IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

BOTOX200 Allergan Units Powder for solution for injection PA1824/017/003

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for BOTOX 50, 100, 200 Allergan units powder for solution for injections from Allergan
The product is indicated for*:*

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

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

Skin and skin appendage disorder:
• Persistent severe primary hyperhidrosis of the axillae, which interferes with the activities of daily living and is resistant to topical treatment,

A comprehensive description of the indications and posology is given in the SmPC.

BOTOX 100 Allergan units powder for solution for injections was granted a national licence in Ireland in 1994. On the basis of the national licence for BOTOX 100 Allergan units, the product was approved in 13 additional European member states (Austria, Belgium, Denmark, Finland, Germany, Greece, Italy, Luxembourg Portugal, Spain & Sweden as well as Iceland and Norway) in 2000 by way of a mutual recognition procedure. Allergan subsequently applied to register two new product strengths: BOTOX 50 and 200 Allergan units. These were submitted as line extensions and granted national licences in 2008. Subsequent to this, the 50 and 200 Allergan unit strengths were approved in a number of additional member states by way of mutual recognition procedure (2008). This is a repeat-use mutual recognition procedure submitted under article 8.3 of Directive 2001/83/EC for BOTOX 50,100 and 200 Allergan units powder for solution for injection to include the following member states. Bulgaria, Cyprus, Estonia, Hungary, Lithuania, Latvia, Malta, Netherlands, Romania, Slovakia, Slovenia.
BOTOX 50, 100 and 200 Allergan units powder for solution for infusion are prescription only status.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product: BOTOX
Name(s) of the active substance(s) (INN): Botulinum toxin type A
Pharmacotherapeutic classification (ATC code): M03A X01
Pharmaceutical form and strength(s) 50, 100 and 200 Allergan units powder for solution for injection
Marketing Authorisation Number(s) in Ireland (PA):
PA1824/017/002 (50 unit)
PA1824/017/001 (100 unit)
PA1824/017/003 (200 unit)
Marketing Authorisation Holder: AbbVie Limited
MRP/DCP No: IE/H/113/001/E/002 & IE/H/113/002-003/E/001
Reference Member State: Ireland
Concerned Member State: AT, BE, BG, CY, DE, EL, ES, FI, DK, EE, HR, HU, IS, IT, LT, LU, LV, MT, NL, NO, PT, SE, RO, SI

II. QUALITY ASPECTS

II.1 Introduction

The application is for BOTOX 50, 100, 200 Allergan units powder for solution for injection.
It should be noted that the Botulinum toxin units are not interchangeable from one product to another and doses recommended in Allergan units are different from other botulinum toxin preparations.

II.2 Drug Substance

The drug substance is botulinum toxin type A, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specification is considered adequate to control the quality and meets appropriate current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal Product

P.1 Composition

BOTOX 50 Allergan units contains 50 Allergan units of Botulinum toxin type A per vial.
BOTOX 100 Allergan units contains 100 Allergan units of Botulinum toxin type A per vial.
BOTOX 200 Allergan units contains 200 Allergan units of Botulinum toxin type A per vial.

It is intended to be reconstituted with appropriate volumes of sterile sodium chloride solution, using amounts specified in the information presented for physicians, before administration to patients.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur. The Human Albumin Solution is an authorised medicinal product and complies with the current Ph. Eur. monograph.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monographs for Ph. Eur. Botulinum toxin type A for injection and parenteral products; the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described and are considered to be validated.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

The packaging components comply with Ph. Eur. requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

Adventitious Agent Safety
Adventitious agents safety is established for the product.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies:
Compliance with current guidelines has been demonstrated or adequate assurance provided.

Adventitious viruses
Appropriate consideration has been given to the potential for viral contamination. Measures have been implemented to reduce viral risk in the biological raw materials. Conventional virus risk is very remote for this product and it is considered that adventitious agents safety is established.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of BOTOX 50, 100 and 200 Allergan units powder for solution for injection.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Botulinum Toxin Type A (BOTOX) contains Clostridium botulinum type A neurotoxin complex [900 kDa] which contains type A neurotoxin, hemagglutinating proteins and a non-toxic non-hemagglutinating protein. Clostridium botulinum toxin type A when released from the complex, blocks cholinergic transport at the neuromuscular junction by preventing the release of acetylcholine. This mechanism of action is responsible for its activity in focal muscle relaxation. The clinical effects of BOTOX are largely dependent upon the anatomical site of injection.

BOTOX is indicated for:

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

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

Skin and skin appendage disorder:

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

III.2 Pharmacology

Botulinum neurotoxins block presynaptic exocytosis of acetylcholine (Ach), thereby preventing chemical neurotransmission at the neuromuscular junction. They exert their effect on cholinergic nerve terminals through a 3-step sequential process: 1) receptor-specific binding to the presynaptic cholinergic axon terminals, 2) internalization or entry into the nerve terminal, and 3) exertion of the enzymatic action (i.e., inhibition of ACh release) within the nerve terminal (Simpson, 1981; Simpson, 1989). Binding and internalization processes involve the ~ 100 kDa heavy chain portion of the toxin, while the pharmacologic (enzymatic) effects are associated with the ~ 50 kDa light chain portion (Bandyopadhyay et al, 1987; Lomneth et al, 1990). The heavy chain is responsible for docking the neurotoxin at the presynaptic nerve terminal acceptors. Subsequent to endocytosis of the botulinum neurotoxin type A complex (BoNTA) into the nerve terminal, the zinc-dependent endopeptidase light chain portion of the type A neurotoxin cleaves synaptosomal associated protein of 25 kDa (SNAP-25), a protein attached to the inner surface of the nerve terminal; each serotype has a specific target protein or peptide bond. SNAP-25 is integral to the membrane-associated protein complex (soluble NSF [N-ethylmaleimide-sensitive factor] attachment protein receptor [SNARE]) that is responsible for docking ACh synaptic vesicles with the nerve terminal membrane and subsequent exocytosis of synaptic vesicle contents.

Cleavage of SNAP-25 by serotypes A, E and C precludes fusion of the vesicles with the nerve membrane and subsequent release of ACh (Blasi et al, 1993). The blockade of ACh release in skeletal muscle induces the formation of active nerve-terminal sprouts (de Paiva et al, 1999). These low-efficiency newly formed sprouts are responsible for the initial phase of re-innervation. In the second phase, there is a return of neurotransmitter release at the original terminals and an elimination of the sprouts. The manner in which BOTOX is metabolized once it is within the neuron is currently unknown.

The described mechanism of action is considered to apply to any physiological activity mediated by the release of ACh from a BoNTA sensitive nerve, when exposed to BoNTA. In the treatment of hyperhidrosis, BoNTA is administered intradermally in proximity to the eccrine sweat glands, which are innervated by cholinergic autonomic nerve fibers. Consequently, the predominant effect of the neurotoxin is deemed to be on cholinergic neurons innervating sweat glands, with the clinical effect of sweat reduction.

BoNTA plays a role in antinociception. In a rat model of inflammatory pain has been used to demonstrate a local antinociceptive effect of subcutaneous BoNTA injections. When administered subcutaneously to the plantar surface of the rat 5 days before a formalin challenge in the same area, BoNTA produced a dose-related inhibition of the phase 2 nociceptive response, which represents a form of experimental chronic pain (Cui et al, 2004). The Phase 1 response, representing an acute pain reaction, was not affected by botulinum toxin. BoNTA inhibits not only the release of Ach, but also the release of substance P from trigeminal nerve ends of the rabbit iris sphincter muscle (Ishikawa et al, 2000). The reduced neuropeptide release may prevent local sensitization of nociceptors and thus reduce the perception of pain (Aoki, 2005). A reduction of nociceptive signals from the periphery is deemed to indirectly reduce the central sensitization associated with chronic pain. These results demonstrate that the inhibition of neurotransmitter release from primary sensory neurons by subcutaneous BOTOX injections mediates at least some of its antinociceptive effect in animals. Local administration of BOTOX may directly inhibit the peripheral sensitization produced by local neurotransmitter release, which then results in an indirect reduction in the central sensitization (Aoki, 2005).

The effect of BOTOXon other sensory neurons or cells relies upon the same biochemical activity in the cleavage of SNAP-25 as described for the motor neuron. BOTOX may play a role in regulating pain pathways by blocking the release of substance P, glutamate, and Calcitonin gene-related peptide (CGRP) as seen in nonclinical pain models (Aoki, 2005). Similarly, neuromodulatory effects on the afferent mediators and TRPV1 and P2X3 receptors have been demonstrated in the laboratory (Morenilla-Palao et al, 2004; Shimizu, 2012) and humans (Apostolides, 2005; Apostolidis et al, 2006; Giannantoni et al, 2006). Because cell surface membrane expression the neuroinflammatory sensors TRPV1 and P2X3 are also dependent on SNARE-mediated synaptic vesicle fusion to the plasma membrane, BOTOX may result in their downregulation in a stimulated pathologic state (Morenilla-Palao, 2004; Zhang, 2005; Camprubí-Robles, 2009). Inhibition of nociceptive processing at the peripheral site may underlie the mechanism by which BOTOX alleviates certain chronic pain conditions, including chronic migraine.

III.3 Pharmacokinetics

To study the systemic distribution, excretion, and local diffusion of BOTOX®, Allergan performed a study in which the gastrocnemius muscle of rats was injected with approximately 210 U/kg of ^{125}I-labeled botulinum neurotoxin A complex (^{125}I-BoNT/A) (Report PK 94-067). Controlled experiments were also conducted in rats administered ^{125}I-labeled botulinum neurotoxin and ^{125}I-iodide (Reports PK 94-099, 1658L, AGN 191622-3, and PK 95-043; Tang-Liu et al, 2003). After an IM injection of ^{125}I-BoNT/A, the half-life of the radiolabeled material at the injection site was approximately 10 hours. The majority of the radioactivity at the injection site was acid precipitable, which indicated that the complex remained as a large protein. Some radioactivity was detected in the plasma but it was primarily in the non-acid precipitable form. This suggested a rapid systemic degradation of some of the complex into small molecules. Additionally, 60% of the radioactivity was rapidly excreted in the urine within 24 hours of dosing, and the majority was either free ^{125}I-iodide or soluble low molecular weight ^{125}I-peptide. In summary, these distribution study results with exaggerated dosing support the local diffusion of botulinum toxin at the injection site, followed by rapid systemic metabolism and excretion in rats. When examining the brain and cardiac tissue there was no accumulation of new radioactivity, establishing that BOTOX or its complex does not enter the brain after intramuscular (IM) administration.

In a rabbit study, the hemagglutinin complex of ^{125}I-BoNT/A was injected IM into the proximal inner surface of the upper eyelids and analyzed autoradiographically at various times post-injection (Report PK 95-023). During the first 6 hours post-injection, radioactivity was limited to a well-defined area in close proximity to the injection site. By 12 hours post-injection, radioactivity was still present at the injection site but was also found at low concentrations in a relatively larger area (around the injection site). By 24 hours post-injection, radioactivity was present at trace levels only at the injection site, but was not detected in adjacent or other structures of the eye. It has been shown that the elimination half-life of botulinum neurotoxin A complex is approximately 4 hours when injected into plasma in mice and rats (Ravichandran et al, 2006). These distribution studies reflect local diffusion of botulinum toxin at the injection site, followed by rapid systemic metabolism and excretion.

III.4 Toxicology

Local and systemic adverse effects following single-dose IM and IV injections of BOTOX to rats were observed at doses greater than 50 U/kg (IM) and 25 U/kg (IV), respectively. These amounted to clinical signs ataxia, chromodacryorrhea, chromorhinorrhea, dyspnea, limping/dragging leg, piloerection, soiled perianal region marked decrements in body weight, and death. IM LD50 values ranged from 72 to 199 U/kg, and the IV LD50 values ranged from 50 to 108 U/kg. Likewise, following single-dose intraprostatic (≥ 30 U/kg), intradetrusor (≥ 50 U/kg), or intra-articular (≥ 12.5 U/kg in males & ≥ 17 U/kg in females) BOTOX injections, clinical and histological signs of systemic toxicity were observed.
Similarly in monkeys, clinical signs of systemic toxicity (decreased activity, drooping of eyelids, hunched appearance, irregular gait, lethargy, slow/shallow breathing, decreased body weight and food consumption, and mortality) were observed at IM doses of 24 and 48 U/kg. The most notable adverse effect observed following intraprostatic injection was the formation of bladder stone. This occurred at doses that were 2.4-fold (12 U/kg) and 4-fold (20 U/kg) higher than the human dose of 300 U (5 U/kg at an average body weight of 60 kg) utilized in clinical development. The mechanism and relevance to humans is unknown. However, the applicant considered that the anatomical and injection administration differences between monkeys and humans may play a role. The monkey urethra is exceedingly narrow and monkey bladders are often contaminated with semen, which can be a nidus for stone formation. In addition, there were differences in the injection methods between monkeys (transabdominal) and humans (transrectal and transperineal) in the clinical development studies. Other adverse findings were comparable to those seen in the rat and were consistent with those following high dosing with BOTOX.

No noteworthy adverse local or systemic effects were observed in rats following repeated monthly IM doses (7 repeated injections) up to 16 U/kg. However, severe adverse systemic clinical signs were observed following high dose (16U/kg) IM repeat-dose (7 injections in 26 weeks) in monkeys. Effects on body weight and body weight gain were also noted but were considered secondary to local leg muscle atrophy and resulting subsequent immobility. There no significant cumulative effects following repeat-dosing as compared to effects seen during the single-dose studies with BOTOX®. No significant cumulative effects were observed following intraprostatic, intradetrusor, or intra-articular administration of BOTOX outside of those seen in the single-dose studies.

Reductions in fertility at doses ≥ 8U/kg were observed in male rats along with increased cohabitation periods at 16 U/kg. These effects were considered secondary to the apparent paralysis of the hind limb and resultant altered copulatory behaviour. Altered estrous cycling (prolonged diestrus) and interrelated reductions in fertility occurred in females receiving 2 doses of 16 U/kg. NOEL for BOTOX on fertility and reproduction in male and female rats was 4 and 8 U/kg, respectively. In embryofetal development studies, fetal affects (decreased body weight or reduced food intake and delayed ossification) were seen only at maternal toxic doses. No significant effects were observed in the prenatal or postnatal development studies.

BOTOX is not genotoxic, antigenic, nor had it any effect on haemolysis of whole blood. No local tolerance issues were seen when examined in rabbits.

III.5 Ecotoxicity/environmental risk assessment (ERA)

BOTOX is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. BOTOX PEC surface water value is below the action limit of 0.01 µg/L Therefore, BOTOX is not expected to pose a risk to the environment.

III.6 Discussion on the non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological effects of BOTOX have been well characterised in the non-clinical studies. Overall, the non-clinical studies are considered appropriate to support the proposed clinical use of BOTOX in the various indications sought for this product.

IV. CLINICAL ASPECTS

IV.1 Introduction

BOTOX contains purified botulinum toxin type A complex. Botulinum toxin, released from the 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 leading to denervation of the corresponding muscle or gland and therefore to temporary paralysis or anhidrosis, respectively.
Evidence suggests that BOTOX reduces or prevents local neuropeptide (NP) release and thus reduces NP-induced sensitization of peripheral nociceptive (pain conducting) nerve fibers, thereby reducing peripheral pain signals to the central nervous system. This peripheral action indirectly blocks the development of central sensitization associated with chronic pain conditions. This is presumed to be the mechanism by which BOTOX has its headache prophylaxis effect. Following intradetrusor injection, BOTOX affects the efferent pathways of detrusor activity via inhibition of acetylcholine release. In addition BOTOX may inhibit afferent neurotransmitters and sensory pathways. The clinical effects of BOTOX are largely dependent upon the anatomical site of injection
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. Recovery of sympathetic nerve endings that innervate sweat glands after intradermal injection with BOTOX has not been studied.
The following indications were approved in the first wave mutual recognition licensing procedure (MRP) application in 2000.

1. Blepharospasm, hemifacial spasm and associated focal dystonias.
2. Idiopathic rotational cervical dystonia (spasmodic torticollis).
3. Focal spasticity associated with dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients, two years of age or older.

Over the following 15 years a further 6 new indications have been approved across a number of therapeutic areas.

1. Focal spasticity of the wrist and hand in adult post stroke patients.

2. Focal spasticity of the ankle in adult post stroke patients.

3. Symptom relief in adults fulfilling criteria for chronic migraine (headaches on ≥ 15 days per month of which at least 8 days with migraine) in patients who have responded inadequately or are intolerant of prophylactic migraine medications.

4. Idiopathic overactive bladder with symptoms of urinary incontinence, urgency and frequency in adult patients who have an inadequate response to, or are intolerant of, anticholinergic medication.

5. Urinary incontinence in adults with neurogenic detrusor over activity resulting from neurogenic bladder due to stable sub-cervical spinal cord injury, or multiple sclerosis.:

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

IV.2 Pharmacokinetics

As BOTOX is administered in very small quantities and binds irreversibly to cholinergic terminals, classic kinetic and distribution studies are not feasible in humans. Consequently no specific pharmacokinetic studies have been performed with BOTOX.

IV.3 Pharmacodynamics

The pharmacodynamics of locally injected BOTOX are well established, with dose related muscle weakness resulting from the irreversible blockade of acetylcholine (ACh) release from presynaptic vesicles. Allergan has further developed and refined a published clinical pharmacology model using a surrogate marker for measuring the pharmacologic effects of BOTOX. The model (referred to as the extensor digitorum brevis [EDB] model) specifically measures changes in the amplitude of the compound muscle action potential (CMAP) obtained through nerve conduction studies. In these studies, varying doses of BOTOX (2 U to 20 U) were injected into the EDB muscle and the amplitude of the CMAP was recorded at multiple time points thereafter (Reports 191622 049; 191622 050). Data from these studies noted that peak reduction in the amplitude of the CMAP occurred between Day 9 and Day 14.

IV.4 Clinical efficacy

Blepharospasm, hemifacial spasm and associated focal dystonias

The indication for use of blepharospasm and hemifacial spasm was first approved in Ireland (RMS) in 1994. The blepharospasm development program consisted of 1 phase 3 study (191622 003 N=98) and 1 phase 2 study (BTOX 507 8051N=55), followed by extension phase. Overall these data, albeit limited, provide support for the current posology of an initial recommended dose of 1.25-2.5 Units injected into the medial and lateral orbicularis oculi of the upper lid and the lateral orbicularis oculi of the lower lid with total dosing not exceeding 100 Units every 12 weeks.

The indication for use in hemifacial spasm is supported by 2 open label phase two studies 191622-904 and BTOX-504-8051 conducted in Japan in the 1990s in a total of 97 patients. While these studies were reviewed as part of the original mutual recognition procedure (MRP) they have obvious limitations in so far they are open label and non-comparative. They do provide supportive evidence to the benefit of BOTOX in the treatment of hemifacial spasm insofar as they include a representative population, where treatment outcomes were independently assessed and derived by objective outcome measurement. The treatment effect reported is consistent across all studies. Despite the limited data supporting these indications EU and US clinical guidelines on diagnosis and treatment of primary dystonias indicate that botulinum toxin (BoNT) type A is the first-line treatment for primary cranial (excluding oromandibular) or cervical dystonia.
Cochrane reviews of botulinum toxin in blepharospasm and hemifacial spasmindicate that although there are no high quality, randomised, controlled efficacy data to support the use of botulinum toxin in the treatment for blepharospasm and hemifacial spasm existing data suggest that BoNT type A is highly effective and safe for treating blepharospasm hemifacial spasm and support its use.

Cervical dystonia.

The indication for use in cervical dystonia (spasmodic torticollis) was first approved in Ireland as a national variation in 1995 and was subsequently reregistered as part of the original MRP in 1999. All of the supporting studies for this indication were conducted in the 1990s and thus have a number of limitations. Four studies involving 247 patients were presented in the original MRP dossier in 1999 supporting introduction of a new botulinum toxin:

1) An open label study of the 'new' toxin - study 191622-004-00
2) A comparative study of 'new' versus 'old' toxin - study 191622-503
3) A comparative study of 'old' toxin versus placebo - study BTOX-140-8051
4) A validation study of the torticollis rating scale - study BTOX-147

Safety and efficacy of BOTOX in the treatment of cervical dystonia is now supported by data from over 1500 patients over 17 studies. In all the phase 3 studies maximum clinical improvement as measured by cervical dystonia-specific scoring instruments, self reported improvement, relief of pain, quality of life measures improvement was observed at between week 2 and week 6 and had fallen off by week 12. There are very limited clinical trial data supporting repeat dosing of BOTOX in this indication. In controlled clinical trials, doses have ranged from 95 to 360 U (with an approximate mean of 240 U). The maximum cumulative dose for cervical dystonia should not exceed 300 U in a 12 week injection cycle. This is reflected in the current approved posology. In controlled clinical trials, doses have ranged from 95 to 360 U (with an approximate mean of 240 U).

Paediatric cerebral palsy

This indication for use was first approved in Ireland as a national variation in 1997. During the mutual recognition procedure in 1999 this indication for use was supported by 4 studies involving just over 400 children aged 2 to 16 years with ambulatory cerebral palsy who had lower limb spasticity with an equinus deformity of the ankle.

1. OCUL-118/118R-8051(double blind placebo controlled
2. OCUL 119/119R- 8051 (follow on open label extension study.

3. OCUL-120-8051 (double-blind, multicentre, parallel group clinical study
4. BTOX- 121-8051(open label

The effectiveness of BOTOX in the treatment of children (2 to 16 years old) with cerebral palsy (CP) with equinus ankle position has been demonstrated in 2 phase 3 studies (OCUL-118-8051 and OCUL-119-8051). Study OCUL-118-8051 was a randomized, double-blind, placebo-controlled, parallel group study in 72 children with ambulatory CP.
Study OCUL-119-8051 was a long-term (39-month) open-label follow-up study that enrolled 207 patients who had completed the 3-month study OCUL-118-8051.
Two more studies, Study OCUL-120-8051 and BTOX-121-8051 were conducted to compare BOTOX to placebo-control. Study OCUL-120-8051 was a randomized, multicentre, double-blind in 2 parallel groups and Study BTOX-121-8051 was an open-label extension of the above-mentioned double-blind placebo-controlled study and aimed to monitor the long-term effect of BOTOX (2-year treatment period).
Efficacy was primarily evaluated through physician's rating of dynamic gait pattern which is an evaluation of the patient's walking performance or ambulatory ability. A dose of 4 units per kg body weight of BOTOX per effected limb up to a maximum total dose of 200U was shown to be effective.

Focal spasticity of the wrist and hand in adult post stroke patients.

This indication was authorised as part of MRP variation IE/H/001/II/003 in October 2001.
The upper limb spasticity development program consisted of 4 double blind placebo controlled Studies,
1. 191622 008,
2. BTOX 130 8051,
3. BTOX 133/134 8051,
4. BTOX 418/422 8051,

3 open label Studies

1. BTOX 428/432 8051,
2. BTOX 416 8051 and
3. OCUL 417 8051.

A total of 344 post-stroke patients with upper limb spasticity affecting the elbow and wrist flexors received 337 BOTOX injections and 117 placebo injections in four placebo controlled trials assessing the effect of BOTOX treatment on post-stroke spasticity in the upper limb (191622-008, BTOX-130-8051, BTOX-133/134-8051, BTOX-418/422-8051.) Across all four studies doses between 200 and 360 Units divided among selected muscles have been used at a given treatment session. Reduction in finger and wrist flexor tone was associated with improvements in upper limb hygiene, ability to dress, improved cosmesis and reduced pain. Intramuscular injection of BOTOX for treatment of flexor spasticity of the wrist and fingers and elbow (biceps brachii) was demonstrated to be effective up to a maximum cumulative dose of 240U and 360 U respectively.

Focal spasticity of the ankle in adult post stroke patients.

This indication was approved as part of MRP variation IE/H/001/II/087 in April 2014. It was supported by data from a single pivotal double-blind, placebo-controlled, randomised, multi-centre, phase 3 clinical study Study GSK BTX108512 (N=120) conducted in adult post stroke patients with lower limb spasticity affecting the ankle. This phase 3 study was the primary efficacy study supporting the lower limb indication. It was further supported by data from a phase 2 studies and 1 health economics study. A subpopulation was identified in the phase 2 study (Study BTOX-702-8051) that closely resembled the population and treatment paradigm utilized in the pivotal phase 3 study, so this was considered a supportive study. Similarly, a relevant subpopulation was identified in the pharmacoeconomic Study AGN/HO/SPA/001-191622, so this study was also considered a supportive study.
The pivotal phase 3 Study BTX108512 study was conducted exclusively in Japanese patients with Modified Ashworth Scale (MAS) ≥ 3 who were on average 6.5 years post-stroke. A dose of 300 Units divided among 3 muscles (Soleus, Tibialis Posterior and Gastrocnemius muscle) was shown to be effective in reducing spasticity based on the modified Ashworth scale (MAS) ankle score, which was supported by a key secondary endpoint based on the clinical global impression (CGI) by the investigator. This study complies with the Guidance on Ethnic Factors in the Acceptability of Foreign Clinical Data (European Agency for the Evaluation of Medicinal Products [EMEA], 1998) and is in accordance with "Points to Consider on Application with 1. Meta-Analyses; 2. One Pivotal Study" (EMEA, 2001). Findings from the Japanese Study BTX108512 can be generalized to the EU population. The 2 additional studies provided further evidence that the reduction in muscle tone demonstrated in patients with lower limb spasticity post stroke in the target stroke population (MAS≥3) is associated with modest but clinically meaningful improvement in function (active and passive) and a reduction in symptoms for patients.
Intramuscular injection BOTOX into the Soleus, Tibialis Posterior and Gastrocnemius muscles in patients with lower limb spasticity post stroke, in the target stroke population (MAS≥3), was demonstrated to be effective up to a maximum dose of 300U.

Hyperhidrosis

This indication was originally approved in 2002. As the addition of this new indication for BOTOX fell within a different therapeutic area requiring a new ATC code it was submitted as a new application (line extension) to the Reference Member State in September 2002 under Regulation (EC) No 541/95 Annexe II. It was submitted as an abridged dossier.
The rationale for this indication was based on the pharmacological effect of botulinum toxin A locally inhibiting the release of acetylcholine from the autonomic sympathetic nerve fibres innervating eccrine sweat glands.

The primary evidence of efficacy supporting the hyperhidrosis indication for BOTOX is based on efficacy data derived from four studies. One phase 3 double blind randomised vehicle controlled study and three open label studies.

1. Study 191622 505
2. Study 191622 506
3. Study 191622-513 (2007)
4. Study 191622 075

The original clinical development plan comprised a single double blind vehicle controlled study with 320 subjects conducted over 16 weeks followed by an open label follow on study with up to three treatments over 12 months.
The pivotal study was well designed with a clearly defined primary efficacy endpoint. The primary endpoint chosen was a quantitative variable, which had been shown to have good intra and inter-rater correlation and although not routinely used in clinical practice, demonstrated a clear method for quantifying sweat production. The 25% point difference between the active treatment and placebo was selected as a clinically relevant endpoint. Bearing in mind that there is a high placebo response to this treatment (20% - 30%) a further 25% reduction in sweat production was considered to be a reasonable response to treatment.

Botulinum toxin type A at a dose of 50U per axilla was very effective at reducing the quantity and area of sweat production with a consistently high mean absolute change from baseline in sweating achieved from 1 month post treatment 1 (-114.68 mg) and continued through the study to 1 month post treatment 8 (-224.52 mg). At week 4, 190/233 (81.5%) of subjects in the BOTOX treatment group had a >70% reduction in sweat production compared to only 14/75 (18.7%) of subjects in the vehicle treatment group. At 16 weeks 81.8% of subjects in the BOTOX treatment group were responders compared to 20.5% of subjects in the vehicle treatment group. The predetermined level of clinical significance of a 25% point difference between the two treatment groups was exceeded at all visits (at the primary endpoint of week 4 the percentage difference was 57.9%). The efficacy findings were consistent across all primary and secondary end-points. The improvement in quality of life endpoints (SF-12 and PGA) reflected the reduction in sweat production noted following injection with Botulinum toxin type A and supported the applicant's claims of subjective improvement following treatment with Botulinum toxin type A. The trend in the quality of life (QoL) data across all scales and across all analyses is consistent and supports a positive effect of sweat reduction on quality of life.

The follow on open label study was primarily designed to assess safety data. It was not powered to demonstrate efficacy. However, the results in the open label study were consistent with those seen in the BOTOX treated group in the double blind study. The response rates of repeat botulinum toxin type A injections are consistent with the response rates reported in the double blind study. A high responder rate was seen in this study following treatment with BOTOX (91.8% (134/146) following the first treatment and 88.2% (45/51) following the second treatment). These results were considered strongly supportive but not confirmatory of the efficacy of repeat botulinum toxin type A injections.

This data also suggested that the effect of BOTOX 50U has a reasonable duration of effect and did not diminish over repeat doses. However, the number of re-treated patients was limited (123 received a second dose, of whom only 30 received a third one).
Axillary intradermal BOTOX treatments were generally well tolerated. The most common clinically significant treatment-related adverse event across all studies was increased non-axillary sweating which was reported overall in less than 5% of participants.
During the original procedure the RMS considered that there was a positive benefit risk ratio in relation to this new indication. Three CMSs had major objections two of whom maintained their major objections throughout the procedure resulting in referral of the application to arbitration.
The then CPMP was asked to reassess the risk –benefit ratio of BOTOX for the proposed indication with particular reference to suitability of the dose elected (50U/axilla), the numbers of patients treated, the number of repeat treatments administered across the two studies, the duration of follow –up and the adequacy of the safety database to support repeat intermittent use of this product for the treatment of hyperhidrosis.
The arbitration procedure concluded positively with the applicant being requested to provide further long-term post-marketing (at least 2 years, corresponding to a mean of 3-4 doses per patient) prospective data in a sufficient cohort of patients allowing to confirm that 50U is a dose with a favourable benefit/risk profile on a long-term basis . Study 191622-513 fulfilled this post approval commitment and was evaluated as part of variation IE/H/001/II/043.

The efficacy data presented in study 191622-075, a non-comparative open label study of BOTOX for primary hyperhidrosis of the axillae in adolescent subjects (12-17 years of age) was reviewed as part of variations IE/H/0113/001/II/053 and IE/H/0113/001/II/054. It was concluded that there was insufficient evidence to support an indication for use in adolescents. However, in line with the SmPC note for guidance suitable wording that summarised the available paediatric data was agreed for inclusion in section 4.2, 4.8 and 5.1 of the SmPC.
The efficacy of intradermal injection of BOTOX 50U per axilla in the management of severe axillary hyperhidrosis that hasn't responded to topical agents has been adequately demonstrated.

Chronic migraine

The indication for use in symptomatic relief of chronic migraine was approved as part of MRP variation IE/H/001-003/II/061 in August 2011 following a CMDh referral procedure. The pivotal data in this application were 2 phase 3 clinical phase 3 studies, 191622-079 and 191622-080, conducted between 2006 and 2008 involving 1364 patients. Patients who during a 28-day baseline period had at least 4 episodes and ≥ 15 headache days (with at least 4 hours of continuous headache), with at least 50% of headache days being migraine/probable migraine days were recruited to the study.
Doses of 155 U to 195 U administered intramuscularly to 31 to 39 injection sites, respectively, across 7 head and neck muscle groups were found to be effective in reducing frequency of headache days and frequency of headache episodes in patients who have previously treated with prophylactic medication. The key efficacy findings from the pooled analysis of Studies 079 and 080 were a 1.9 reduction in headache days against a baseline rate of 19 headache days and a reduction in frequency of headache episodes of 0.3 against a backdrop of 12 headache episodes per 28 day period.A reduction in total cumulative hours of headache on headache days has also been demonstrated. Across both studies approximately 50% of patients had a reduction in headache days. Impact on quality of life was also measured using the HIT-6 tool. BOTOX patients reported a decrease in their HIT-6 score (i.e. an improvement in the indicators included in the assessment) of -4.8 compared with -2.4 for placebo.
During the original procedure concerns regarding the clinical relevance of key efficacy findings from the pooled analysis of studies 079 and 080 were not adequately addressed and a CMDh referral was initiated. The key issues discussed during the referral were the heterogeneity of the Allergan defined chronic migraine study population, inconsistent outcomes in various study subpopulations, the potential for unblinding effects of BOTOX due to its muscle relaxant effect and lack of supporting evidence of efficacy of BOTOX in patients with episodic migraine (and tension headache) and the lack of convincing dose-finding data and a clear rationale for the proposed treatment paradigm (fixed dose-fixed site vs. follow-the–pain). These issues were satisfactorily addressed by the applicant during the referral procedure and the procedure concluded positively.
Due to the specialised nature of the diagnosis and management of chronic migraine, the small treatment effect and dose related side effect profile, BOTOX is restricted to use under the supervision of neurologists who are experts in the treatment of chronic migraine

The final approved indication was for the symptomatic relief in adults fulfilling criteria for chronic migraine (headaches on ≥ 15 days per month, of which at least 8 days are with migraine) in patients who have responded inadequately to or are intolerant of prophylactic migraine medications.

Overactive bladder (OAB)

The indication for use in idiopathic overactive bladder with symptoms of urinary incontinence, urgency and frequency in adult patients who have an inadequate response to, or are intolerant of, anticholinergic medication was approved as part of MRP variation IE/H/001-003/II/077 in Dec 2012.
Two pivotal double-blind, placebo-controlled, randomised, multi-centre, 24 week Phase 3 clinical studies (191622-095 and 191622-520) were conducted in patients with overactive bladder with symptoms of urinary incontinence, urgency and frequency. A total of 1105 patients, whose symptoms had not been adequately managed with at least one anticholinergic therapy (inadequate response or intolerable side effects), were randomised to receive either 100 Units of BOTOX (n=557), or placebo (n=548). Significant improvements compared to placebo were observed for number of episodes of urinary incontinence, the daily frequency of micturition, urgency and nocturia episodes. Volume voided per micturition was also significantly higher. The improvement in urinary parameters was supported by improvements in the Treatment Benefit Scale (TBS), improvements in Incontinence Quality of Life (I-QOL) domains and all multi-item King's Health Questionnaire (KHQ) domains.
The efficacy of intradetrusor injection of 100U of BOTOX in OAB has been adequately demonstrated in patients who are not adequately controlled with anticholinergics.

Neurogenic detrusor over activity (NDO)

The indication for use in urinary incontinence in adults with neurogenic detrusor over activity resulting from neurogenic bladder due to stable sub-cervical spinal cord injury, or multiple sclerosis was approved as part of MRP variation IE/H/001-003/II/064 in Aug 2011.
This application was supported with data from two well designed double-blind, placebo-controlled, randomised, multi-centre Phase 3 clinical studies conducted in patients with urinary incontinence due to neurogenic detrusor overactivity who were either spontaneously voiding or using catheterisation. A total of 691 spinal cord injury or multiple sclerosis patients, not adequately managed with at least one anticholinergic agent, and were enrolled. Participants were randomised to receive either 200 Units (n=227), 300 Units of BOTOX (n=223), or placebo (n=241).
Based on the data presented the applicant has demonstrated that both 200U and 300U of BOTOX injected into the detrusor musculature of patients in patients with NDO who have failed anticholinergic therapy has beneficial effects in terms of clinical and urodynamic outcomes. Both doses (200U and 300U) were associated with significant decreases in incontinence episodes, improved urodynamics and QoL parameters. Dose-dependent increases over the 300U and 200U BOTOX doses were noted for many of the clinically significant adverse.
Overall, the benefit risk profile was considered more favourable for the dose of 200 U BOTOX given the significant and clinically relevant treatment benefit, as measured by improvement in urinary incontinence, urodynamic parameters , patient-reported quality of life and the favourable safety profile seen with the 200U dose. The efficacy of BOTOX in NDO has been adequately demonstrated in patients with sub-cervical spinal cord injury, or multiple sclerosis who are not adequately controlled with anticholinergics and who are willing and able to initiate catheterisation post-treatment if required.

IV.5 Clinical safety

Blepharospasm, hemifacial spasm and associated focal dystonias

Safety data for blepharospasm and hemifacial spasm were compiled from controlled clinical trials and open-label studies involving 1732 patients. The adverse event profile for the blepharospasm population were evaluated in studies 1) 191622-003 2) BTOX-507-8051 and for
hemifacial spasm population; 1) BTOX-504-8051 (22-Week and long Term Observation Studies)
2) 191622-904. Across all studies the commonest reported treatment related side effects were eyelid ptosis, ecchymosis, irritation, face oedema, punctate keratitis, lagophthalmos, dry eye, photophobia, eye irritation and increase in lacrimation.

Cervical dystonia

The safety profile of BOTOX for the treatment of cervical dystonia (spasmodic torticollis) was investigated in 4 Phase 3 studies (191622-503, BTOX-140-8051, BTOX-707-8051/9060, 109/93); and 5 Phase 2 studies (191622-004, 191622-906, BTOX-503-8051, BTOX-505-8051, and
OCUL-712-8051); 7 supportive studies (OCUL-101-8051, OCUL-102-8051, OCUL-103-8051,

OCUL-104-8051, OCUL-105-8051, OCUL-106-8051 and OCUL-108-8051); and 1 scale reliability study (BTOX-147-0000). The most frequently occurring and clinically significant side effects were pain, dysphagia and local weakness. Additional warnings have been included in section 4.4 outlining the risks of dysphagia. Dysphagia in cervical dystonia is included as an important identified risk in the current risk management plan for BOTOX. Other commonly reported adverse reactions were rhinitis, upper respiratory tract infection, dizziness, hypertonia, hypoaesthesia, somnolence, headache, dry mouth, nausea, musculoskeletal stiffness, soreness, asthenia, influenza-like illness, malaise.

Paediatric cerebral palsy

At the time of approval the safety data for paediatric cerebral palsy (PCP)/lower limb spasticity associated with PCP were compiled from 4 studies, two double-blind, randomized, placebo controlled studies and two open-label extension study involving approximately 412 patients treated with BOTOX. OCUL-118-8051: OCUL-119-8051; OCUL-120-8051 and BTOX-121-8051.
The commonest adverse reactions were viral infection, ear infection, somnolence, gait disturbance, paraesthesia, rash, myalgia, and muscular weakness, pain in extremity, urinary incontinence, fall, malaise, injection site pain, and asthenia. No serious BOTOX-related adverse events were reported during the original review. BOTOX was well tolerated and had an acceptable safety profile at a dose of 4.0 U/kg body weight administered as a divided dose through single injections into the medial and lateral heads of the affected gastrocnemius muscle.
Review of post marketing safety data over the period since this indication has been licensed has resulted in a number of significant safety reviews. Section 4.4 of the current BOTOX SmPC highlights in very strong terms that extreme caution should be exercised when treating paediatric patients who have significant neurologic debility, dysphagia, or have a recent history of aspiration pneumonia or lung disease. Treatment in patients with poor underlying health status should be administered only if the potential benefit to the individual patient is considered to outweigh the risks. Death following treatment with BOTOX is included as an important potential risk in the current risk management plan and remains under review. Treatment with BOTOX into the gastrocnemius muscle is effective and possesses an acceptable safety profile if used at the correct dose by experienced practitioners for the treatment of equinus foot deformity due to spasticity in paediatric cerebral palsy patients however it should be used with caution and the risks need to be careful weighed against the possible benefits.

Focal spasticity of the wrist and hand in adult post stroke patients.

At the time of approval the safety profile of BOTOX was investigated in 4 double-blind, placebo-controlled Studies (191622-008 [pivotal study], BTOX-130-8051, BTOX-133/134-8051, BTOX-418/422-8051); and 3 open-label Studies (OCUL-416-8051, BTOX-417-8051, and BTOX-428/432-8051). 18.2% of events were reported as treatment related across the double blind and open-label studies. The most commonly reported adverse reactions were muscular weakness 5.5%, injection site pain 3.6%, injection site haemorrhage, ecchymosis and hypertonia 2.7%, arm pain, asthenia, hypoaesthesia and incoordination 1.8%. It was found that BOTOX was generally well tolerated and was safe for use at doses between 200 and 240 Units divided among selected upper limb muscles at a given treatment session

Focal spasticity of the ankle in adult post stroke patients.

At the time of approval the safety profile of BOTOX for treatment of lower limb spasticity in adult post-stroke patients was evaluated in 8 studies involving 625 patients with lower limb spasticity treated with BOTOX. (3 double-blind, placebo-controlled (DBPC) studies with open-label follow-up: BTX108512, BTOX-702-8051, and AGN/HO/SPA/001-191622, 3 DBPC studies: BTOX-138/139-8051, 191622-501, and 191622-030, 1 double-blind extension study (of 191622-501): 191622-502, 1 open-label study: 191622-911). Treatment-related adverse event rates during DBPC exposure in the studies were 14.5% in the BOTOX group and 12.1% in the placebo group. The incidence of fall was 5.9% and 5.3% in the BOTOX and placebo groups, respectively. Arthralgia, oedema peripheral, musculoskeletal stiffness, and rash were commonly occurring adverse drug reactions. Single or repeated exposure to BOTOX at doses ranging from 25 to 800 U was not associated with systemic effects. No patient tested positive for neutralizing antibodies. It was concluded that BOTOX was generally well tolerated and was safe for use at doses of 300U divided between the Gastrocnemius, Soleus and Tibialis Posterior muscles at a given treatment session.

Chronic migraine

The safety profile for BOTOX for the indication of 'Symptom relief in adults fulfilling criteria for chronic migraine (headaches on ≥15 days per month of which at least 8 days with migraine) in patients who have responded inadequately or are intolerant of prophylactic migraine medications' was based on integrated review of 11 studies comprising a total of 3,235 patients that supported the application. The primary evidence of safety that supported this indication was based on pooled safety data from 2 pivotal phase 3 studies conducted in patients with chronic migraine, studies 191622-080 and 191622-079. Additional

evidence of safety in the chronic migraine population is based on pooled safety data from the phase 2 studies, 191622-038 and 191622-039 and safety results from 7 exploratory phase 2 studies in patients with episodic migraine.
The following Adverse drug reactions were identified : neck pain (8.7%), headache (4.7%),eyelid ptosis (3.6%), musculoskeletal stiffness (3.6%), migraine (3.8%), muscular weakness (3.5%), injection site pain(3.3%), myalgia(3.1%), musculoskeletal pain (2.6%), facial paresis (2.2%),muscle spasms (1.9%) , muscle tightness (1.3%) , pruritus (1.0%), rash (1.0%).
Multiple treatments with BOTOX at doses of 155 U up to 195 U administered IM every 12 weeks were considered to be safe and well tolerated. During the MRP variation for the BOTOX Chronic Migraine indication, Allergan made a commitment to expand a UK observational study (a non-interventional post authorisation safety study [PASS]) evaluating dysphagia and migraine (intractable) to include additional EU countries (Germany, Spain, and Sweden) to broaden the relevance of the study to different health care settings across Europe. This Post-Authorisation Safety Study titled 'BOTOX Prophylaxis in Chronic Migraine: Post-authorization Observational Study' was completed in May 2015. A total of 1,168 patients were enrolled. The final study report is pending.

Hyperhidrosis

The safety profile for BOTOX for the indication of persistent severe primary hyperhidrosis of the axillae, which interferes with the activities of daily living and is resistant to topical treatment was investigated in two phase 3 studies (191622-505 and 191622-506) and two phase 4 studies (191622-513 and 191622-075). Over the whole study period of the two phase three studies, 10/207 subjects (4.8%) reported adverse drug reactions. The most common treatment-related adverse event was perceived increased non-axillary sweating, which was seen in 6 subjects (2.9%). Muscular weakness was reported in 1% (2/207). Asthenia, flu syndrome, injection site pain, nausea, hypertonia, paraesthesia, skin discolouration and stinging sensation were all reported in 1 (0.5%) subject. In all these studies, patients received 50 Units (U) per axilla for a total dose of 100 U BOTOX per patient per treatment.It was concluded that BOTOX was generally well tolerated and was safe for use at doses of 50U per axilla for the second line treatment of severe persistent hyperhidrosis.

Idiopathic overactive bladder (OAB)

The primary evidence of safety that supported this target indication is based on pooled safety data from the following studies conducted in patients with idiopathic OAB and urinary incontinence:
Two completed double-blind, placebo-controlled, pivotal phase 3 clinical studies (191622-095 and 191622-520) a long-term, open-label, extension Study (191622-096) and a completed double-blind, placebo-controlled, phase 2 clinical study (191622-077).
A total of 1242 patients received study drug at doses of 100 U BOTOX, 150 U BOTOX, or placebo. In total 607 patients received 100 U BOTOX and 585 patients received placebo during the first treatment cycle. In addition, 50 patients in the phase 2 Study, 191622-077, received 150 U BOTOX. However, the incidences of adverse drug reactions (Adverse drug reactions) are based on the pivotal phase 3 studies only (i.e., the placebo-controlled pivotal study safety population), which consists of 1094 patients, of whom 552 patients received 100 U BOTOX during the first treatment cycle. During the complete placebo-controlled treatment cycle 1, the following adverse drug reactions with 100 U BOTOX were reported: urinary tract infection (25.5%), bacteriuria (8.0%), dysuria (10.9%), urinary retention (5.8%), residual urine volume (3.4%), and pollakiuria (2.0%). Significant increases in PVR urine volume from baseline were observed in the BOTOX treated group. The increased reporting rate for UTIs following treatment with BOTOX was associated with an elevation in PVR and initiation of CIC. There was no evidence of distant spread of toxin and no development of neutralising antibodies. From a safety perspective increased risk of UTI, PVR urine volume, urinary retention and the need for CIC were identified as significant concerns. An increased incidence of UTI was identified in patients > 65. The SmPC was updated to include warnings that BOTOX should be administered by physicians who are experienced in the assessment and treatment of bladder dysfunction (e.g., urologists and urogynaecologists) For the management of urinary incontinence and to highlight the fact that the incidence of urinary tract infection was higher in elderly patients. It was concluded that BOTOX was generally well tolerated and safe for use in the management of idiopathic overactive bladder with symptoms of urinary incontinence, urgency and frequency in adult patients who have an inadequate response to, or are intolerant of, anticholinergic medication

Neurogenic Detrusor Overactivity (NDO)

The applicant presented a pooled safety analysis of the 5 of the 6 studies submitted in this application. A total of 843 patients received study drug in the 6 clinical studies conducted in patients with NDO.
The overall adverse event rates for the BOTOX 200U and 300U were similar 80.5% and 79.6% compared with 72. % for placebo. However the reporting rates for the more commonly occurring clinically significant adverse events (urinary tract infection (UTI) and urinary retention) did increase with increasing dose of BOTOX. The proportion of treatment-related adverse events and serious adverse events were higher in the 300U treatment group across all analyses. Dose dependent increases in UTI and urinary retention were primarily observed in the multiple sclerosis (MS) population in patients who were not using clean intermittent catheterization (CIC) prior to starting the study and who had a post void residual (PVR) urine vol. ≥200mls. There

was an increased incidence of PVR and urinary retention, use of CIC and catheterisation for urinary retention in the MS subgroup but not in the spinal cord injury (SCI) group.
The following additional adverse drug reactions were reported with an incidence of ≥ 1% during the complete treatment cycle 1: constipation (4.2%), muscular weakness (3.8%), fall (3.1%), gait disturbance (2.7%), muscle spasm (2.3%), and bladder diverticulum (1.1%).
Haematuria (3.8%) dysuria (2.3%) and autonomic dysreflexia 1.5% were identified as injection procedure related adverse drug reactions.
In advance of the approval of (IE/H/0113/001-.003/II/064) for the management of 'urinary incontinence in adults with neurogenic detrusor overactivity resulting from neurogenic bladder due to stable sub-cervical spinal cord injury, or multiple sclerosis' (approved via the Mutual Recognition Procedure on 5th August 2011) the MAH accepted to undertake 5 post-approval commitments.

1. To further evaluate the BOTOX injection technique/paradigm for the indication of urinary incontinence associated with NDO

2. To explore efficacy at a lower dose (i.e., < 200U BOTOX) in MS patients

3. To further evaluate the use of antibiotic prophylaxis in the treatment of urinary incontinence associated with NDO with BOTOX

4. To monitor MS relapse/exacerbation, spread of toxin and pyelonephritis in subsequent PSURs

5. To undertake focused user testing of the PIL for the new indication

Study 191622-117 (EudraCT Number: 2012-000957-30)) is being conducted by the MAH to further evaluate the BOTOX injection technique/paradigm for the indication of urinary incontinence associated with NDO, to explore efficacy at a lower dose (i.e., < 200U BOTOX) in MS patients and to provide general guidance for the treating physician on antibiotic prophylaxis for patients receiving intradetrusor BOTOX injections. This study is currently ongoing and is due for completion in 2015.
Focused user testing for this indication was satisfactorily completed on 30.08.2012.
There was no evidence of distant spread of toxin and no development of neutralising antibodies. The safety profile is consistent with the local effect of BOTOX on the bladder. The safety profile of BOTOX 200U for the indication of urinary incontinence associated with NDO has been adequately characterized during the clinical development program.

Adverse events of special interest across all indications

For the majority of indications safety assessments included comprehensive reviews of adverse events of special interest (AEs indicative of local and remote spread of effect of toxins, and hypersensitivity, antibody data). These extensive integrated analyses have resulted in a comprehensive review of safety data from clinical trials and have adequately characterised the focal, general and procedure related adverse events associated with each indication. Spread of toxin was the subject of a PhVWP review in 2007.This resulted in a common definition of spread of toxin being adopted across all manufacturers. Terms for a common definition are referenced in a Sentinel Event List. Distant spread of toxin is reviewed as a special safety topic in each PSUR. Post-marketing reports of possible distant effects from the site of injection have been very rarely reported in adults and paediatric patients with comorbidities, predominantly paediatric patients with cerebral palsy who received >8 U/kg. Extreme caution should be exercised when treating patients who have significant neurologic debility, dysphagia, or have a recent history of aspiration pneumonia or lung disease.
Serious and/or immediate hypersensitivity reactions such as anaphylaxis and serum sickness have been rarely reported, as well as other manifestations of hypersensitivity including urticaria, soft tissue edema, and dyspnoea. However the risk of developing hypersensitivity in patients treated with botulinum toxin A is considered minimal. Antibody testing has been performed over the last few years in clinical trial subjects in a range of indications. The number of patients that developed antibodies to BOTOX was minimal.

Postmarketing data

Postmarketing spontaneous reports were presented and discussed in the regular safety updates provided by the sponsor to the regulatory authorities since 1999. Twenty-one (21) PSURs have been reviewed since the original MRP in 1999 resulting in regular updates to the SmPC. A number of significant safety concerns have been identified during routine postmarketing pharmacovigilance: Potential distant spread of toxin, deaths in adults and children with underling neurological problems, off-label use, and potential reconstitution errors and have resulted in updates to the SmPC. These safety issues continue to be actively monitored through the risk management plan (RMP).
This has resulted in a number of safety updates to section 4.4 and 4.8 of the SmPC.

A number of variations to amend the warnings and side effects profile of BOTOX following reviews of postmarketing data have been completed since this product were first licensed. (MRP variations IE/H/0113/001-003/011, 016, 029, 039, 043, 044, 053, 054, 067, 075, 083, 086, 092.) The overall safety profile of BOTOX is in accordance with the known safety profile of other botulinum toxin A containing preparations.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the key safety concerns, pharmacovigilance activities and risk minimisation measures designed to identify, further characterise, and prevent or minimise the risks relating to the use of BOTOX.

Summary table of safety concerns as approved in RMP

Important Identified Risks	**All Indications**
	Pre-existing Neuromuscular Disorders
	Immunogenicity, Drug Resistance, and Antibody Formation
	Distant Spread of Toxin
	Neurology Indications
	Dysphagia in Cervical Dystonia and in Chronic Migraine patients
Important Potential Risks	**All Indications**
	Medication Error (Reconstitution With Lidocaine)
	Bladder Disorder Indications
	Pyelonephritis in Patients With Bladder Disorders With Urinary Incontinence
Missing Information	**All Indications**
	None

Summary of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
Important Identified Risks		
All Indications		
Pre-existing neuromuscular disorders	Routine risk minimisation measures: Routine risk communication: BOTOX® and VISTABEL® SmPC section 4.4, where advice is provided for use with caution in this population. Routine risk minimisation activities recommending specific clinical measures to address the risk: BOTOX® and VISTABEL® PL section 2, where advice is given for patients Other routine risk minimisation measures beyond the Product Information: Pack size: single use vial Legal status: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities only
Immunogenicity, drug resistance, and antibody formation	Routine risk minimisation measures: Routine risk communication: Listed in the BOTOX® and VISTABEL® SmPC section 4.4 Listed in the BOTOX® and VISTABEL® PL section 2 Routine risk minimisation activities recommending specific clinical	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection, as follows: • Detachable sticker to support traceability of the productAdditional

	measures to address the risk: • Recommendation to analyse the formation of toxin-neutralising antibodies in case of treatment failure is included in the BOTOX® and VISTABEL® SmPC section 4.2. • Recommendation not to exceed the dosages and frequencies of drug administration due to formation of neutralising antibodies is included in BOTOX® and VISTABEL® SmPC section 4.4.Other routine risk minimisation measures beyond the Product Information:Pack size: single use vialLegal status: Prescription only medicine Additional risk minimisation measures: None	pharmacovigilance activities:None
Distant spread of toxin	Routine risk minimisation measures Routine risk communication: Listed the BOTOX® SmPC sections 4.4 and 4.9, and VISTABEL® SmPC sections 4.4, 4.8, and 4.9 Listed in the BOTOX® PL sections 2 and 3 Listed in the VISTABEL® PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation not to exceed the dosages and frequencies of drug administration due to potential of distant spread of toxins is listed BOTOX® SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: Pack size: single use vial Legal status: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection, as follows: • Adverse Event Report Form to follow-up on case reports • Monitoring potential "spread of toxins reaction" • Monitor reactions reported in ongoing clinical trials by using common definition of distant spread of toxin reactions across manufacturers (based on MedDRA terms) • Common definition of distant spread of toxin reactions across manufacturersAdditional pharmacovigilance activities:None
Neurology Indications		
Dysphagia in cervical dystonia and in chronic migraine patients	Routine risk minimisation measures Routine risk communication: Listed in the BOTOX® SmPC sections 4.4 and 4.8 Listed in the BOTOX® PL sections 2 and 4 Routine risk minimisation activities	Routine pharmacovigilance activities only

	recommending specific clinical measures to address the risk: Recommendation for dose limiting in cervical dystonia patients with risk of dysphagia is included the BOTOX® SmPC sections 4.2 and 4.4 Other routine risk minimisation measures beyond the Product Information: Pack size: single use vial Legal status: Prescription only medicine Additional risk minimisation measures: None	
Important Potential Risks		
All Indications		
Medication error (reconstitution with lidocaine)	Routine risk minimisation measures Routine risk communication: Not applicable Routine risk minimisation activities recommending specific clinical measures to address the risk: Reconstitution instructions are provided in the BOTOX® SmPC sections 4.2 and 6.6 and in the VISTABEL® SmPC section 6.6. Other routine risk minimisation measures beyond the Product Information: Pack size: single use vial Legal status: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities only
Bladder Disorder Indications		
Pyelonephritis in patients with bladder disorders with urinary incontinence	Routine risk minimisation measures Routine risk communication: Not applicable Routine risk minimisation activities recommending specific clinical measures to address the risk: BOTOX® SmPC section 4.2 and BOTOX® PL section 2, where recommendations are provided for use of prophylactic antibiotics. Other routine risk minimisation measures beyond the Product Information: Pack size: single use vial Legal status: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection, as follows: • Targeted questionnaire to monitor post marketing data that has been utilized since April 2011Additional pharmacovigilance activities:None

Additional Pharmacovigilance Activities

Study short name and title (191622-146) Observational Post-authorisation Safety Study of VISTABEL® for the				

Treatment of Crow's Feet Lines				
Rationale and study objectives	**Study design**	**Study population**	**Milestones**	**Due date**
Post-authorisation Safety Study to assess the long-term safety profile of VISTABEL® for the treatment of CFL Ongoing Category 3 safety study	Observational, prospective, multicentre	Adult patients with CFL	Registration in EU PAS Register	Q1/2017
			First patient enrolled	12/2016
			Year 1 Progress Report submitted to the Agence Nationale de Sécurité du Médicament (ANSM)	29/03/2018
			Last patient enrolled	10/12/2018
			Last patient out	15/03/2021
			Final study report available	26/07/2021

Periodic Safety Update Reports (PSURs)
The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under article 107c (7) of Directive 2001/83//EC and published on the European medicines web portal.

IV.7 Discussion on the clinical aspects

The applicant has provided a comprehensive overview of the 9 currently approved indications for use for BOTOX including the three indications registered as part of the original MRP in 1999 and the 6 indications for use that have been authorised since then.
For some of the older indications (Cervical dystonia, blepharospasm and hemifacial spasm) authorised pre 2000) the data sets are limited. No new studies have been conducted by the applicant in these indications. However the clinical use of BOTOX in these approved indications is well established and is reflected in a number of international clinical guidelines.
For some of the indications (e.g. paediatric cerebral palsy) there has been very little new research conducted by the applicant since the time of first approval and thus there is limited information regarding patient selection, definition of appropriate individual goals, optimal timing of treatment, dosing and dilution, accuracy of injection technique and measurement outcomes. Similar concerns arose during assessment of more recent indications (NDO, Chronic Migraine, Lower limb spasticity in adults). Additional information of this nature would further enhance optimal use of this treatment in the approved indications.

For the majority of indications, safety assessments included comprehensive reviews of all adverse events including adverse events of special interest (AEs indicative of local and remote spread of effect of toxins, and hypersensitivity, antibody data). These extensive integrated analyses have resulted in a comprehensive review of safety data from clinical trials and have adequately characterised the focal, general and procedure related adverse events associated with each indication.
Postmarketing spontaneous reports were presented and discussed in the regular safety updates provided by the sponsor to the regulatory authorities since 1999. 21 PSURs have been reviewed since the original MRP in 1999. A number of significant safety concerns have been identified during routine postmarketing pharmacovigilance (e.g. Potential distant spread of toxin, deaths in patients and children with underling neurological problems, off-label use etc) and have resulted in updates to the SmPC. These safety issues continue to be actively monitored through the RMP.
No new efficacy or safety concerns were identified during the course of the repeat use procedure.

V. OVERALL CONCLUSIONS

V. User consultation

1) The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. Overall conclusion, benefit/risk assessment and recommendation

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of BOTOX 50, 100 and 200 Allergan units powder for solution for injection.

From a clinical perspective sufficient clinical data has been submitted to support the therapeutic efficacy of the currently approved indications. No new safety concerns have been identified for any of the approved indications.

The benefit risk is therefore considered to be positive for all of the approved indications.

VI. REVISION DATE

August 2023

VII. UPDATES

Procedure number*	**Scope**	**Product Information affected**	**Date of end of procedure**	**Approval/ non approval**	**Summary/ Justification for refuse**
IE/H/0113/001-003/II/097/G	Update of SmPC and PIL in line with commitments made during the Repeat-Use MRP	Update 4.2 & 6.3 section of the SmPC. Consequential updates to the PIL and TIL. Updates to section 2 and 3 of the PIL	21.01.2016	Approval	
IE/H/xxxx/WS/026	Update of SmPC in line with CCDS v18.0:	Updates to sections, 4.2, 4.8 & 5.1 of the SmPC with consequential updates to sections 1 the Package Leaflet (PL)	16.02.17	Approval	
IE/H/113/II/113/G	Update to Product Information to align with Company Core Data Sheet (CCDS) v19.0 and expansion of description of Pharmaceutical Form: IE/H/0113/001-003/II/113/G	Update to section 4.8 with a consequential update to the PIL Update to Section 3 of the SmPC with a consequential update to the PIL	12.09.18	Approval	
UK/W/0100/pdWS/001	Incoming Article 45 Paediatric Study review	Update to section 4.2 to	11.05/2018	Concluded	

	(UK RMS for this procedure)	clarify the paediatric indications in line with the SmPC guideline.			
IE/H/xxxx/WS/062	Modification of the indication treatment of focal spasticity of the lower limb including ankle and foot and to update the associated posology and administration information	Updates to sections 4.1, 4.2, 4.4, 4.8, 5.1 & 5.3 of the SmPC with consequential updates to sections 1, 2, 3 & 4 of the Package Leaflet (PL)	12.10.2018	Approval	
IE/H/xxxx/WS/072	Update to section 4.2 Following completion of the Article 45 paediatric work-sharing procedure UK/W/0100/pdWS/001	Section 4.2 with consequential updates to the PIL	7.3.2019	Approval	
BOTOX MRP Renewal IE/H/0113/001/R/003 IE/H/0113/002-3/R/002		Renewal was granted with unlimited validity Common Renewal Date: 06/07/2020	22.5.2020	Approval	
IE/H/xxxx/WS/111	'Eyelid oedema' included as an ADR for the chronic migraine indication in line with the outcome of the assessment of botulinum toxin a, PSUR 27 -PSUSA/00000426 /201812,	Section 4.8 of the SmPC and section 4 of the PIL	5.8.2020	Approval	
IE/H/xxxx/WS/110	1) the addition of upper limb spasticity 2) the expansion of the lower limb spasticity from equinus foot deformity for paediatric population	Updates to sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.3 of the SmPC and consequential updates to sections 1, 2, 3 & 4 of the Package Leaflet (PL)	21.12.2020	1) non-approval 2)Approval	The indication for use in <u>upper limb</u> paediatric spasticity was refused on the grounds that clinical relevance of the reduction in muscle tone in terms of improvement in function for the upper limb had not been demonstrated and that the design of the pivotal study treating only one UL muscle group did not support the assessment of functionality. Study results were included in

					section 5.1.
IE/H/xxxx/WS/111	Update to section 4.8	Section 4.8 and PIL	10.7.2020	Approval	
CRN00CNKP	MA Transfer	SmPC section 7, 8 and 10. Package Leaflet New MA Holder: AbbVie Limited Citywest Business Campus Co Dublin 24 Ireland New PA number: PA1824/017/003	01.04.2022		
IE/H/xxxx/WS/166	Variation request toexpand the adult upper limb spasticity indication to include dosingguidance for 12 additional muscles of the elbow, wrist and hand, and shoulder,and an increase in the maximum dose from 240 U to 400 U for the treatment ofadult upper limb spasticity across multiple joints.	Variation request toexpand the adult upper limb spasticity indication to include dosingguidance for 12 additional muscles of the elbow, wrist and hand, and shoulder,and an increase in the maximum dose from 240 U to 400 U for the treatment ofadult upper limb spasticity across multiple joints	11/11/2022	Partial approval	Dosing guidance for 5 additional muscles of the hand and wrist, (pronator quadratus, Flexor pollicis brevis/opponens pollicis , Lumbricals /interossei) were approved. The evidence to support improvement of limb function associated with reduction in spasticity following injection of the additional elbow and shoulder muscles was insufficient to support extension of the indication and an increase in the maximum adult upper limb spasticity dose of Botox from 240 U to 400 U