recommended dose did not result from a dose-finding study but rather from a confirmatory study (the pivotal trial). The choice of dose used in the pivotal trial was based on common practice of off-label use. The dose proved to be efficacious with an acceptable safety profile.

The efficacy and safety of Botox, on repetitive use for primary axillary hyperhidrosis is not firmly established by direct data. However taking into consideration the large database generated by the use in other indications and the lack of evidence to the contrary, it is accepted that the Benefit/Risk of Botox for long-term use is favourable. It is also important to recognise that Botox duration of effect in primary hyperhidrosis is longer than in focal dystonias, which would imply a very long (several years) clinical trial if efficacy of repetitive injections was to be established by such a clinical study.

Benefit/Risk

Intradermal injection of Botox, 50 U per axilla in a placebo-controlled clinical trial setting reduced mean sweat production to physiological levels within one week of administration and benefit was maintained on average for 30.6 weeks. These clinical findings, along with the high levels of patient satisfaction with treatment, were consistently statistically significantly superior to those seen with placebo. In addition, the safety profile of this treatment was remarkably benign, with no serious treatment related adverse events seen among over 440 exposures to treatment, no statistically significant difference in overall adverse events compared with placebo and no change of adverse event profile with repeat exposures. Therefore, the benefit-risk profile of Botox in the proposed indication can be considered as favourable.

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS

Whereas

- it is acknowledged that no specific dose-finding study was conducted, the data available is considered to be sufficient to support the 50U/axilae proposed by the applicant.

- there is a lack of data on repetitive use and the number of patients studied in this indication is small, the available data is considered to be sufficient to support the efficacy of Botox in primary axillary hyperhidrosis. Botox has now been used on thousands of patients for different indications and the safety data generated by the total use in all of the indications is reassuring taking into account the data generated specifically for this application.

- the data generated by the 30 patients in the present dossier can be considered small to support the indication, considering all the data available on maintenance of efficacy over repetitive treatments with Botox; the duration of follow – up to support the efficacy of repeat doses is considered to be adequate.

- the safety database to support repeat intermittent use of Botox and the suitability of the safety parameters recorded in the pivotal study is small, when taken together with the supportive data it is considered to be adequate since the dose used is well in the range of the established indications and the safety profile seen in the pivotal trial does not suggest that in primary hyperhidrosis there are any specific side-effects.

the CPMP has recommended the granting of the Marketing Authorisation for which the Summary of Product Characteristics is set out in Annex III for Botox (see Annex I).

ANNEX III

AMENDED SUMMARY OF PRODUCT CHARACTERISTICS OF THE REFERENCE MEMBER STATE

1. NAME OF THE MEDICINAL PRODUCT

BOTOX
100 Units
Powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains: *Clostridium botulinum* type A neurotoxin complex (900 kD), 100 unit/vial.

One unit corresponds to the median lethal dose (LD_{50}) when the reconstituted product is injected intraperitoneally into mice under defined conditions.

These units are specific to BOTOX and are not applicable to other botulinum toxin preparations.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.
White powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BOTOX is indicated for the management of:

Blepharospasm, hemifacial spasm and associated focal dystonias.

Idiopathic rotational cervical dystonia (spasmodic torticollis).

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

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

4.2 Posology and method of administration

Doses recommended for BOTOX are not interchangeable with other preparations of botulinum toxin.

Dosages for the elderly are as for other adults.

The safety and effectiveness of BOTOX in the treatment of blepharospasm, hemifacial spasm, or idiopathic cervical dystonia in children (under 12 years) have not been demonstrated.
The safety and effectiveness of BOTOX in the treatment of primary hyperhidrosis of the axillae have not been investigated in children and adolescents under 18 years.

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

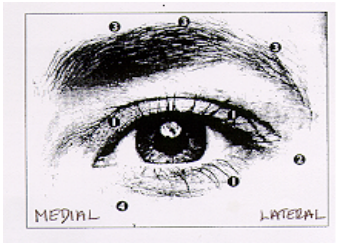
Generally valid optimum dose levels and number of injection sites per muscle have not been established. Individual treatment regimens should therefore be drawn up by the physician. Optimum dose levels should be determined by titration.

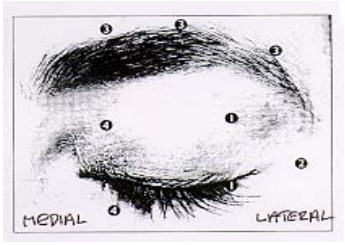
The recommended injection volumes per muscle site range from 0.05-0.1 ml (blepharospasm, hemifacial spasm) to 0.1-0.5 ml (cervical dystonia, cerebral palsy). The recommended injection volume per intradermal injection in primary axillary hyperhidrosis is 0.1-0.2 ml.

See also dilution table in Section 6.6.

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

Blepharospasm/hemifacial spasm
Reconstituted BOTOX is injected using a sterile, 27-30 gauge / 0.40 – 0.30 mm needle. Electromyographic guidance is not necessary. The initial recommended dose is 1.25-2.5 U 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. Avoiding injection near levator palpebrae superioris may reduce the complication of ptosis. Avoiding medial lower lid injections, and thereby reducing diffusion into the inferior oblique, may reduce the complication of diplopia. The following diagrams indicate the possible injection sites:





In general, the initial effect of the injections is seen within three days and reaches a peak at one to two weeks post-treatment. Each treatment lasts approximately three months, following which the procedure can be repeated as needed. At repeat treatment sessions, the dose may be increased up to two-fold if the response from the initial treatment is considered insufficient. However, there appears to be little benefit obtainable from injecting more than 5.0 U per site. The initial dose should not exceed 25 U per eye. Normally no additional benefit is conferred by treating more frequently than every three months.

In the management of blepharospasm total dosing should not exceed 100 U every 12 weeks.

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
Reconstituted BOTOX is injected using an appropriately sized needle (usually 25-30 gauge / 0.50 – 0.30 mm).

The treatment of cervical dystonia typically may include injection of BOTOX into the sternocleidomastoid, levator scapulae, scalene, splenius capitis, and/or the trapezius muscle(s). The muscle mass and the degree of hypertrophy or atrophy are factors to be taken into consideration when selecting the appropriate dose.

In case of any difficulty in isolating the individual muscles, injections should be made under electromyographic assistance. In initial controlled clinical trials to establish safety and efficacy for cervical dystonia, doses of reconstituted 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 drug

treatment, initial dosing in a naïve patient should begin at the lowest effective dose. No more than 50 U should be given at any one site. No more than 100 U should be given to the sternomastoid. To minimise the incidence of dysphagia, the sternomastoid should not be injected bilaterally. No more than 200 U total should be injected for the first course of therapy, with adjustments made in subsequent courses dependent on the initial response. A total dose of 300 U at any one sitting should not be exceeded. The optimal number of injection sites is dependent upon the size of the muscle.

Clinical improvement generally occurs within the first two weeks after injection. The maximum clinical benefit generally occurs approximately six weeks' post-injection. Treatment intervals of less than 10 weeks are not recommended. The duration of beneficial effect reported in clinical trials showed substantial variation (from 2 to 33 weeks) with a typical duration of approximately 12 weeks.

Paediatric cerebral palsy
Reconstituted BOTOX is injected using a sterile 23-26 gauge / 0.60 – 0.45 mm needle. It is administered into each of two sites in the medial and lateral heads of the affected gastrocnemius muscle. In hemiplegia, the initial recommended total dose is 4 U/kg body weight in the affected limb. In diplegia, the initial recommended total dose is 6 U/kg body weight divided between the affected limbs. The total dose should not exceed 200 U.

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
Reconstituted BOTOX is injected using a sterile 25, 27 or 30 gauge needle for superficial muscles, and a longer needle for deeper musculature. Localisation of the involved muscles with electromyographic guidance or nerve stimulation techniques may be useful. Multiple injection sites may allow BOTOX to have more uniform contact with the innervation areas of the muscle and are especially useful in larger muscles.

The 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 controlled clinical trials the following doses were administered:

Muscle	Total Dosage; Number of 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

In controlled and open non-controlled clinical trials doses between 200 and 240 U divided among selected muscles have been used at a given treatment session.

In controlled clinical trials patients were followed for 12 weeks after single treatment. Improvement in muscle tone occurred within two weeks with the peak effect generally seen within four to six weeks. In an open, non-controlled continuation study, most of the patients were re-injected after an interval of 12 to 16 weeks, when the effect on muscle tone had diminished. These patients received up to four injections with a maximal cumulative dose of 960 Units over 54 weeks. If it is deemed appropriate by the treating physician, repeat doses may be administered, when the effect of a previous injection has diminished. Re-injections should not occur before 12 weeks. 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.

Primary hyperhidrosis of the axillae
Reconstituted BOTOX (100 U/4.0 mL) is injected using a 30 gauge needle.
50 U of BOTOX is injected intradermally, evenly distributed in multiple sites approximately 1-2 cm apart within the hyperhidrotic area of each axilla. The hyperhidrotic area may be defined by using standard staining techniques, e.g. Minor´s iodine-starch test. Doses other than 50U per axilla have not been studied and therefore cannot be recommended.

Clinical improvement generally occurs within the first week after injection. Repeat injection of BOTOX can be administered when the clinical effect of a previous injection diminishes and the treating physician deems it necessary. Injections should not be repeated more frequently than every 16 weeks. (See section 5.1)

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

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

4.3 Contraindications

BOTOX is contraindicated:
- in individuals with a known hypersensitivity to *Clostridium botulinum* type A neurotoxin complex (900 kD) or to any of the excipients
- in the presence of myasthenia gravis or Eaton Lambert Syndrome.

4.4 Special warnings and special precautions for use

The relevant anatomy, and any alterations to the anatomy due to prior surgical procedures, must be understood prior to administering BOTOX. The recommended dosages and frequencies of administration of BOTOX should not be exceeded.

An anaphylactic reaction may occur very rarely after injection of botulinum toxin. Epinephrine (adrenaline) and other anti-anaphylactic measures should therefore be available. Please see section 4.8c) for further information.

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

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

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

Too frequent or excessive dosing can result in antibody formation, which may lead to resistance to treatment.

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.

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. Caution should also be exercised when BOTOX is used for treatment of patients with amyotrophic lateral sclerosis or disorders that produce peripheral neuromuscular dysfunction.

BOTOX contains human serum albumin. When medicinal products derived from human blood or plasma are administered, the possibility of transmitting infectious agents cannot be totally excluded. To reduce the risk of transmission of infective agents, stringent controls are applied to the selection of blood donors and donations. In addition, virus inactivation procedures are included in the production process.

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

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

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

Cervical dystonia
Patients with cervical dystonia should be informed of the possibility of experiencing dysphagia which may be very mild, but could be severe. Consequent to the dysphagia there is the potential for aspiration, dyspnoea and occasionally the need for tube feeding. In rare cases dysphagia followed by aspiration pneumonia and death has been reported. Dysphagia may persist for two to three weeks after injection, but has been reported to last up to five months post-injection.

Limiting the dose injected into the sternocleidomastoid muscle to less than 100 U may decrease the occurrence of dysphagia. Patients with smaller neck muscle mass, or patients who receive bilateral injections into the sternocleidomastoid muscle, have been reported to be at greater risk of dysphagia. Dysphagia is attributable to the spread of the toxin to the oesophageal musculature.

Focal spasticity associated with paediatric cerebral palsy 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 likely to be effective in improving range of motion at a joint affected by a fixed contracture.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

No specific tests have been carried out to establish the possibility of clinical interaction with other medicinal products. No interactions of clinical significance have been reported.

4.6 Pregnancy and lactation

Pregnancy
There are no adequate data from the use of botulinum toxin type A in pregnant women. Studies in animals have shown reproductive toxicity (see Section 5.3). The potential risk for humans is unknown. BOTOX should not be used during pregnancy unless clearly necessary.

Lactation
There is no information on whether BOTOX is excreted in human milk. The use of BOTOX during lactation cannot be recommended.

4.7 Effects on the ability to drive and use machines

The effects of BOTOX on the ability to drive or to use machines can only be assessed after treatment.

4.8 Undesirable effects

a) General
Based on controlled clinical trial data patients would be expected to experience an adverse reaction after treatment with BOTOX at the rates of 35% for blepharospasm, 28% for cervical dystonia, 17% for paediatric cerebral palsy and 11% for primary hyperhidrosis of the axillae.
16% of participants in clinical trials treated with BOTOX® for focal spasticity of the upper limb associated with stroke experienced an adverse reaction

In general, adverse reactions occur within the first few days following injection and are transient.

Local muscle weakness represents the expected pharmacological action of botulinum toxin in muscle tissue.

As is expected for any injection procedure, localised pain, tenderness and/or bruising may be associated with the injection. Fever and flu syndrome have also been reported after injections of botulinum toxin.

b) Adverse reactions - frequency by indication

For each indication the frequency of adverse reactions arising from clinical experience is given. The frequency is defined 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).

Blepharospasm/hemifacial spasm

Very common:	Ptosis.
Common:	Superficial punctate keratitis, lagophthalmos, dry eye, irritation, photophobia, lacrimation.
Uncommon:	Keratitis, ectropion, diplopia, dizziness, diffuse skin rash/ dermatitis, entropion, facial weakness, facial droop, tiredness, visual disturbance, blurring of vision.
Rare:	Eyelid swelling.
Very rare:	Angle closure glaucoma, corneal ulceration.

Cervical dystonia

Very common:	Dysphagia (See Section c) below.), local weakness, pain.
Common:	Dizziness, hypertonia, numbness, general weakness, drowsiness, flu syndrome, malaise, oral dryness, nausea, headache, stiffness, soreness, rhinitis, upper respiratory infection.
Uncommon:	Dyspnoea, diplopia, fever, ptosis, voice alteration.

Paediatric cerebral palsy

Very common:	Viral infection, ear infection.
Common:	Myalgia, muscle weakness, urinary incontinence, somnolence, gait abnormality, malaise, rash, tingling.

Focal upper limb spasticity associated with stroke

Common:	ecchymosis/purpura/injection site hemorrhage, arm pain, muscle weakness, hypertonia, injection site burning
Uncommon:	*hypesthesia, arthralgia, asthenia, pain, bursitis, dermatitis, headache, injection site hypersensitivity, malaise, nausea, paresthesia, postural hypotension, pruritus, rash, in coordination, amnesia, circumoral paresthesia,depression, insomnia, peripheral oedema, vertigo (some of the uncommon events may be disease related)*

Primary hyperhidrosis of the axillae

Common:	Non-axillary sweating, injection site reactions, pain, vasodilation (hot flushes)
Uncommon:	Weakness of the arms, pruritus, myalgia, joint disorder, arm pain

c) Additional information

Dysphagia ranges in severity from mild to severe, with potential for aspiration, which occasionally may require medical intervention. See Section 4.4, Special Warnings and Special Precautions for Use.

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

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

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.

Rare reports of an anaphylactic reactions associated with BOTOX use in conjunction with other agents known to cause similar reactions have been received..

A case of peripheral neuropathy has been reported in a large adult male after receiving four sets of BOTOX injections, totalling 1800 U (for neck and back spasm, and severe pain) over an 11 week period.

Angle closure glaucoma has been reported very rarely following botulinum toxin treatment for blepharospasm.

A female patient developed brachial plexopathy two days after injection of 120 units of BOTOX for the treatment of cervical dystonia, with recovery after five months.

In the management of primary axillary hyperhidrosis, increase in non axillary sweating was reported in 4.5% of patients within 1 month after injection and showed no pattern with respect to anatomical sites affected. Resolution was seen in approximately 30% of the patients within four months. Weakness of the arm has been also reported uncommonly (0.7%) and was mild, transient, did not require treatment and recovered without sequelae. This adverse event may be related to treatment, injection technique, or both. In the uncommon event of muscle weakness being reported a neurological examination may be considered. In addition, a re-evaluation of injection technique prior to subsequent injection is advisable to ensure intradermal placement of injections.

4.9 Overdose

There have not been any reported instances of systemic toxicity resulting from accidental injection of BOTOX. Ingestion of BOTOX is unknown. Signs of overdose are not apparent immediately post-injection. Should accidental injection or ingestion occur, the patient should be medically supervised for several days for signs and symptoms of systemic weakness or muscle paralysis.

Patients presenting with the symptoms of botulinum toxin type A poisoning (generalised weakness, ptosis, diplopia, swallowing and speech disorders, or paresis of the respiratory muscles) should be considered for admission to hospital.

With increasing dosage, generalised and profound muscular paralysis occurs. When the musculature of the oropharynx and oesophagus are affected, aspiration pneumonia may ensue. If the respiratory muscles become paralysed, intubation and assisted respiration will be required until recovery takes place.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Muscle relaxant, peripherally acting agent
ATC code: M03A X01

Pharmacotherapeutic group: Other Dermatological Preparation
ATC codeD11AX

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

After injection, there is an initial rapid high-affinity binding of toxin to specific cell surface receptors. This is followed by transfer of the toxin across the plasma membrane by receptor-mediated endocytosis. Finally, the toxin is released into the cytosol. This latter process is accompanied by progressive inhibition of acetylcholine release, clinical signs are manifest within 2-3 days, with peak effect seen within 5-6 weeks of injection.

Recovery after intramuscular injection takes place normally within 12 weeks of injection as nerve terminals sprout and reconnect with the endplates. After intradermal injection, where the target is the eccrine sweat glands the effect lasted an average of 7.5 months after the first injection in patients treated with 50 U per axilla. However, in 27.5 % of patients the duration of effect was1 year or greater. Recovery of sympathetic nerve endings that innervate sweat glands after intradermal injection with BOTOX has not been studied.

The neurotoxin complex in BOTOX is derived from a new Master Cell Bank. Clinical studies in adults of this new preparation of BOTOX have demonstrated its similar efficacy across the dosage range to the previously available BOTOX preparation. No clinical studies in children have been conducted with the new preparation.

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

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

5.2 Pharmacokinetic properties

a) General characteristics of the active substance:

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

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

b) Characteristics in patients:

It is believed that little systemic distribution of therapeutic doses of BOTOX occurs. Clinical studies using single fibre electromyographic techniques have shown increased electrophysiologic

neuromuscular activity in muscles distant to the injection site, unaccompanied by any clinical signs or symptoms.

5.3 Preclinical safety data

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

Other studies
In addition to the reproductive toxicology, the following preclinical safety studies of BOTOX have been performed: Acute toxicity, toxicity on repeated injection, local tolerance, mutagenicity, antigenicity, human blood compatibility. These studies revealed no special hazard for humans at clinically relevant dose levels. The maximum recommended dose in humans at one treatment session is 300 U (corresponding to 6 U/kg in a 50 kg person). The published intramuscular LD_{50} in juvenile monkeys is 39 U/kg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Albumin, human
Sodium chloride

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial: 2years.

Reconstituted vial: 4hours.

6.4 Special precautions for storage

Unopened vial: Store at 2°C-8°C (in a refrigerator), or Store in a freezer (at or below -5°C).

Reconstituted vial: Store at 2°C – 8°C (in a refrigerator).

6.5 Nature and contents of container

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

6.6 Instructions for use and handling, and disposal

It is good practice to perform vial reconstitution and syringe preparation over plastic-lined paper towels to catch any spillage. Reconstitute BOTOX with sterile unpreserved normal saline (0.9% sodium chloride for injection). Draw up an appropriate amount of diluent (see dilution table below) into a syringe.

Amount of diluent added (0.9% Sodium chloride injection)	Resulting dose (Units per 0.1 ml)
0.5 ml	20.0 U
1.0 ml	10.0 U
2.0 ml	5.0 U
4.0 ml	2.5 U
8.0 ml	1.25 U

Since BOTOX is denatured by bubbling or similar vigorous agitation, inject the diluent gently into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Reconstituted BOTOX is a clear colourless to slightly yellow solution free of particulate matter. The reconstituted solution should be visually inspected for clarity and absence of particles prior to use. When reconstituted, BOTOX may be stored in a refrigerator (2-8°C) for up to 4 hours prior to use. This product is for single use only and any unused solution should be discarded.

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

7. MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals Ireland
Castlebar Road
Westport
County Mayo
Ireland

(Plus, for some countries, country-specific information.)

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

February 2003

ANNEX IV

CONDITIONS OF THE MARKETING AUTHORISATION

Conditions of the Marketing Authorisation

CPMP requirements in relation to the follow-up safety study for assessing prospectively the long-term impact of Botox

Further safety data should be provided for assessing prospectively the long-term impact of Botox therapy in axillary hyperhidrosis.

A long-term safety study should be performed in accordance with the outline of the clinical protocol reviewed by the CPMP, which should provide data (safety – primary analysis, and descriptive efficacy) on at least 100 patients exposed to 3 treatments with BTX-A (all patients should be followed at least 30 months).

The CPMP will be notified of the start of recruitment of patients and a Status Report will be provided at the end of recruitment. A final study report will be provided 6 months following the end of the study.

