Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Botulinum toxin Type A

Proprietary Product Name: Botox

Sponsor: Allergan Australia Pty Ltd

June 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	Extension of indications
Decision:	Approved
Date of Decision:	15 March 2011
Active ingredient(s):	Botulinum toxin Type A
Product Name(s):	Botox
Sponsor's Name and Address:	Allergan Australia Pty Ltd 810 Pacific Highway, Gordon NSW 2072
Dose form(s):	Sterile, vacuum-dried, powder for reconstitution
Strength(s):	100 U, 200 U
Container(s):	Vial
Approved Therapeutic use:	Prophylaxis of headaches in adults with chronic migraine (headache on at least 15 days per month of which at least 8 days are with migraine). For full indications see the Product Information (Attachment 1).
Route(s) of administration:	Intramuscular (IM)
Dosage:	155 to 195 U IM. The recommended re-treatment schedule is every 12 weeks.
ARTG Number (s)	67311 and 172264

Product Background

Botox (botulinum toxin type A) purified neurotoxin complex blocks neuromuscular conduction by binding to receptor sites on motor or parasympathetic nerve terminals, entering the nerve terminals and inhibiting the release of acetylcholine. When injected intramuscularly (IM) at therapeutic doses, Botox produces a localised partial but reversible chemical denervation of the muscle and localised muscle paralysis. When the muscle is chemically denervated, it atrophies and may develop extra-junctional acetylcholine receptors. There is evidence that the nerve can sprout and re-innervate the muscle, with the weakness thus being reversible.

Current indications for Botox include: blepharospasm; strabismus; focal spasticity in adults and children two years and older; cervical dystonia (spasmodic torticollis); primary hyperhidrosis of the axillae; spasmodic dysphonia; and decreasing the severity of glabellar lines; crow's feet and forehead lines.

There has been some variability in the diagnostic categorisation of migraine in recent years. The most recent definition of chronic migraine was proposed in 2007 in the

International Classification of Headache Disorders 2nd edition (ICHD-2R[1]) but does not appear to have been confirmed. The diagnostic ICHD-2R criteria are:

A. Headache (tension-type and/or migraine) on ≥15 days per month for at least 3 months*.

B. Occurring in a patient who has had at least five attacks fulfilling criteria for 1.1 Migraine without aura according to the ICHD-2R classification criteria.

C. On ≥ 8 days per month for at least 3 months headache has fulfilled C1 and/or C2 below, that is, has fulfilled criteria for pain and associated symptoms of migraine without aura:

1. Has at least two of a-d

   (a) unilateral location

   (b) pulsating quality

   (c) moderate or severe pain intensity

   (d) aggravation by or causing avoidance of routine physical activity (for example, walking or climbing stairs)

   and at least one of a) or b)

   (a) nausea and/or vomiting

   (b) photophobia and phonophobia

2. Treated and relieved by triptan(s) or ergot before the expected development of C1 above

D. No medication overuse† and not attributed to another causative disorder‡

*Characterization of frequently recurring headache generally requires a headache diary to record information on pain and associated symptoms day-by-day for at least 1 month. Sample diaries are available at http://www.i-h-s.org. †Medication overuse as defined under 8.2 *Medication-overuse headache*. ‡History and physical and neurological examinations do not suggest any of the disorders listed in groups 5-12 (see [1]), or history and/or physical and/or neurological examinations do suggest such a disorder but it is ruled out by appropriate investigations, or such disorder is present but headache does not develop in close temporal relation to the disorder.

Proposed indication: The initially proposed indication was prophylaxis of headaches in adults with chronic migraine. On receipt on the initial clinical evaluation report (CER) the sponsor amended the requested indication to *prophylaxis of headaches in adults with chronic migraine (headaches on ≥ 15 days per month).*

Proposed administration:

For "chronic migraine" the sponsor has proposed 155 to 195 U IM with a 30-guage, 0.5 inch needle with 0.1 mL (5U) injections to each site. The injections to be divided across 7 specific head/ neck muscle areas as specified in the table below (Table 1). A 1-inch needle may be needed in the neck region for patients with extremely thick neck muscles. With the exception of the procerus muscle, which should be injected at 1 site (midline), all muscles should be injected bilaterally with the minimum dose per muscle as indicated in the table, with half the number of injection sites administered to the left and half to the right side of the head and neck. If there is a predominant pain location(s), additional

[1]Headache Classification Committee of the International Headache Society. The International Classification
of Headache Disorders: 2nd edition. *Cephalalgia* 2004; 24(Suppl. 1): 9–160.

injections to one or both sides may be administered in up to 3 specific muscle groups (occipitalis, temporalis and trapezius), up to the maximum dose per muscle as indicated in the table.

The recommended re-treatment schedule is every 12 weeks.

Table 1.

Head/ Neck Area	**Recommended Dose** **Total number of units (U) (number of IM injection sites [a])**
Frontalis [b]	20 U (4 sites)
Corrugator [b]	10 U (2 sites)
Procerus	5 U (1 site)
Occipitalis [b]	30 U (6 sites) up to 40 U (8 sites)
Temporalis [b]	40 U (8 sites) up to 50 U (up to 10 sites)
Trapezius [b]	30 U (6 sites) up to 50 U (up to 10 sites)
Cervical Paraspinal muscle group [b]	20 U (4 sites
Total Dose Range	**155 – 195 U**

[a] 1 IM injection site = 0.1 mL = 5 U Botox. [b] Dose distributed bilaterally for minimum dose

Regulatory Status

Applications for this extension of indications have been approved the USA and United Kingdom (UK). The table below lists countries in which Botox has been approved for the prophylaxis of headache in adults with chronic migraine.

Table 2.

Country	Approval date	Indication
Estonia	8/25/2010	The Prophylaxis of headache in adults with chronic migraine.
Malta	11/03/2010	The prophylaxis of headaches in adults with chronic migraine (headaches on >15 days per month of which at least 8 days are with migraine).
Slovak Republic	10/12/2010	The Prophylaxis of headache in adults with chronic migraine.
United States	10/15/2010	The Prophylaxis of headaches in adult patients with chronic migraine (≥15 days per month with headache lasting 4 hours a day or longer).
United Kingdom	7/8/2010	The prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine).

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

No new quality data were submitted.

III. Nonclinical Findings

Pharmacology

The nonclinical component of this submission consisted of three behavioural studies in rat models of nociception: a capsaicin-induced mechanical allodynia model, a streptozocin-induced diabetic neuropathic pain model, and a capsaicin-induced thermal hyperalgesia model. Several published papers focussing on the relevant literature were also provided. The results of the nonclinical studies presented a consistent profile of activity of Botox under these experimental conditions. In these rat models, a heightened state of peripheral nociception was induced by the intraplantar injection of capsaicin or the induction of experimental diabetes by intravenous (IV) streptozocin, with the treated animals displaying allodynia to non-noxious mechanical stimulation or hyperalgesia to noxious radiant heat stimulation to the hind paw. Intraplantar injection of Botox prior to capsaicin, or after diabetes was established, inhibited the allodynia and hyperalgesia. Similar antinociceptive effects were noted with other pharmacological treatments (gabapentin, naproxen, morphine). This effect of Botox lasted for 2-8 weeks, depending on the model. Botox did not affect acute nociceptive responses in the absence of prior development of allodynia/hyperalgesia.

The described experimental procedures are believed to create a state of peripheral sensitisation, in which enhanced activity in nociceptors and consequent antidromic stimulation produces release of compounds such as neuropeptides and amino acids[2] from the peripheral terminals of nociceptors and other primary afferents, contributing to local vasodilatation and the release of other inflammatory mediators from surrounding tissue, namely the development of neurogenic inflammation. A possible interpretation of the current studies is that botulinum toxin blocks the neuronal release of compounds from the primary afferents, thereby reducing the peripheral inflammatory cascade and inhibiting the development of sensitisation. The observed outcome would then be reduced nociceptive behavioural responses. Botulinum toxin blocks neuromuscular transmission via a 3-step process at the terminals of motoneurones: binding of the toxin to a membrane receptor, internalisation of the toxin, and then inhibition of acetylcholine release[3]. The latter stage appears to involve cleavage of a protein (SNAP-25) which is important in exocytosis, thus preventing effective docking and release of acetylcholine and temporarily inactivating the neuromuscular junction. A botulinum toxin-mediated similar effect at the peripheral terminals of primary afferents could explain the reduced behavioural nociceptive responses in these animal models.

There are significant limitations in the above hypothesis. A major consideration is the lack of direct evidence for the proposed mechanism of action. Release *per se* of compounds from peripheral afferent terminals was not actually measured in these studies but only surmised, in the interpretation of the behavioural observations[4]. More extensive

[2] Probable candidates: neurokinins, calcitonin-gene related peptide (CGRP) and glutamate.

[3] There is evidence that botulinum toxin affects cholinergic nerve endings in general, but its molecular size (~150 kDa) precludes its passage across the blood-brain barrier.

[4] Limited mechanistic evidence in the literature (BOTOX-mediated inhibition of SC glutamate release detected by microdialysis in rat formalin inflammatory pain model (Cui *et al*., *Pain*, 107 (2004) 125-133)).

investigations involving release techniques may have been able to provide more substantive evidence. In any event, the applicability of these rat models to the pathogenesis of clinical migraine is uncertain. The animal experiments involved fairly extreme conditions, either a pronounced artificial peripheral sensitisation induced by intraplantar administration of a very noxious chemical or induction of a severe diabetic state. Thus, even if it is assumed that the positive results obtained with Botox in these nonclinical studies did result from inhibition of release of neuronal mediators, it is uncertain whether these conditions would be relevant to any potential contribution of afferent pathway sensitisation to the pathogenesis of migraine.

In summary, the nonclinical data describe an antinociceptive action of Botox, in particular animal models of peripheral sensitisation, which might be due to inhibition of release of compounds from primary afferent nerve terminals. The relevance of these models/findings to migraine pathophysiology is unclear.

Pharmacokinetics

There were no new data submitted under this heading.

Toxicology

There were no new data submitted under this heading.

Nonclinical Summary and Conclusions

- Three submitted nonclinical pharmacological studies described rat models of nociception involving peripheral sensitisation. In these models, allodynia or hyperalgesia was inhibited by intraplantar injection of Botox; other analgesics administered systemically were also effective. Acute nociception was unaffected by Botox.

- The nonclinical results might be explained by botulinum toxin-mediated inhibition of release of compounds from the peripheral primary afferent terminals, although direct evidence is lacking. The extrapolation of such a mechanism of action to a similar inhibitory effect in the pathogenesis of migraine is tenuous.

Recommendations

The nonclinical reports in this submission describe some interesting actions of Botox in experimental models of nociception involving peripheral sensitisation. However, the relevance and applicability of the animal findings and proposed underlying mechanisms to sensitisation of afferent pathways in migraine pathogenesis are uncertain, and the nonclinical studies are not considered supportive of the submission. The PI was amended to include the following statement: *"Limited nonclinical data suggest that Botox may reduce sensitisation processes, but the actual mechanism of action for headache prophylaxis is not known."*

IV. Clinical Findings

Introduction

A threshold problem for the sponsor in its development program was identification of a population of patients whose disease state – involving a diagnosis of migraine, and occurrence of headaches on many (typically > 15) days each month – was sufficiently well

defined to enable the conduct of a series trials over several years in patients meeting the definition. When Allergan initiated the first of the Phase II studies included in the current Australian submission, the terms "CDH" (chronic daily headache) and "transformed migraine" were widely used to describe such patients. In 2004, the International Headache Society (IHS) first published diagnostic criteria for chronic migraine (HCCIHS, 2004[5]; Silberstein *et al*, 2005[6]). Allergan refers to revision of these criteria, but it appears from the IHS website[7] that no revision has yet been finalised. Appendix 1 on this website shows the evolution of relevant terminology and criteria over the past 20 years or so.

Good Clinical Practice (GCP) aspects

All clinical study reports contained GCP certification.

Pharmacokinetics

No new data was submitted under this heading.

Drug Interactions

No new data were submitted under this heading.

Pharmacodynamics

No new data were submitted under this heading.

Efficacy

Introduction

Two major Phase III studies were submitted in support of the proposed indication (nos. 191622-079 and 91622-080). Supporting these were two placebo-controlled Phase II studies of Botox in chronic headache (nos. 191622-038 and 91622-039), and 7 placebo-controlled Phase II studies of Botox in other headache conditions (nos. 191622-509, 191622-037, 191622-036, 191622-026, 191622-024, 191622-009 and 191622-005).

Phase III studies and Phase II studies presented as pertinent to the claimed indication

Pivotal studies

Study 191622-079

Methods

This was a double-blind, 2-arm, placebo-controlled study. Although the relevant guideline (EMEA, 2003)[8] recommends the use of an active control it was not included in the design of this study.

[5] Headache Classification Committee for the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain 2nd edition. *Cephalgia* 2004, 24 (Suppl 1):1-60.

[6] Silberstein SD *et al*. The International Classification of Headache Disorders, 2nd Edition (ICHD-II) – revision of criteria for 8.2 *Medication-overuse headache*. *Cephalalgia* 2005; 25:460-465.

[7] http://ihs-classification.org/en/

[8] EMEA/CPMP/EWP/788/01 revision 1 *Note for guidance on clinical investigation of medicinal products for the treatment of migraine.* London: 2007. CPMP=Committee for Proprietary Medicinal Products.

Objectives

Double-blind phase: To evaluate the efficacy and safety of Botox compared to placebo as headache prophylaxis in migraine patients with ≥ 15 headache days per 4-week period.

Open-label phase: To evaluate the long-term safety of Botox as headache prophylaxis in migraine patients with ≥ 15 headache days per 4-week period.

Study Participants

Main inclusion criteria:

- Patients 18 – 65 years old.
- History of migraine headache disorder meeting any of the diagnostic criteria listed in
  ICHD-2 Section 1, Migraine, with the exception of "complicated migraine" (for example
  hemiplegic migraine [1.2.4, 1.2.5], basilar migraine [1.2.6], ophthalmoplegic migraine [13.17], or migrainous infarction [1.5.4]).
  Note: Patients with only a diagnosis of retinal migraine [1.4], persistent aura without infarction [1.5.3], or migraine-triggered seizure [1.5.5] were not to be enrolled (for example, a patient with migraine without aura [1.1] and retinal migraine [1.4] could be enrolled in the study.
- Four or more distinct headache episodes during the 4-week "baseline phase" (that is, the four weeks preceding randomisation), each with a duration of≥ 4 hours.
- Fifteen or more headache days during the 4-week baseline phase, with each day consisting of four or more hours of continuous headache.
- At least 50% of baseline headache days were migraine or probable migraine days (ICHD-2 Sections 1.1 (migraine without aura), 1.2 (migraine with aura), and 1.6 (probable migraine)).

Main exclusion criteria:

- Uncontrolled clinically significant medical condition other than headache.
- Any medical condition that may put the patient at increased risk with exposure to Botulinum Toxin Type A.
- Use of any headache prophylactic medication within 28 days before the 4-week baseline period.
- Headache diagnosis of chronic tension-type headache (ICHD-2 2.3), hypnic headache (ICHD-2 4.5), hemicrania continua (ICHD-2 4.7), or new daily persistent headache (ICHD-2 4.8)
- Headache attributed to another disorder (for example, cervical dystonia, craniotomy, head/neck trauma)
- Unremitting headache lasting continuously throughout the 4-week baseline period
- Patients with a known or suspected temporomandibular disorder, including pain in or around the temporomandibular joint.
- Patients with a concurrent diagnosis of fibromyalgia.
- Beck Depression Inventory score > 24 at the beginning of the baseline period.

Treatments

Patients were stratified based on medication overuse in the 4-week baseline phase. They were classified as medication overusers if they met one or more of the criteria listed below (Table 3).

Table 3.

Drug	Criteria for overuse
Overall: combined across at least two categories among ergotamines, triptans, analgesics (including simple analgesics and combination analgesics as one category) and opioids.	≥10 days per month and ≥2 days per week
Ergotamine	≥10 days per month and ≥2 days per week
Triptan	≥10 days per month and ≥2 days per week
Simple Analgesic	≥15 days per month and ≥2 days per week
Opioid	≥10 days per month and ≥2 days per week
Combination analgesic medication	≥10 days per month and ≥2 days per week

On Day 0, patients within each stratum were randomised to receive either two treatments with Botox or two treatments with placebo (Day 0 and Week 12) in a 1:1 ratio. Treatment was administered whether or not the patient had a headache at the time. Patients who completed the 24-week double-blind phase were eligible for the open-label phase. During the 32-week open-label phase, all patients were to receive three treatments of Botox (Weeks 24, 36, and 48). In the double-blind phase, each treatment consisted of a minimum dose of 155 U Botox or placebo IM as 31 fixed-site, fixed-dose injections across seven specific head/neck muscle areas as shown below (Table 4).

Table 4.

	Number of units per muscle (Number of injection sites)[a]		
Head/neck area	**Left**	**Right**	**Total**
Frontalis	10 (2 sites)	10 (2 sites)	20 (4 sites)
Corrugator	5 (1 site)	5 (1 site)	10 (2 sites)
Procerus			5 (1 site)
Occipitalis	15 (3 sites)	15 (3 sites)	30 (6 sites)
Temporalis	20 (4 sites)	20 (4 sites)	40 (8 sites)
Trapezius	15 (3 sites)	15 (3 sites)	30 (6 sites)
Cervical Paraspinal Muscle Group	10 (2 sites)	10 (2 sites)	20 (4 sites)
Minimum Total			155 U (31 sites)

[a] The injection volume at each site was 0.1 mL, and the dose was either 0 U (placebo) or 5 U of Botox

Optional additional dosing at ≤ 8 sites in the occipitalis, temporalis, and trapezius could be given at the discretion of the investigator, using a "follow-the-pain paradigm". These optional additional injections did not have to be consistent across treatment visits, with

respect to dose or number of injection sites. Thus, if all optional injections were given, the maximum overall total dose was 195 U.

Additional medication: Current use of any headache prophylactic medication was prohibited. Patients could take acute headache medications as prescribed; use to be recorded in a diary.

Primary efficacy variable

The primary efficacy variable was the frequency of headache episodes per 28-day period with the primary endpoint being the 28-day period ending with Week 24. A headache episode was defined as patient-reported headache pain with a start and stop time that indicated that the pain lasted at least 4 continuous hours per patient diary.

Evaluator's comment: In accordance with the relevant guideline (EMEA/CPMP/EWP/2158/99[9]), this was stipulated as frequency of headache episodes per 28-day period. The primary efficacy analysis was to be based on the change from baseline to Week 24. On the other hand, the EMEA's recommendations (*ibid*) for distinguishing an attack of long duration from 2 attacks, or for distinguishing between attacks and relapses, were not followed. The population recruited for this study was required to have had ≥ 15 headache days and ≥ 4 distinct headache episodes during the 28-day baseline period. The mean number of episodes in the population recruited turned out to be about 13, so the duration of each episode must often have been several days.

Other pre-specified efficacy measures

Frequency of headache days per 28-day period

Frequency of migraine/probable migraine days per 28-day period

Frequency of migraine/probable migraine headache episodes per 28-day period

Frequency of acute headache pain medication intakes per 28-day period

Headache Impact Test Questionnaire (HIT-6)

Migraine Specific Quality of Life (MSQ)

Migraine Treatment Satisfaction Questionnaire (MTSQ)

Migraine Impact Questionnaire (MIQ)

EuroQual-5D (EQ-5D)

Blinding

According to the protocol, this was a double-blind study, but it is uncertain whether one can be confident of this. It was clear from the consent form that patients knew the active under study was Botox. Through visual inspection in a mirror, or with a little self-experimentation on the scalp muscles, many patients on active would have developed at least a strong suspicion about the identity of their treatment. In Studies 191622-038 and 191622-039, patients were asked at various stages to guess whether they had received active or placebo treatment, but this appears not to have been done in the present study.

The sponsor argues that if patients on active could guess their treatments, then so could patients on placebo, but the evaluator did not agree that this necessarily follows. The sponsor then argues that knowledge of being on placebo would have caused a nocebo effect (reduction of the placebo effect), and that the fact that a marked placebo effect was

[9] EMEA/CPMP/EWP/2158/99 Guideline on the choice of the non-inferiority margin. http://www.tga.gov.au/docs/pdf/euguide/ewp/215899en.pdf.

observed is evidence of successful blinding. The clinical evaluator considered this speculative as the effectiveness of blinding is unproven and suggested the sponsor be invited to comment on this issue.

Statistical methods

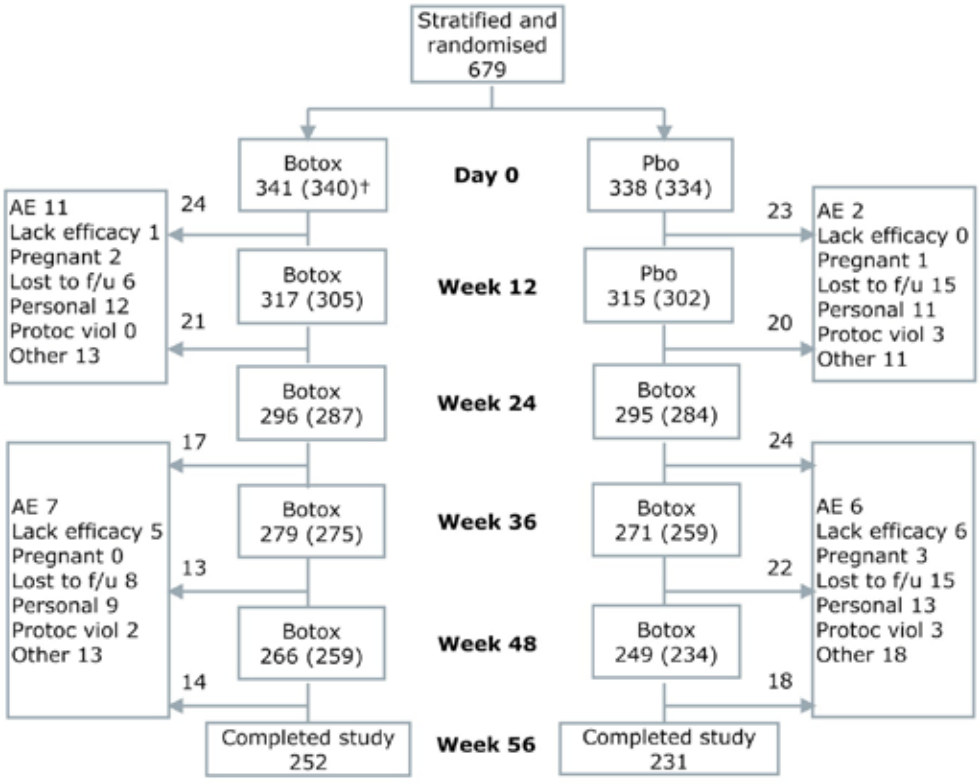
The primary comparison between treatment groups was to be done in the Intent-To-Treat (ITT) population by analysis of co-variance (ANCOVA), with baseline headache count as the covariate. In addition to treatment group and baseline covariate, the specified main effects for the ANCOVA were centre and medication-overuse strata. This was consistent with the relevant guideline (EMEA/CPMP/EWP/2158/99).

Missing values: For a patient who reported any diary data in less than 10 days of a 28-day period, the score of the period was to be imputed by a modified last observation carried forward (mLOCF) analysis – the substitution to be the patient's previous 28-day period score (that is, the last observation) adjusted in proportion to the change in the mean over all treatment groups from that 28-day period to the missing-data 28-day period and rounded to the nearest whole number.

Results

Participant flow is described in Figure 1.

Figure 1. Patient flow. Study 191622-079



†Number treated is in brackets. Stipulated primary outcome

Frequency of headache episodes at Week 24: The Baseline, and Change from Baseline are tabulated below (Table 5).

Table 5.

	Mean (sd)	
	Botox (N=341)	**Placebo (N=338)**
Baseline	12.3 (5.2)	13.4 (5.7)
Change	-5.2 (5.3)	-5.3 (5.8)

Difference between treatment groups was not statistically significant (using ANCOVA analysis as described under *Statistical methods*, above).

First-listed secondary outcome

Frequency of headache days at Week 24: The Baseline, and Change from Baseline are tabulated below.

Table 6.

	Mean (sd)	
	Botox (N=341)	**Placebo (N=338)**
Baseline	20.0 (3.7)	19.8 (3.7)
Change	-7.8 (6.6)	-6.4 (6.7)

Difference between treatment groups was statistically significant (P=0.006).

Results for The *medication overuse: no stratum* alone, for the above outcome are shown below.

Table 7.

	Mean (sd)	
	Botox (N=115)	**Placebo (N=103)**
Baseline	19.3 (3.6)	19.9 (4.0)
Change	-7.9 (6.9)	-6.3 (6.7)

For this stratum, difference between treatment groups was not statistically significant.

The above outcome measures do not relate specifically to migraine headache. A specified secondary outcome measure which did so was *Frequency of migraine/probable migraine days per 28-day period*, results for which are tabulated below at Week 24.

Table 8.

	Mean (sd)	
	Botox (N=341)	**Placebo (N=338)**
Baseline	19.1 (4.0)	19.1 (4.0)
Change	-7.6 (6.5)	-6.1 (6.8)

For this measure, the difference between treatment groups was statistically significant (P=0.002).

Ancillary analyses

Statistically significant differences between groups (favouring Botox) were observed between baseline and primary endpoint for HIT-6 and MSQ. For MTSQ, differences between groups were significant for 10/17 questions (in favour of Botox). Between-group differences for MIQ and EQ-5D were not statistically significant.

Comments on Study 191622-079

The exception of "complicated migraine" noted in the inclusion criterion above [the quotes are the sponsor's own] is confusing. Not only was the clinical evaluator unable to find the term "complicated migraine" in ICHD-2, but also, the condition "chronic migraine" is itself classified in ICHD-2 under the heading "Complications of migraine".

The table under the heading Treatments, showing criteria for medication overuse, appears to be an over-simplification of the condition defined as *medication overuse headache* (and coded 8.2) by the IHS (see HCCIHS, 2004). The definition used by the sponsor is of no practical utility in that it relies on identifying (for example) a population group whose members suffer from headache ≥ 15 days per month, but who do not use even simple analgesics at the rate specified.

With respect to the sponsor's choice of primary efficacy variable, it is unlikely that the EMEA did not envisage this sort of disease group when it recommended headache frequency as primary efficacy variable. The problem is that this measure does not have a close connection to an outcome which the usual patient would regard as beneficial. The value can be low as a result of (a) patients experiencing few, brief headaches, or (b) patients experiencing long periods of uninterrupted headache, such that the total number of interruptions is few. Pursuing this to its logical conclusion, suppose the effect of the active drug is to extend headache duration so that the patient suffers one continuous headache during the 28-day efficacy assessment period. This would be recorded as one episode and an excellent result as far as the primary efficacy variable is concerned. Thus, the "number of episodes" is not suitable as the primary efficacy variable in the present study. In fact, on the basis of baseline characteristics alone, the clinical evaluator believed the results should be disregarded. The first of the secondary efficacy variables should be used instead.

Study 191622-080

Methods, Objectives, Study Participants, Treatments

These were the same as those for Study 191622-079 (see above).

Primary efficacy endpoint:

The final version of the *Protocol* stipulated: Frequency of headache days per 28-day period.

Other pre-specified efficacy measures

Frequency of migraine/probable migraine days per 28 day period

Frequency of moderate/severe headache days per 28 day period

Total cumulative hours of headache occurring on headache days per 28 day period

Proportion of patients with severe HIT-6 impact category score per 28 day period

Frequency of headache episodes per 28 day period

Headache Impact Test Questionnaire (HIT-6)

Migraine Specific Quality of Life (MSQ)

Migraine Treatment Satisfaction Questionnaire (MTSQ)

Migraine Impact Questionnaire (MIQ)

EuroQual-5D (EQ-5D)

Illness Behaviour Questionnaire (IBQ)

Blinding

As for Study 191622-079.

Statistical methods

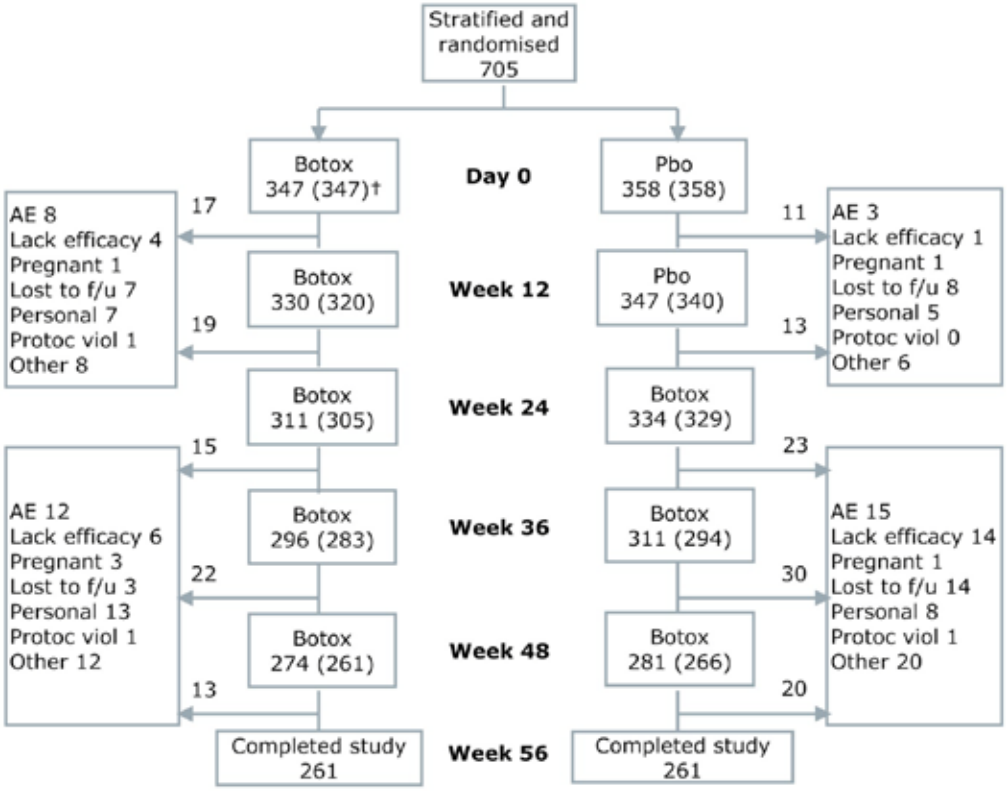
The primary comparison between treatment groups was to be done in the ITT population by ANCOVA, with baseline headache day count as the covariate. In addition to treatment group and baseline covariate, the specified main effects for the ANCOVA were medication-overuse strata. This was consistent with the relevant guideline (EMEA, 2003).

Missing values: As for Study 191622-079.

Results

Participant flow is described in Figure 2.

Figure 2. Patient flow. Study 191622-080



†Number treated is in brackets.

Stipulated primary outcome

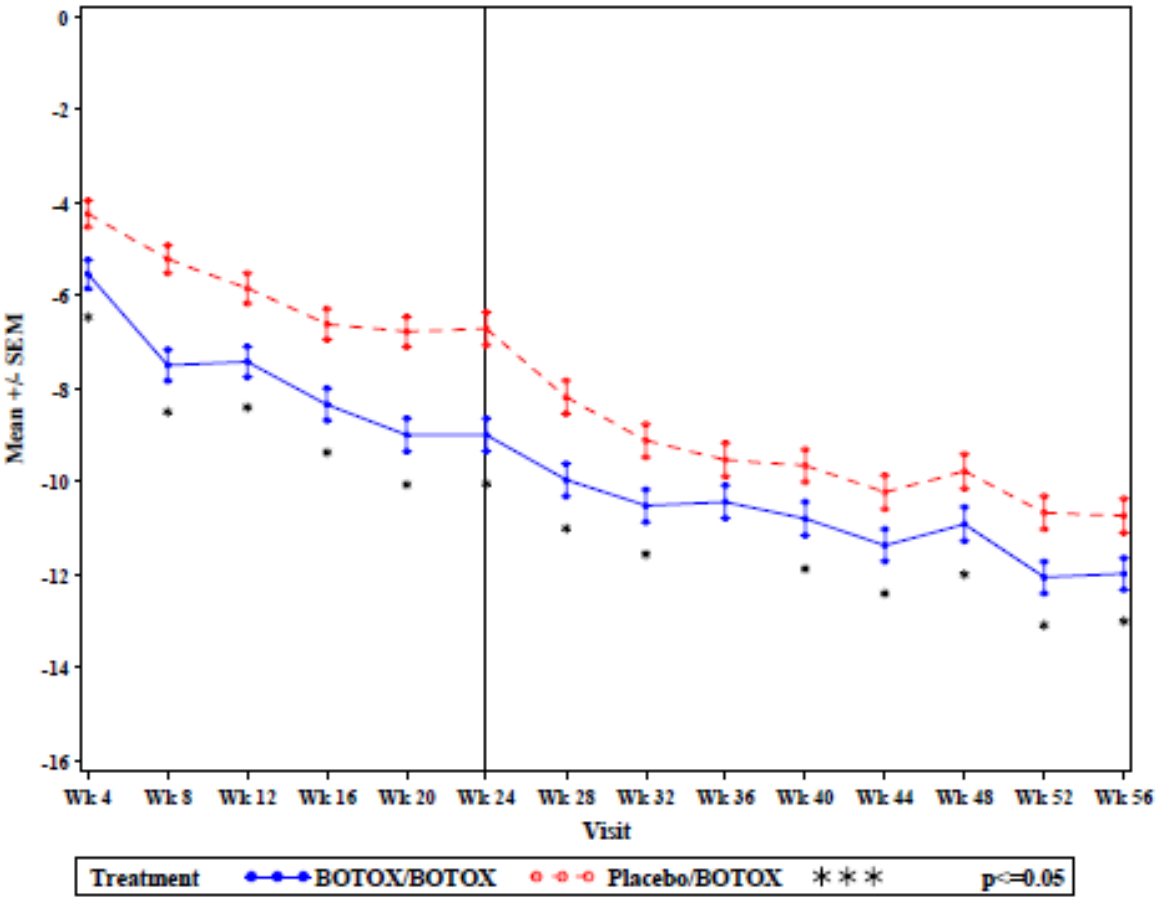
Frequency of headache days at Week 24: The Baseline, and Change from Baseline, are tabulated below.

Table 9.

	Mean (sd)	
	Botox (N=347)	**Placebo (N=358)**
Baseline	19.9 (3.6)	19.7 (3.6)
Change	-9.0 (6.5)	-6.7 (6.7)

The difference between treatment groups was statistically significant (P < 0.001). Figure 3 shows the time course of the variable.

Figure 3. Mean Change From Baseline in Frequency of Headache Days per 28-day Period (ITT Population). Study 191622-080



Results for The *medication overuse: no* stratum alone, for the above outcome are tabulated below.

Table 10.

	Mean (sd)	
	Botox (N=128)	**Placebo (N=134)**
Baseline	19.9 (3.6)	19.6 (3.7)
Change	-9.7 (6.7)	-8.1 (6.8)

For this stratum, difference between treatment groups was not statistically significant.

Secondary outcomes

Statistically significant results were obtained, consistent with those for the primary outcome. In particular, *Frequency of migraine/probable migraine days per 28-day period* at Week 24 are tabulated below.

Table 11.

	Mean (sd)	
	Botox (N=347)	Placebo (N=358)
Baseline	19.2 (3.9)	18.7 (4.0)
Change	-8.7 (6.6)	-6.3 (6.7)

For this measure, the difference between treatment groups was statistically significant ($P < 0.001$).

Ancillary analyses

The results were as for Study 191622-079.

Comments on Study 191622-080

The comments made regarding Study 191622-079 also apply to this study.

Phase II studies presented as pertinent to the claimed indication (191622-038 and 191622-039)

Outcomes for the primary efficacy variable were as follows:

191622-038: There were no statistically significant differences between Botox and placebo at any time point, including Day 180 (the primary endpoint) for placebo non-responders or placebo responders.

191622-039: There were no statistically significant differences between Botox and placebo at Day 180 (the primary endpoint) for placebo non-responders or placebo responders.

Comments on the Phase II studies presented as pertinent to the claimed indication (191622-038 and 191622-039)

The disease populations studied were dissimilar to those of the pivotal studies. This, and the lack of positive efficacy outcomes, render studies 191622-038 and 191622-039 of dubious value as "supporting studies" for the pivotal studies.

In relation to blinding, it was noted that at several points patients were asked to guess whether they were on Botox or placebo treatment. The results of guessing at the Day 90 visit the treatment which had been received on Day 0 are tabulated below.

Table 12.

	Guessed treatment	Actual treatment	
		Botox	Placebo
Study 191622-038	N	134	145
	Botox	97/114 (85.1%)	51/123 (41.5%)
	Placebo	17/114 (14.9%)	72/123 (58.5%)
	Missing	20	22
Study 191622-039	N	399	139
	Botox	298/346 (86.1%)	49/116 (42.2%)
	Placebo	48/346 (13.9%)	67/116 (57.8%)
	Missing	53	23

Other studies

The sponsor's overview of its clinical development program describes these (nos. 191622-005, 191622-009, 191622-024, 191622-026, 191622-036, 191622-037 and 191622-509) as "exploratory Phase II studies in patients with episodic migraine".

These studies are relevant to the present application mainly in respect of their safety data. Outcomes are listed below.

Study 191622-005: Neither active treatment group showed significant benefit compared to placebo at Day 30 in the reduction in frequency of moderate to severe migraine headaches. However, the low-dose group did show a statistically significant reduction in the frequency of moderate to severe migraine headaches compared to placebo at Day 60 and Day 90.

Study 191622-009: There were no significant differences among the treatment groups in the frequency of migraine headaches of any severity at Day 60 or any other follow-up visit. Similar results were obtained in **Studies 191622-024, 191622-026** and **191622-036**.

Study 191622-037: There were no statistically significant differences between treatment groups in the changes from baseline in the number of migraine headaches per 30-day period for either the placebo responders or non-responders, nor the pooled population at any timepoint.

Study 191622-509: At the primary endpoint, no statistically significant among-group differences were observed. Pairwise comparisons between groups did not show any statistically significant differences, with the exception of Day 60 between the Botox 150U and placebo groups, in favour of the Botox group.

PI with respect to efficacy

The proposed additional indication is "Prophylaxis of headaches in adults with chronic migraine." The following table outlines the disease groups studied in the trials presented as pertinent to the claimed indication (Table 13).

Table 13. Disease groups studied in the trials presented as pertinent to the claimed indication. Table continued across two pages.

<table>
<tr><th>Study</th><th>Disease group</th></tr>
<tr><td>191622-079</td><td>Patients with chronic migraine[1], except that
(a) patients with medication-overuse (461/679 enrolled participants) were admitted to the trial, and
(b) patients were not required to have had symptoms for ≥ 3 months.</td></tr>
<tr><td>191622-080</td><td>Patients with chronic migraine, except that
(a) patients with medication-overuse (443/705 enrolled participants) were admitted to the trial, and
(b) patients were not required to have had symptoms for ≥ 3 months.</td></tr>
<tr><td>191622-038</td><td>Patients with primary headache disorder, who in the 30-day baseline period had ≥ 16 headache days which could include any combination of migraines with or without aura, episodic/chronic TTHs, and/or migrainous headaches[2]. Patients were not required to have had symptoms for ≥ 3 months. Patients with medication-overuse were perhaps excluded by the Exclusion criteria "Symptomatic medication overuse or abuse in the investigator's opinion" or "Analgesic rebound headache".
The sponsor asserts that baseline data indicated 87.0% patients suffered from chronic migraine, but the primary source of this information is not clear. Table 1-7 (see excerpt below) which is cited as the source, appears to be derived from an analysis of data from Studies 191622-038 and 191622-039 in an effort to determine the extent to which their admission criteria matched those of Studies 191622-079 and 191622-080. However, it is not clear from the Clinical Study Report (CSR) for Study 191622-038 how this information could be ascertained. The data for Headache subtype at entry in Study 191622-038 give the number with "Transformed migraine" as 113/279 (the other subtypes and numbers being: CTTH 20, New daily persistent 3, Hemicrania continua 0, Other 3, Not recorded 140).
Information in Table 1-7 includes (for Study 191622-038):
<table>
<tr><th>Classification</th><th>Yes</th><th>No</th></tr>
<tr><td>HA[3] days ≥ 15 & ≥ half being MPM[3] days</td><td>309</td><td>46</td></tr>
<tr><td>No baseline prophylactic medication use</td><td>228</td><td>127</td></tr>
<tr><td>≥ 4 HAs with ≥ 4 hours duration</td><td>289</td><td>66</td></tr>
</table>
Even if the data in Table 1-7 were correctly extracted from original study findings, they do not show that 87% patients in Study 191622-038 suffered from chronic migraine.</td></tr>
</table>

<table>
<tr>
<td>191622-039</td>
<td>
Patients with primary headache disorder, who in the 30-day baseline period had ≥ 16 headache days which could include any combination of migraines with or without aura, episodic/chronic TTHs, and/or migrainous headaches[2]. Patients were not required to have had symptoms for ≥ 3 months. Patients with medication-overuse were perhaps excluded by the Exclusion criteria "Symptomatic medication overuse or abuse in the investigator's opinion" or "Analgesic rebound headache".

The sponsor asserts that baseline data indicated 84.6% patients suffered from chronic migraine, but the primary source of this information is not clear. Table 1-7 which is cited as the source appears to be derived from an analysis of data from Studies 191622-038 and 191622-039 in an effort to determine the extent to which their admission criteria matched those of Studies 191622-079 and 191622-080. However, it is not clear from the CSR for Study 191622-039 how this information could be ascertained. Data for Headache subtype at entry in Study 191622-039 give the number with "Transformed migraine" as 289/538 (the other subtypes and numbers being: CTTH 68, New daily persistent 15, Hemicrania continua 0, Other 5, Not recorded 161).

Information in Table 1-7 includes (for Study 191622-039):
<table>
<tr><th>Classification</th><th>Yes</th><th>No</th></tr>
<tr><td>HA[3] days ≥ 15 & ≥ half being MPM[3] days</td><td>594</td><td>108</td></tr>
<tr><td>No baseline prophylactic medication use</td><td>354</td><td>348</td></tr>
<tr><td>≥ 4 HAs with ≥ 4 hours duration</td><td>565</td><td>137</td></tr>
</table>
Even if the data in Table 1-7 were correctly extracted from original study findings, they do not show that 84.6% patients in Study 191622-039 suffered from chronic migraine.
</td>
</tr>
</table>

[1]As defined by IHS (see section 3.5.1 below).

[2]Using HS 1988 criteria.

[3]HA = Headache; MPM = Migraine/Probable Migraine.

The IHS definition of chronic migraine

> "Migraine headache occurring on 15 or more days per month for more than 3 months in the absence of medication overuse."

does not match precisely the patient population recruited to the pivotal studies, in that patients were not required to comply with the conditions "for more than 3 months" or "in the absence of medication overuse". In fact, patients enrolled in the pivotal studies were stratified by medication overuse.

This does not affect the validity of the trials themselves, but it underlines the importance of describing the indication in PI strictly in accordance with evidence from the clinical trials, and in terms which will be readily understood by prescribers.

Evaluator's overall conclusions on clinical efficacy

The population studied

The sponsor states that it follows the IHS in defining *chronic migraine* as migraine in which the frequency of headaches progresses to ≥ 15 days per month and is sustained for ≥ 3 months. In fact, the IHD definition (HCCIHS, 2004) defines chronic migraine (assigning code 1.5.1) as:

A. Headache fulfilling [the criteria for 1.1 Migraine without aura] on ≥15 days/month for >3 months.
B. Not attributed to another disorder.

Notes in the IHS source document explain that:

- As most cases of chronic migraine start as 1.1 m*igraine without aura*, chronicity may be regarded as a complication of episodic migraine.
- Medication-overuse headache is regarded as another disorder, so the definition of chronic migraine generally excludes these patients:
  "When medication overuse is present (that is, fulfilling criterion B for any of the subforms of 8.2 Medication-overuse headache), this is the most likely cause of chronic symptoms. Therefore, the default rule is to code such patients according to the antecedent migraine subtype (usually 1.1 Migraine without aura) plus 1.6.5 Probable chronic migraine plus 8.2.8 Probable medication-overuse headache. When these criteria are still fulfilled 2 months after medication overuse has ceased, 1.5.1 Chronic migraine plus the antecedent migraine subtype should be diagnosed, and 8.2.8 Probable medication-overuse headache discarded. If at any time sooner they are no longer fulfilled, because improvement has occurred, code for 8.2.8 Medication-overuse headache plus the antecedent migraine subtype and discard 1.6.5 Probable chronic migraine."

The summary description for chronic migraine given in the IHS source is: "Migraine headache occurring on 15 or more days per month for more than 3 months in the absence of medication overuse." IHS classifies its condition 1.5.1 as falling under the ICD-10 code G43.3 (*Complicated migraine*).

Thus, it seemed to this evaluator that the pivotal studies deal with a population which does not satisfactorily match a recognised diagnostic group. External validity would therefore appear problematic.

Dosage used

There were no adequate dose-finding results underpinning the pivotal studies. In Study 191622-038 the dosages given were at the discretion of investigators. In Study 191622-039 the dosages were stipulated, but no clear dose-response relationship was observed. In both Studies 191622-038 and 191622-039, the disease groups studied were substantially different from those in Studies 191622-079 and 191622-080 (see Table 13). The additional seven studies do not assist, because they generally studied different disease groups, did not demonstrate efficacy and did not establish a dose-response relationship.

Dosage cannot be rationally based on that used in other indications, because it is suggested that the mode of action is different. Thus, the dosage used in the pivotal studies appears to be arbitrary.

Blinding

The consideration of blinding discussed above applies to all the purported double-blind studies.

The primary efficacy variable

Normally, use *post hoc* of a secondary efficacy variable for the main analysis instead of the stipulated primary efficacy variable (as in Study 191622-079), or amendment of the primary efficacy variable late in the study (as in Study 191622-080), should disqualify a study from being regarded as pivotal. However, in the present case, it seems to me that the original choice of primary efficacy variable was so untenable that it is appropriate to substitute for it the next highest status efficacy variable designated in the protocol.

Repeated treatment

No evidence of continued efficacy with repeated treatment was available from the double-blind, placebo-controlled (DBPC) phases of the pivotal studies.

Conclusion on efficacy

Evidence of efficacy is weak. To the extent that between-treatment outcomes reached statistical significance in "double-blind" studies, this evaluator believed this may have resulted from failure of blinding. Even if formal proof of efficacy is accepted at face value, the patient group to which this result can be applied is unclear, dosage is not soundly based, continued efficacy of repeated treatment has not been established, the clinical significance of any benefit is questionable, and the relative magnitude of the benefit compared to that of other agents used in migraine prophylaxis is unknown.

Safety

Introduction

The safety evidence presented comprises routine safety monitoring (adverse events (AEs) and clinical laboratory monitoring) from the clinical studies presented as pertinent to the claimed indication (that is, the studies claimed to support efficacy), and also safety evidence from seven Phase II studies of Botox in other headache conditions (nos. 191622-509, 191622-037, 191622-036, 191622-026, 191622-024, 191622-009 and 191622-005).

Patient exposure

Information on overall exposure in the studies presented in the current Australian submission is summarised below (Table 14). Included are the 4076 patients who received ≥ 1 injection of study medication: 3235 any Botox dose; 841 placebo.

Table 14.

Safety Population	DBPC exposure			Open-label exposure			Any Botox
	Botox	Pbo	Total	Botox/Botox[4]	Pbo/Botox[5]	Total	
Phase III chronic migraine[1]	687	692	1379	592	613	1205	1300
All chronic migraine[2]	1384	1052	2436				1997
All migraine[3]	2532[6]	1544[6]	4076				3235[7]

[1]Studies 191622-079 and 191622-080. [2]Studies 191622-079, 191622-080; 191622-038 and 191622-039.

[3]Studies 191622-079, 191622-080; 191622-038, 191622-039; 191622-005, 191622-009, 191622-024, 191622-026, 191622-036, 191622-037 and 191622-509. [4]Patients received Botox during both DBPC exposure and open-label exposure. [5]Patients received placebo during DBPC exposure and Botox during open-label exposure. [6]For the 3-study sequence 191622-024/-026/-036, only 191622-024 is included. [7]For the 3-study sequence 191622-024/-026/-036, the 90 patients who first received Botox in Study 191622-026 after receiving placebo in Study 191622-024 are included.

Adverse events

Data from the Phase III studies and Phase II studies presented as pertinent to the claimed indication

AEs relating to these studies are displayed separately, as follows:

191622-079: AEs reported in the double-blind period are shown in Table 15, classified by System Organ Class (SOC). AEs reported by ≥ 1% patients in either treatment group in the open-label period are shown in Table 16.

191622-080: AEs reported in the double-blind period are shown in Table 17, classified by SOC. AEs reported by ≥ 1% patients in either treatment group in the open-label period are shown in Table 18.

Table 15. AEs. Double-blind period. Study 191622-079 (table continued across two pages.)

SOC[1]	Botox (n=340)		Placebo (n=334)	
Preferred Term	**n**	**%**	**n**	**%**
Patients with one or more AEs	203	59.7	156	46.7
Blood And Lymphatic System Disorders	3	0.9	1	0.0
Cardiac Disorders	2	0.6	1	0.0
Ear And Labyrinth Disorders	4	1.2	1	0.0
Endocrine Disorders	1	0.3	1	0.0
Eye Disorders	18	5.3	7	0.0
Eyelid ptosis	13	3.8	1	0.0
Gastrointestinal Disorders	22	6.5	24	0.1
Nausea	7	2.1	7	0.0
Vomiting	1	0.3	4	0.0
Toothache	0	0.0	5	0.0
General Disorders And Administration Site Cond.	20	5.9	19	0.1
Injection site pain	7	2.1	4	0.0
Hepatobiliary Disorders	1	0.3	2	0.0
Immune System Disorders	3	0.9	2	0.0
Infections And Infestations	79	23.2	83	0.2
URTI	13	3.8	20	0.1
Sinusitis	15	4.4	17	0.1
Nasopharyngitis	12	3.5	16	0.0
Bronchitis	9	2.6	4	0.0
Gastroenteritis viral	5	1.5	8	0.0
Influenza	4	1.2	7	0.0
Injury, Poisoning And Procedural Complications	32	9.4	24	0.1
Muscle strain	6	1.8	2	0.0
Fall	5	1.5	3	0.0
Investigations	6	1.8	4	0.0
Metabolism and Nutrition Disorders	3	0.9	3	0.0
Musculoskeletal	78	22.9	34	0.1
Neck pain	28	8.2	11	0.0
Muscular weakness	20	5.9	0	0.0
Musculoskeletal pain	10	2.9	4	0.0
Arthralgia	7	2.1	3	0.0

Muscle spasms	7	2.1	2	0.0
Musculoskeletal stiffness	6	1.8	3	0.0
Myalgia	6	1.8	3	0.0
Intervertebral disc protrusion	4	1.2	2	0.0
Back pain	4	1.2	0	0.0
Neoplasms	5	1.5	3	0.0
Nervous System Disorders	46	13.5	29	0.1
Headache	15	4.4	10	0.0
Migraine	12	3.5	4	0.0
Dizziness	3	0.9	2	0.0
Syncope	1	0.3	4	0.0
Psychiatric Disorders	10	2.9	5	0.0
Anxiety	2	0.6	4	0.0
Insomnia	3	0.9	0	0.0
Renal And Urinary Disorders	2	0.6	1	0.0
Reproductive System And Breast	7	2.1	3	0.0
Respiratory, Thoracic and Mediastinal Disorders	11	3.2	13	0.0
Pharyngolaryngeal pain	4	1.2	4	0.0
Skin and Subcutaneous Tissue Disorders	27	7.9	16	0.0
Swelling face	3	0.9	3	0.0
Skin tightness	5	1.5	0	0.0
Vascular Disorders	6	1.8	5	0.0
Hypertension	6	1.8	1	0.0

[1]Each AE which began during the double-blind period is included in an SOC count. Only selected Preferred Terms are shown. Within a Preferred Term, a patient is counted at most once.

Table 16. AEs reported by ≥ 1% patients. Open-label period. (table continued across 3 pages.)

SOC	Botox/Botox (n=287)		Pbo/Botox (n=284)	
Preferred Term	**n**	**%**	**n**	**%**
OVERALL	155	54.0	165	58.1
Eye Disorders	7	2.4	18	6.3
Eyelid ptosis	4	1.4	11	3.9
Gastrointestinal Disorders	21	7.3	26	9.2
Nausea	6	2.1	7	2.5
Vomiting	4	1.4	5	1.8
Toothache	2	0.7	4	1.4
GORD	3	1.0	1	0.4
General Disorders And Administration Site Cond.	22	7.7	20	7.0
Injection site pain	9	3.1	6	2.1
Fatigue	4	1.4	1	0.4
Non-cardiac chest pain	4	1.4	1	0.4
Injection site reaction	2	0.7	3	1.1
Flu like illness	1	0.3	3	1.1
Oedema peripheral	0	0.0	3	1.1
Infections And Infestations	73	25.4	65	22.9
Sinusitis	20	7.0	13	4.6
URTI	16	5.6	11	3.9
Nasopharyngitis	11	3.8	11	3.9
UTI	7	2.4	8	2.8
Bronchitis	4	1.4	8	2.8
Gastroenteritis viral	5	1.7	3	1.1
Influenza	4	1.4	3	1.1
Diverticulitis	1	0.3	3	1.1
Pneumonia	3	1.0	0	0.0
Injury, Poisoning And Procedural Complications	20	7.0	16	5.6
Contusion	4	1.4	2	0.7
Excoriation	3	1.0	0	0.0
Muscle strain	3	1.0	0	0.0
Investigations	1	0.3	13	4.6
ALT increased	4	1.4	3	1.1
AST increased	2	0.7	3	1.1

WBC increased	1	0.3	4	1.4
Musculoskeletal	40	13.9	65	22.9
Neck pain	14	4.9	22	7.7
Muscle spasms	5	1.7	6	2.1
Muscular weakness	3	1.0	14	4.9
Myalgia	3	1.0	7	2.5
Musculoskeletal stiffness	3	1.0	6	2.1
Musculoskeletal pain	1	0.3	11	3.9
Back pain	4	1.4	3	1.1
Intervertebral disc protrusion	3	1.0	1	0.4
Arthralgia	1	0.3	3	1.1
Pain in jaw	0	0.0	4	1.4
Nervous System Disorders	32	11.1	31	10.9
Migraine	9	3.1	10	3.5
Headache	8	2.8	8	2.8
Dizziness	2	0.7	6	2.1
hypoesthesia	4	1.4	0	0.0
Head discomfort	0	0.0	3	1.1
Psychiatric Disorders	10	3.5	15	5.3
Insomnia	4	1.4	6	2.1
Anxiety	1	0.3	5	1.8
Depression	1	0.3	5	1.8
Renal And Urinary Disorders	4	1.4	6	2.1
Nephrolithiasis	1	0.3	5	1.8
Respiratory, Thoracic and Mediastinal Disorders	10	3.5	12	4.2
Pharyngolaryngeal pain	2	0.7	4	1.4
Cough	2	0.7	3	1.1
Nasal congestion	1	0.3	3	1.1
Skin and Subcutaneous Tissue Disorders	11	3.8	16	5.6
Acne	4	1.4	0	0.0
Rash	1	0.3	3	1.1
Skin tightness	0	0.0	4	1.4
Vascular Disorders	4	1.4	3	1.1
Hypertension	3	1.0	3	1.1

Table 17. AEs. Double-blind period. Study 191622-080 (table continued across 3 pages).

SOC[1]	Botox (n=347)		Placebo (n=358)	
Preferred Term	**n**	**%**	**n**	**%**
Patients with one or more AEs	226	65.1	202	56.4
Blood And Lymphatic System Disorders	0	0.0	3	0.8
Cardiac Disorders	3	0.9	5	1.4
Ear And Labyrinth Disorders	4	1.2	2	0.6
Endocrine Disorders	0	0.0	1	0.3
Eye Disorders	19	5.5	3	0.8
Eyelid ptosis	11	3.2	1	0.3
Gastrointestinal Disorders	27	7.8	30	8.4
Nausea	7	2.0	10	2.8
Vomiting	4	1.2	6	1.7
Diarrhoea	2	0.6	4	1.1
General Disorders And Administration Site Cond.	40	11.5	38	10.6
Injection site pain	16	4.6	10	2.8
Fatigue	2	0.6	10	2.8
Flu like illness	4	1.2	3	0.8
Injection site bruising	1	0.3	6	1.7
Hepatobiliary Disorders	0	0.0	3	0.8
Immune System Disorders	7	2.0	6	1.7
Drug hypersensitivity	2	0.6	1	0.3
Anaphylactic reaction	1	0.3	0	0.0
Infections And Infestations	91	26.2	84	23.5
URTI	14	4.0	17	4.7
Sinusitis	13	3.7	10	2.8
Nasopharyngitis	16	4.6	14	3.9
Injury, Poisoning And Procedural Complications	17	4.9	30	8.4
Procedural pain	4	1.2	4	1.1
Contusion	1	0.3	4	1.1
Investigations	3	0.9	8	2.2
Metabolism and Nutrition Disorders	6	1.7	3	0.8
Musculoskeletal	99	28.5	50	14.0
Neck pain	34	9.8	8	2.2
Muscular weakness	18	5.2	2	0.6
Musculoskeletal pain	8	2.3	6	1.7

Arthralgia	5	1.4	6	1.7
Muscle spasms	4	1.2	4	1.1
Musculoskeletal stiffness	16	4.6	3	0.8
Back pain	4	1.2	9	2.5
Myalgia	15	4.3	3	0.8
Neoplasms	7	2.0	5	1.4
Nervous System Disorders	59	17.0	45	12.6
Headache	16	4.6	12	3.4
Migraine	14	4.0	14	3.9
Dizziness	8	2.3	10	2.8
Pregnancy, Puerperium	1	0.3	0	0.0
Psychiatric Disorders	16	4.6	23	6.4
Depression	6	1.7	9	2.5
Insomnia	5	1.4	8	2.2
Renal And Urinary Disorders	2	0.6	1	0.3
Reproductive System And Breast	9	2.6	8	2.2
Respiratory, Thoracic and Mediastinal Disorders	23	6.6	23	6.4
Skin and Subcutaneous Tissue Disorders	22	6.3	18	5.0
Rash	4	1.2	4	1.1
Pruritus	4	1.2	1	0.3
Pain of skin	3	0.9	1	0.3
Skin tightness	3	0.9	1	0.3
Social Circumstances	0	0.0	1	0.3
Vascular Disorders	7	2.0	8	2.2
Hypertension	5	1.4	6	1.7

[1]Each AE which began during the double-blind period is included in an SOC count. Only selected Preferred Terms are shown. Within a Preferred Term, a patient is counted at most once.

Table 18. AEs reported by ≥ 1% patients in either treatment group. Open-label period. Study 080. (table continued across 3 pages).

SOC	Botox/Botox (n=305)		Pbo/Botox (n=329)	
Preferred Term	**n**	**%**	**n**	**%**
OVERALL	174	57.0	209	63.5
Endocrine Disorders	4	1.3	1	0.3
Hypothyroidism	3	1.0	0	0.0
Eye Disorders	17	5.6	17	5.2
Eyelid ptosis	9	3.0	6	1.8
Gastrointestinal Disorders	20	6.6	31	9.4
Nausea	6	2.0	3	0.9
Vomiting	6	2.0	2	0.6
Diarrhoea	4	1.3	3	0.9
Gastric ulcer	4	1.3	3	0.9
Abdominal pain	4	1.3	2	0.6
General Disorders And Administration Site Cond.	24	7.9	24	7.3
Injection site pain	6	2.0	5	1.5
Flu like illness	3	1.0	5	1.5
Fatigue	4	1.3	2	0.6
Non-cardiac chest pain	3	1.0	2	0.6
Infections And Infestations	71	23.3	87	26.4
Nasopharyngitis	15	4.9	20	6.1
Sinusitis	12	3.9	16	4.9
URTI	8	2.6	13	4.0
Influenza	8	2.6	10	3.0
Bronchitis	4	1.3	7	2.1
UTI	5	1.6	5	1.5
Gastroenteritis	3	1.0	4	1.2
Pharyngitis	0	0.0	5	1.5
Tooth abscess	4	1.3	0	0.0
Injury, Poisoning And Procedural Complications	30	9.8	15	4.6
Fall	6	2.0	0	0.0
Foot fracture	3	1.0	2	0.6
Ligament rupture	3	1.0	0	0.0
Investigations	12	3.9	14	4.3
ALT increased	3	1.0	7	2.1

AST increased	1	0.3	6	1.8
Musculoskeletal And Connective Tissue Disorders	50	16.4	84	25.5
Neck pain	14	4.6	21	6.4
Muscular weakness	8	2.6	23	7.0
Muscle tightness	5	1.6	10	3.0
Musculoskeletal stiffness	1	0.3	13	4.0
Musculoskeletal pain	3	1.0	10	3.0
Back pain	7	2.3	4	1.2
Arthralgia	6	2.0	4	1.2
Myalgia	1	0.3	9	2.7
Muscle spasms	5	1.6	3	0.9
Pain in extremity	3	1.0	1	0.3
Nervous System Disorders	38	12.5	34	10.3
Migraine	13	4.3	7	2.1
Headache	4	1.3	14	4.3
Dizziness	10	3.3	3	0.9
Tension headache	3	1.0	0	0.0
Psychiatric Disorders	9	3.0	16	4.9
Depression	2	0.7	8	2.4
Insomnia	1	0.3	4	1.2
Respiratory, Thoracic and Mediastinal Disorders	13	4.3	10	3.0
Pharyngolaryngeal pain	4	1.3	2	0.6
Sleep apnoea syndrome	3	1.0	0	0.0
Skin and Subcutaneous Tissue Disorders	12	3.9	27	8.2
Rash	3	1.0	7	2.1
Skin tightness	1	0.3	9	2.7
Vascular Disorders	7	2.3	8	2.4
Hypertension	5	1.6	5	1.5

191622-038: Reported AEs are shown in Table 19, classified by SOC.

Table 19. AEs. Study 191622-038. (table continued across two pages.)

SOC[1]	Botox (n=173)		Placebo (n=182)	
Preferred Term	**n**	**%**	**n**	**%**
Patients with one or more AEs	138	79.8	119	65.4
Body as a Whole	86	49.7	67	36.8
Headache	19	11.0	12	6.6
Neck pain	23	13.3	2	1.1
Neck rigidity	9	5.2	5	2.7
Pain	9	5.2	5	2.7
Arm pain	10	5.8	2	1.1
Injection site haemorrhage	2	1.2	9	4.9
Cardiovascular System	11	6.4	15	8.2
Digestive System	31	17.9	23	12.6
Dysphagia	4	2.3	0	0.0
Endocrine System	2	1.2	3	1.6
Haemic and Lymphatic System	1	0.6	6	3.3
Ecchymosis	0	0.0	4	2.2
Metabolism and Nutrition Disorders	5	2.9	2	1.1
Musculoskeletal	48	27.7	6	3.3
Muscular weakness	38	22.0	0	0.0
Joint disorder	4	2.3	3	1.6
Tenosynovitis	3	1.7	2	1.1
Myalgia	2	1.2	0	0.0
Arthritis	1	0.6	1	0.5
Nervous System	32	18.5	30	16.5
Hypertonia	10	5.8	5	2.7
hypoesthesia	10	5.8	5	2.7
Depression	2	1.2	7	3.8
Respiratory System	48	27.7	36	19.8
Pharyngitis	10	5.8	7	3.8
Infection sinus	10	5.8	6	3.3
Skin and Appendages	20	11.6	16	8.8
Skin tightness	9	5.2	0	0.0
Special Senses	29	16.8	10	5.5
Blepharoptosis	13	7.5	1	0.5
Urogenital System	14	8.1	9	4.9

[1]Every AE is included in an SOC count. Only selected Preferred Terms are shown. Within a Preferred Term, a patient is counted at most once.

191622-039: Reported AEs are shown in Table 20, classified by SOC.

Table 20. AEs. Study 191622-039 (table continued across two pages).

SOC[1]	Botox 225U (n=182)		Botox 150U (n=168)		Botox 75U (n=174)		Placebo (n=178)	
Preferred Term	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Patients with one or more AEs	146	80.2	133	79.2	142	81.6	121	68.0
Body as a Whole	120	65.9	91	54.2	100	57.5	78	43.8
Neck pain	46	25.3	42	25.0	34	19.5	4	2.2
Headache	24	13.2	23	13.7	18	10.3	26	14.6
Neck rigidity	29	15.9	14	8.3	14	8.0	2	1.1
Pain	6	3.3	5	3.0	4	2.3	6	3.4
Arm pain	15	8.2	15	8.9	11	6.3	5	2.8
Injection site pain	17	9.3	10	6.0	8	4.6	10	5.6
Cardiovascular System	18	9.9	22	13.1	16	9.2	11	6.2
Digestive System	31	17.0	36	21.4	39	22.4	26	14.6
Dysphagia	11	6.0	6	3.6	3	1.7	2	1.1
Gastroenteritis	3	1.6	6	3.6	9	5.2	1	0.6
Endocrine System	3	1.6	3	1.8	4	2.3	0	0.0
Haemic and Lymphatic System	3	1.6	3	1.8	4	2.3	2	1.1
Ecchymosis	1	0.5	1	0.6	1	0.6	0	0.0
Metabolism and Nutrition Disorders	9	4.9	3	1.8	3	1.7	9	5.1
Musculoskeletal	64	35.2	54	32.1	48	27.6	12	6.7
Muscular weakness	57	31.3	47	28.0	31	17.8	2	1.1
Joint disorder	1	0.5	6	3.6	4	2.3	1	0.6
Tenosynovitis	3	1.6	1	0.6	1	0.6	5	2.8
Nervous System	45	24.7	45	26.8	45	25.9	29	16.3
Hypertonia	14	7.7	16	9.5	14	8.0	2	1.1
Hypoesthesia	15	8.2	12	7.1	13	7.5	4	2.2
Respiratory System	39	21.4	35	20.8	46	26.4	38	21.3
Pharyngitis	5	2.7	9	5.4	8	4.6	6	3.4
Infection sinus	8	4.4	10	6.0	11	6.3	8	4.5

Cough increased	1	0.5	1	0.6	2	1.1	7	3.9
Skin and Appendages	18	9.9	16	9.5	19	10.9	15	8.4
Rash	0	0.0	3	1.8	3	1.7	8	4.5
Skin tightness	3	1.6	2	1.2	3	1.7	0	0.0
Special Senses	27	14.8	25	14.9	19	10.9	11	6.2
Blepharoptosis	12	6.6	8	4.8	6	3.4	2	1.1
Eyelid oedema	2	1.1	4	2.4	0	0.0	0	0.0
Urogenital System	7	3.8	16	9.5	14	8.0	14	7.9

[1]Every AE is included in an SOC count. Only selected Preferred Terms are shown. Within a Preferred Term, a patient is counted at most once.

Pooled data from all studies (including the above, and the seven exploratory studies)

See Tables 21 and 22.

Table 21. Number (%) of patients with AEs reported by ≥ 2 patients in either treatment group (all migraine population; DBPC exposure)

SOC Preferred Term	**Botox (N = 544)**	**Placebo (N = 544)**
OVERALL	1754 (69.3%)	871 (56.4%)
Eye Disorders	290 (11.5%)	36 (2.3%)
Eyelid ptosis	156 (6.2%)	11 (0.7%)
Gastrointestinal Disorders	267 (10.5%)	131 (8.5%)
Nausea	76 (3.0%)	35 (2.3%)
General & Administration Site	335 (13.2%)	139 (9.0%)
Injection site pain	117 (4.6%)	38 (2.5%)
Infections & Infestations	675 (26.7%)	409 (26.5%)
Upper respiratory tract infection	128 (5.1%)	95 (6.2%)
Sinusitis	122 (4.8%)	68 (4.4%)
Nasopharyngitis	120 (4.7%)	68 (4.4%)
Influenza	79 (3.1%)	49 (3.2%)
Bronchitis	68 (2.7%)	28 (1.8%)
Injury Poisoning & Procedural	183 (7.2%)	143 (9.3%)
Contusion	20 (0.8%)	31 (2.0%)
Musculoskeletal & Connective Tissue	848 (33.5%)	207 (13.4%)
Neck pain	274 (10.8%)	39 (2.5%)
Musculoskeletal stiffness	189 (7.5%)	29 (1.9%)
Muscular weakness	194 (7.7%)	7 (0.5%)
Musculoskeletal pain	111 (4.4%)	25 (1.6%)
Muscle tightness	103 (4.1%)	7 (0.5%)
Myalgia	89 (3.5%)	14 (0.9%)
Back pain	57 (2.3%)	23 (1.5%)
Nervous System Disorders	630 (24.9%)	203 (13.1%)
Facial paresis	248 (9.8%)	7 (0.5%)
Headache	165 (6.5%)	81 (5.2%)
Migraine	90 (3.6%)	35 (2.3%)
Dizziness	63 (2.5%)	25 (1.6%)
Psychiatric Disorders	115 (4.5%)	75 (4.9%)
Depression	45 (1.8%)	31 (2.0%)
Skin & Subcutaneous Tissue Disorders	220 (8.7%)	88 (5.7%)
Hypoesthesia facial	60 (2.4%)	8 (0.5%)

Table 22. Number (%) of patients with serious AEs reported by ≥ 2 patients (all migraine population; any Botox exposure)

System Organ Class Preferred Term	**Any Botox** **(N = 3235)**
OVERALL	2383 (73.7%)
Eye Disorders	380 (11.7%)
Eyelid ptosis	198 (6.1%)
Gastrointestinal Disorders	398 (12.3%)
Nausea	107 (3.3%)
General Disorders & Administration Site	459 (14.2%)
Injection site pain	152 (4.7%)
Infections & Infestations	1039 (32.1%)
Sinusitis	219 (6.8%)
Nasopharyngitis	200 (6.2%)
Upper respiratory tract infection	199 (6.2%)
Influenza	131 (4.0%)
Bronchitis	107 (3.3%)
Urinary tract infection	70 (2.2%)
Musculoskeletal & Connective Tissue	1100 (34.0%)
Neck pain	343 (10.6%)
Muscular weakness	228 (7.0%)
Musculoskeletal stiffness	214 (6.6%)
Musculoskeletal pain	139 (4.3%)
Muscle tightness	138 (4.3%)
Myalgia	110 (3.4%)
Back pain	86 (2.7%)
Muscle spasms	68 (2.1%)
Arthralgia	65 (2.0%)
Nervous System Disorders	814 (25.2%)
Facial paresis	279 (8.6%)
Headache	208 (6.4%)
Migraine	132 (4.1%)
Dizziness	96 (3.0%)
Psychiatric Disorders	195 (6.0%)
Depression	66 (2.0%)
Skin & Subcutaneous Tissue Disorders	309 (9.6%)
Hypoesthesia facial	72 (2.2%)

Specific AEs

AEs potentially associated with effects remote from the site of injection

These were specifically sought by the sponsor. AEs were ascertained under the general headings: Airway reflexes and breathing, Body weakness, Ocular manifestations, Cranial neuropathies, Autonomic manifestations, Speech and swallowing and Botulism. These were assessed in the light of patient comorbidities, concomitant medications and non-specific or constitutional symptoms. AEs among 17 relevant Preferred Terms (dyspnoea, pneumonia aspiration, respiratory failure, hypotonia, muscular weakness, diplopia, extraocular muscle paresis, eyelid ptosis, vision blurred, facial palsy, facial paresis, bradycardia, constipation, dry mouth, urinary retention, dysarthria, and dysphagia) were

reported from 34 patients following placebo treatment and 658 patients following Botox treatment. Based upon individual case review and the muscles required to be injected in the migraine studies, ten terms (eyelid ptosis, diplopia, vision blurred, extraocular muscle paresis, facial palsy, facial paresis, dysarthria, dysphagia, dry mouth, and hypotonia) were identified as local AEs and therefore not the result of possible distant spread of toxin. This left the following terms for further consideration: dyspnoea, pneumonia aspiration, respiratory failure, muscular weakness, bradycardia, constipation, urinary retention.

Detailed analysis of the one patient in whom all of dyspnoea, pneumonia aspiration, urinary retention, and bradycardia were reported eliminated these as resulting from remote effects of Botox, and left respiratory failure, muscular weakness and constipation for further consideration.

Constipation was reported in twelve patients on Botox and two on placebo. The sponsor noted

> "Individual case review demonstrated that the patients who reported constipation either had underlying confounding medical conditions predisposing to constipation (for example, hypothyroidism, irritable bowel, or spastic colon) or were taking concomitant medications known to cause constipation (opioids). The adverse event of constipation was observed across a wide dose range of Botox (9 U to 200 U)."

and assessed the cases as not the result of possible distant spread of toxin.

Muscular weakness was reported in 228 patients on Botox and seven on placebo. In 223/228 of the Botox cases, reported events were isolated to the head and neck, shoulders, and/or arms.

Dyspnoea was reported in ten patients on Botox and two on placebo. Factors unrelated to study drug, or local effects of Botox on neck muscles, were considered likely causes.

Serious adverse events and deaths

Data from the Phase III studies and Phase II studies presented as pertinent to the claimed indication

191622-079: No deaths. Numbers of SAEs reported were as follows:

Double-blind period: 18/340 on Botox; 8/334 on placebo. None was considered related to study drug.

Open-label period: 28/571. Only one of these was considered treatment-related (intractable migraine).

191622-080: No deaths. Numbers of SAEs reported were as follows:

Double-blind period: 15/347 on Botox; 8/358 on placebo. Only one of these was considered treatment-related (intractable migraine, in a Botox patient).

Open-label period: 18/634. Only one of these was considered treatment-related (intractable migraine).

191622-038: One death (cardiovascular disorder; on placebo (pbo)). Other SAEs: 6/173 on Botox; 8/182 on placebo. One of these was considered possibly treatment-related (migraine, in a placebo patient).

191622-039: No deaths. Other SAEs: 11/182 on Botox 225U; 8/168 on Botox 150U; 7/174 on Botox 75U; 8/178 on placebo. None of these was considered treatment-related.

Pooled data from all studies (including the above, and the seven exploratory studies)

Deaths: Only the one listed above. Serious AEs: See Tables 23 and 24.

Table 23. Number (%) of patients with serious AEs reported by ≥ 2 patients in either treatment group (all migraine population; DBPC exposure)

SOC Preferred Term	**BOTOX (N = 2532)**	**Placebo (N = 1544)**
OVERALL	83 (3.3%)	36 (2.3%)
Gastrointestinal Disorders	9 (0.4%)	3 (0.2%)
Abdominal pain	2 (0.1%)	1 (0.1%)
Hepatobiliary Disorders	4 (0.2%)	1 (0.1%)
Cholelithiasis	2 (0.1%)	1 (0.1%)
Infections & Infestations	13 (0.5%)	9 (0.6%)
Pneumonia	3 (0.1%)	2 (0.1%)
Appendicitis	2 (0.1%)	1 (0.1%)
Gastroenteritis	0 (0.0%)	2 (0.1%)
Musculoskeletal & Connective Tissue	6 (0.2%)	3 (0.2%)
Intervertebral disc protrusion	2 (0.1%)	3 (0.2%)
Neoplasms	9 (0.4%)	3 (0.2%)
Uterine leiomyoma	3 (0.1%)	1 (0.1%)
Breast cancer	2 (0.1%)	1 (0.1%)
Nervous System Disorders	17 (0.7%)	4 (0.3%)
Migraine	5 (0.2%)	1 (0.1%)
Headache	4 (0.2%)	0 (0.0%)
Psychiatric Disorders	5 (0.2%)	0 (0.0%)
Depression	2 (0.1%)	0 (0.0%)
Major depression	2 (0.1%)	0 (0.0%)
Reproductive System & Breast	7 (0.3%)	4 (0.3%)
Endometriosis	1 (0.0%)	3 (0.2%)

Table 24. Number (%) of patients with SAEs reported by ≥2 patients All migraine population. Any Botox exposure (table continued across two pages).

SOC Preferred Term	**Any Botox** **(N = 3235)**
OVERALL	136 (4.2%)
Cardiovascular disorders	11 (0.3%)
Tachycardia	2 (0.1%)
Gastrointestinal disorders	21 (0.6%)
Abdominal pain	4 (0.1%)
Abdominal pain upper	2 (0.1%)
Small intestinal obstruction	2 (0.1%)
General Disorders & Administration Site	7 (0.2%)
Non-cardiac chest pain	4 (0.1%)
Hepatobiliary Disorders	6 (0.2%)
Cholecystitis	2 (0.1%)
Cholelithiasis	2 (0.1%)
Infections & Infestations	21 (0.6%)
Pneumonia	5 (0.2%)
Appendicitis	2 (0.1%)
Metabolism & Nutrition Disorders	2 (0.1%)
Hypokalaemia	2 (0.1%)
Musculoskeletal & Connective Tissue	10 (0.3%)
Intervertebral disc protrusion	3 (0.1%)
Neoplasms	17 (0.5%)
Uterine leiomyoma	6 (0.2%)
Breast cancer	3 (0.1%)
Basal cell carcinoma	2 (0.1%)
Squamous cell carcinoma	2 (0.1%)
Nervous System Disorders	25 (0.8%)
Migraine	10 (0.3%)
Headache	4 (0.1%)
Status migrainosus	2 (0.1%)
Syncope	2 (0.1%)
Psychiatric Disorders	9 (0.3%)
Depression	3 (0.1%)
Major depression	3 (0.1%)
Renal & Urinary Disorders	5 (0.2%)
Calculus ureteric	2 (0.1%)

Table 24 continued.	
Nephrolithiasis	2 (0.1%)
Reproductive System & Breast Disorders	11 (0.3%)
Menorrhagia	3 (0.1%)
Ovarian cyst	2 (0.1%)

Laboratory findings-Data from the Phase III studies and Phase II studies presented as pertinent to the claimed indication

191622-079

Routine clinical haematology and biochemistry tests were done at baseline, Week 24 (end of double-blind period) and Week 56. No meaningful trends were identified, and none of the individual abnormal values was considered clinically significant.

191622-080

As for Study 191622-079.

191622-038

No meaningful trends were identified. Three patients, all on Botox, had abnormal laboratory values reported as AEs. One of these is listed as a discontinuation below. The others were: one diabetes and one elevated liver enzymes, positive hepatitis B core antibody. None of these was considered study drug-related. Three others had abnormal laboratory values reported as "medical events" before Day 0.

191622-039

No meaningful trends were identified. Fifteen abnormal laboratory values were reported as AEs: seven in patients on Botox (one leucocytosis, one thrombocythaemia, two anaemia, two raised alkaline phosphatase, one raised AST); and eight in patients on placebo (one leucocytosis, one thrombocythaemia, three raised cholesterol, one raised urea, one raised creatinine, one raised ALT).

Pooled data from all the DBPC studies

Table 25 shows laboratory abnormalities meeting potentially clinically significant values obtained in the nine DBPC studies (the four studies considered above plus Studies 191622-005, 191622-009, 191622-024, 191622-037 and 191622-509). "Potentially clinically significant" meant meeting ≥ 1 of the criteria: (a) the investigator's opinion; or (b) tables of values considered clinically significant (for example, 3 x upper limit of normal (ULN) for AST).

Table 25. Potentially clinically significant laboratory abnormalities. Pooled data from DBPC phases of all studies

= direction of laboratory values as reported by < 3 patients. ▼ ▲ = direction of laboratory values as reported by 3 to 5 patients

Possible Direction	Study	191622-080		191622-079		191622-038		191622-039		191622-037		191622-509		191622-024		191622-		191622-005	
	Treatment Group	BTX	PBO	BTX	PBO	BTX	PBO	BTX	PBO	BTX	PBO	BTX	PBO	BTX	PBO	BTX	PBO	BTX	PBO
	N	347	358	340	334	173	182	524	178	187	182	377	118	312	106	187	45	82	41
↓↑	Calcium					↓								↓					
	Phosphorus	▲	↑	↓▲	▲	▲	↓	↓▲	▲	↓	↑	↓		↓↑	↓	↑			
	Potassium	↑	↓↑	↑	↑	↑		↑											
	Sodium	↓	↓		↓														
↓↑	ALT	↑	▲	↑	↑			▲	↑					↑				↑	
	AST		↑				↑											↑	
	Alkaline phosphatas																		
	Bilirubin, total	↑						↑				↑	↑			↑		Not evaluated	
	Creatinine			↑															
	Blood urea nitrogen					↑	↑	↑	▲	↑	↑	↑				↑			
	Uric acid (female)	↑	↑	▲	↑	↑	↑	↑	▲	↑	↑								
	Uric acid (male)					↑			↑						↑				
↓↑	Albumin													↓					
↓↑	Glucose		↓		▲		↓							↑	↑	↓		↓	
↓↑	Hematocrit													↓					
	Hemoglobin		↓	▼				↓	↓		↓		↓	↓		↓	↓		
	Platele t count		↓					↑	↑	↑		↑		↑		↑			
	WBC count		↓↑	↓	↓↑		↓	▼↑	↑			↓	↑	↑					

Comment on laboratory monitoring

There is no indication of any consistent pattern of abnormalities.

Discontinuation due to adverse events-Data from the Phase III studies and Phase II studies presented as pertinent to the claimed indication

Note that in this section, the AEs for Studies 191622-038 and 191622-039 are collected together and presented by patient, whereas the AEs for Studies 191622-079 and 191622-080 have not been sorted in that way, as the presentation in the current Australian submission did not permit this.

191622-079

Double-blind period: 14/340 on Botox (3 headache, 2 neck pain, 1 atrial fibrillation, 1 carotid artery occlusion, 1 cerebral infarction, 1 confusional state, 1 eyelid ptosis, 1 hypertension, 1 hypoesthesia, 1 injection site pain, 1 intermittent explosive disorder, 1 major depression, 1 muscle spasms, 1 muscular weakness, 1 syncope, 1 whiplash injury); 3/334 on placebo (1 anxiety, 1 migraine, 1 panic attack, 1 temporomandibular joint syndrome).

Open-label period: 9/571 (3 muscle spasms, 3 neck pain, 2 dizziness, 2 headache, 2 injection site pain, 1 joint stiffness, 1 back pain, 1 chills, 1 dry mouth, 1 head discomfort, 1 influenza like illness, 1 injection site bruising, 1 injection site swelling, 1 malaise, 1 migraine, 1 muscle tightness, 1 muscular weakness, 1 musculoskeletal pain, 1 myalgia, 1 nausea, 1 skin tightness, 1 vomiting).

191622-080

Double-blind period: 12/347 on Botox (3 migraine, 2 breast cancer, 2 muscular weakness, 2 neck pain, 1 eyelid ptosis, 1 facial paresis, 1 pleurisy, 1 pneumonia, 1 skin tightness); 5/358 on placebo (1 headache, 1 papillary thyroid cancer, 1 pulmonary sarcoidosis, 1 thrombocytopenia, 1 urticaria).

Open-label period: 22/634 (2 eyelid ptosis, 2 migraine, 2 neck pain, 2 muscular weakness, 1 constipation, 1 joint stiffness, 1 muscle spasms, 1 musculoskeletal stiffness, 1 non-cardiac chest pain, 1 pain in jaw, 1 tachycardia, 1 tension headache, 1 brain neoplasm malignant, 1 depression, 1 headache, 1 musculoskeletal pain, 1 pain, 1 paraesthesia, 1 rash, 1 skin tightness, 1 viral infection, 1 vision blurred).

191622-038

4/173 on Botox (2 neck pain or weakness; 1 neck rigidity and pain, muscular weakness, worsening headache, moderately elevated ALT, AST and calcium; 1 injection site pain); **1/182 on placebo** (depression).

191622-039

9/182 on Botox 225U (2 hypoesthesia; 1 headache, neck weakness; 1 neck weakness, neck pain, nausea, eyebrow weakness; 1 neck pain, forehead weakness, headache, shoulder pain; 1 blepharitis, sinus infection, blepharoptosis, headache, hypoesthesia, eyebrow weakness; 1 neck weakness, back pain, dysphagia, respiratory infection; 1 neck pain, injection site pain, headache, nausea, neck weakness, dysphagia, knee pain; 1 neck pain, neck weakness, shoulder hypertonia, dizziness, facial hypertonia; 1 shoulder pain, neck pain, neck weakness, headache, respiratory infection).

13/168 on Botox 150U (1 neck pain, neck rigidity, dysphagia, headache, neck weakness, back pain, chalazion, parathyroid disorder, psoriasis; 1 brain abscess; 1 body pain, dysphagia; 1 accidental injury, insomnia, haematemesis, pharyngitis, diarrhoea, pruritus, dyspepsia, neck pain, abnormal LFTs; 1 leg pain, leg weakness, cellulitis, infection,

arthritis, cardiovascular disorder, abnormal LFTs, iron deficiency anaemia, chest pain, haematuria, thrombocythaemia, urinary retention, gastroenteritis, joint disorder, hypothyroidism; 1 neck weakness, neck pain, kidney calculus; 1 forehead weakness, kidney infection, depression; 1 injection site ecchymosis, neck pain, neck rigidity; 1 dysphagia, shoulder pain, neck pain; 1 neck pain, weakness; 1 injection site pain, back pain, alopecia, respiratory infection, anisocoria; 1 injection site stinging, back pain, eyelid oedema, facial oedema, hypertonia, neck rigidity, weakness, blepharoptosis, hypertonia, injection site pain, weakness, back pain, asthenia, dry skin, skin discoloration, respiratory infection, shoulder pain, joint disorder, breast enlargement, rhinitis, urticaria, dysphagia; 1 headache, blepharoptosis, nausea).

3/174 on Botox 75U (1 neck weakness, neck pain, pharyngitis, herpes zoster; 1 dehydration, skin discoloration, hypoesthesia, respiratory infection, somnolence (secondary to Depakote), headache; 1 shoulder pain, neck pain);

2/178 on placebo (1 injection site haemorrhage, injection site pain, headache, respiratory infection; 1 respiratory infection, traumatic fracture, neck pain, neuropathy, hypoesthesia, arm weakness, skin laceration).

The seven exploratory studies

AEs reported in patients who discontinued are shown in Table 26.

Table 26. AEs reported in patients who discontinued. Exploratory studies. (table continued across two pages.)

Study	Treatment group	AEs
191622-005	None	
191622-009	None	
191622-024	Botox 50U	dizziness and sweating at the time of the injections
191622-026	Botox 50U/50U	bone disorder (bone spur C-5), cough increased, depression, ALT increased, headache
	Botox 50U/50U	visual disturbance, urinary tract infection, ecchymosis, asthenia, blepharoptosis, pain (left temple sensitive to touch)
	Botox 25U/25U	migraine (worsening), eye oedema, eye pain
	Botox 25U/25U	endometrial disorder
	Pbo/Botox 25U	hypokinesia (loss of right eyebrow movement), hypoesthesia (numbness right brow/temple), asthenia, jaw ache, nausea, flu syndrome, cough increased, rhinitis
	Pbo/Botox 25U	sinus infection, joint disorder (left shoulder rotator cuff repair), migraine, anxiety (worsening)
191622-036	Botox 25U/Pbo	sinus infection, recurrent pituitary adenoma
191622-037	Botox	neck pain, eyebrow weakness, facial weakness, neck pain, blepharoptosis, bursitis

	Botox	headache
	Botox	eyelid oedema, headache, muscular weakness, blepharoptosis, bone fracture
	Botox	forehead tightness, neck pain, migraine, blepharoptosis
	Botox	upper respiratory viral infection, bilateral knee abrasions, hip and leg muscular pain, neck weakness, shoulder pain, neck pain
	Botox	neck weakness, neck pain, shoulder weakness, arm pain, erythema, paraesthesia, urticaria, migraine, sinusitis
	Placebo	injection site haemorrhage, arm pain, muscular weakness, neck pain, blepharoptosis
191622-509	Botox 225U	muscular weakness, dysphagia
	Botox 225U	blepharoptosis
	Botox 225U	neck pain, neck rigidity, conjunctival hyperaemia
	Botox 225U	blepharoptosis, neck rigidity, paraesthesia
	Botox 150U	cerebrovascular accident
	Botox 150U	chalazion, neck pain
	Botox 150U	neck pain, muscular weakness
	Botox 150U	eyelid (not specified), blepharoptosis
	Botox 75U	neck pain, myalgia
	Botox 75U	neck rigidity
	Botox 75U	skin tightness, rash, conjunctival hyperaemia
	Botox 75U	neck rigidity, muscular weakness
	Placebo	back pain
	Placebo	migraine

Evaluator's overall conclusions on clinical safety

The sponsor's remarks on Constipation and Dyspnoea do not appear to completely resolve the question of a possible relationship to Botox. The *Precautions* section of the approved PI touches upon this. It is suggested that continuing vigilance should be exercised.

The data presented in support of the present application do not appear to raise any safety concerns which are not already addressed in the approved PI. The proposed dosage for chronic migraine prophylaxis (5U per site; maximum total dose at each treatment 195U; repetition 12-weekly) is encompassed by the dosage recommendations for approved indications (specifically – for blepharospasm; focal limb spasticity; cervical dystonia).

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a "List of Questions" to the sponsor is generated. The following two questions were posed by the evaluator:

1. The clinical evaluator suggested the sponsor be invited to comment on the adequacy of blinding.

2. The sponsor should be asked to clarify the source of the data (see discussion relating to Study 191622-038 in Table 13.)

Following receipt of the first CER the sponsor submitted supplementary data that were evaluated in a second CER, referred to below as the supplementary CER. The supplementary CER evaluated justifications, literature and additional analyses of the studies evaluated in the initial CER.

Clinical Summary and Conclusions (1)

The evidence of efficacy in a well defined population is inadequate. The clinical evaluator therefore recommended rejection of the application.

Clinical evaluation of supplementary data

Introduction

The Clinical Evaluation Report (CER) recommended rejection of the application on the grounds that "evidence of efficacy in a well defined population is inadequate". The main problems were:

The studies did not enrol a population that corresponded with the definition of chronic migraine according to the ICHD-2. The enrolment criteria for the pivotal studies did not include two components of the ICHD-2 definition of chronic migraine, namely:

Headaches should be present on ≥15 days per month for more than 3 months. The pivotal studies required headaches to have been present on≥15 days per month, but did not specify a minimum duration for which headaches must have been present at this frequency (other than the 4-week duration implied by the 4-week screening period).

No medication overuse, where "medication overuse" is defined according to ICHD-2 criteria as the overuse of medications intended to abort a migraine attack (ergotamine, triptans, opioids or combination analgesics on≥10 days per month, or simple analgesics on≥15 days per month). Instead, the pivotal studies allowed the enrolment of patients with medication overuse.

Although the studies were intended to be double-blind, botulinum toxin has an effect (muscle paralysis or weakness) that would be apparent to some study participants and that would tend to unblind their treatment allocation. Unblinding would be expected to bias the study results in favour of the presumed active treatment (Botox). The sponsor argued that blinding was preserved, but the pivotal studies did not include any assessments to show that this was actually the case and the clinical evaluator did not accept the sponsor's arguments.

The selection of doses for the pivotal studies (and hence for the product information) was arbitrary and not evidence-based. The mechanism of action of Botox in chronic migraine has not been determined but is postulated to differ from the mechanism of action in the existing indications. It is therefore not reasonable to simply use the doses that have been approved for other indications. The preliminary studies in patients with migraine and other forms of headache did not show a statistically significant treatment effect of Botox at any dose, failed to demonstrate a dose-response relationship, and failed to delineate either a minimal effective dose or a maximum tolerated dose.

No evidence of continued efficacy with repeated treatment was available from double-blind placebo- (or active-) controlled trials. Only weak and potentially biased evidence (from open-label studies) was presented.

There were no clinical objections to registration on safety grounds. The safety profile of Botox in the submitted studies was similar to that seen in previously-submitted studies in other indications, and the proposed dosage (5 U per site, maximum total dose 195 U per treatment, repetition 12-weekly) is within the range that is already approved for other indications.

The CER did not include an explicit benefit-risk assessment. However, it should be evident from the above discussion that the known risks of Botox, comprising a range of local and systemic adverse effects, when balanced against a failure to adequately demonstrate efficacy (that is, benefit) in the proposed indication, would lead to an unfavourable benefit-risk balance.

Proposed Indication

The indication as originally proposed was "prophylaxis of headaches in adults with chronic migraine".

The TGA's Risk Management Plan Evaluation Report recommended that "The case definition for chronic migraine should be based on evidence in the clinical trials and needs to be clearly described in the PI. This is to ensure consistency for prescribers and to reduce the potential for off-label use in episodic migraine and chronic tension-type headache populations".

In response, the sponsor changed the proposed indication to "prophylaxis of headaches in adults with chronic migraine (headaches on ≥ 15 days per month)".

Comment: The proposed new indication still does not satisfactorily describe the population that was actually studied, and further modification is recommended.

Scope of the Supplementary Data Package Submitted by the Sponsor

The sponsor's response to the CER covered three areas:

Concerns relating to the patient population in terms of:

Clarification of the diagnostic criteria for chronic migraine;

Justification of the Phase II population in support of the Phase III studies.

Issues regarding the Phase III study design and the strength of the evidence of efficacy demonstrated in the Phase III studies summarised as:

Justification for use of placebo comparator in the context of the EMA Guideline (EMEA/CPMP/EWP/2158/99);

Rationale for the dose used in the Phase III studies;

Clinical significance of the efficacy results for chronic migraine;

Adequacy of blinding during the Phase III studies.

Additional concerns raised by the clinical evaluator:

Relationship between Botox and the reported adverse events (AEs) of constipation and dyspnoea;

Use of the term "Complicated Migraine";

Validation of the HIT-6 questionnaire;

Clarification on the source data for Table 1-7 (see Table 13).

The response was accompanied by supporting analyses of the previously-submitted studies and several published references. No new clinical studies of the use of Botox for the treatment of chronic migraine were submitted.

Evaluation of the Sponsor's Response and Supporting Data

The sponsor's response and associated supporting data were considered in the order that it was presented, as per the dot points above.

Concerns Relating to the Patient Population

Clarification of the diagnostic criteria for chronic migraine

An issue raised in the CER related to the status of revised criteria for diagnosing chronic migraine (CM) that had been referred to by the sponsor when justifying the enrolment criteria for the pivotal studies. In the original submission, the sponsor cited a 2007 paper by Bigal *et al*[10] and it was not clear from that paper whether the revised criteria had been formally adopted. In their response, the sponsor has cited another published paper (Headache Classification Committee 2006[11]) which states that the revised criteria (hereafter referred to as the ICHD-2R criteria for CM) "are included in the Appendix of ICHD-2 and are meant primarily for further scientific evaluation but may be used already now for inclusion into drug trials, etc". The revised criteria are reproduced below:

[10] Bigal ME *et al*. The International Classification of Headache Disorders revised criteria for chronic migraine – field testing in a headache specialty clinic. *Cephalalgia* 2007; 27:230–234.

[11] Headache Classification Committee: Olesen J, Bousser MG, Diener HC, Dodick D, First M, Goadsby PJ, *et al*. New appendix criteria open for a broader concept of chronic migraine. Cephalalgia 2006;26:742-746.

Table 27. ICHD-2R criteria for chronic migraine.

Appendix 1.5.1 Chronic migraine A. Headache (tension-type and/or migraine) on ≥15 days per month for at least 3 months* B. Occurring in a patient who has had at least five attacks fulfilling criteria for 1.1 Migraine without aura C. On ≥ 8 days per month for at least 3 months headache has fulfilled C1 and/or C2 below, that is, has fulfilled criteria for pain and associated symptoms of migraine without aura 1. Has at least two of a-d (a) unilateral location (b) pulsating quality (c) moderate or severe pain intensity (d) aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs) and at least one of a or b (a) nausea and/or vomiting (b) photophobia and phonophobia 2. Treated and relieved by triptan(s) or ergot before the expected development of C1 above D. No medication overuse† and not attributed to another causative disorder‡
*Characterization of frequently recurring headache generally requires a headache diary to record information on pain and associated symptoms day-by-day for at least 1 month. Sample diaries are available at http://www.i-h-s.org †Medication overuse as defined under 8.2 *Medication-overuse headache*. ‡History and physical and neurological examinations do not suggest any of the disorders listed in groups 5-12, or history and/or physical and/or neurological examinations do suggest such a disorder but it is ruled out by appropriate investigations, or such disorder is present but headache does not develop in close temporal relation to the disorder.

The paper clarifies that the Headache Classification Committee (HCC) had found that the ICHD-2 criteria for CM were not workable and the revision was an attempt to address the problem. The main problem with the original CM criteria was that they required patients to experience characteristic migraine headaches on ≥15 days per month. This prevented a diagnosis of chronic migraine in patients whose symptoms were partially averted by acute treatment of the episodes, so that their treated headache episodes had the characteristics of tension-type headache (TTH) rather than those of full-blown migraine. To formally qualify for the diagnosis of CM, such patients would have to abstain from acute treatment until they had accumulated the required number of full-blown migraine days in a month and it was found that patients would not do this. It was also considered clinically unhelpful in patients with CM to attempt to classify individual headache episodes as either TTH or true migraine. Firstly, some headaches might start as TTH but then trigger or transform into a migraine. Secondly, it was found that in patients with migraine, headaches that had the characteristics of TTH rather than those typical of migraine would nevertheless respond well to triptans. This is in contrast to studies showing that in pure TTH the effect of triptans is modest or non-existent. The inference is that in patients with CM at least some headaches fulfilling TTH criteria are actually mild migraines rather than true TTH. Accordingly, the criteria for CM were "relaxed" to include patients with "Headache

(tension-type and/or migraine) on ≥15 days per month for at least 3 months". To confirm that the patient does indeed have migraine and not just TTH, the revised criteria also require characteristic migraine headaches, or characteristic migraine headaches whose expected development was averted by triptan(s), on ≥8 days per month for at least 3 months.

The ICHD-2R criteria for CM also include "No medication overuse". The reason for this criterion is that in patients who are using "abortive" headache medications (that is, medications such as triptans, ergotamine, opioids and other analgesics) on a very frequent basis, the medication overuse itself is a potential contributor to the high frequency of headaches (possibly related to rebound when the medication wears off). At the same time, the ICHD-2R criteria for medication overuse headache (MOH) were revised to allow a diagnosis of MOH without withdrawing abortive medications (previously, the diagnosis could only be made if the headaches failed to respond to withdrawing such medications for a minimum of two months). Nevertheless, in the absence of a genuine attempt at abortive medication withdrawal, one cannot be certain whether a patient's chronic headaches are due to migraine, medication overuse, or a combination of both.

The revised criteria are "formal" in the sense that they were developed by the HCC and have been published in an appendix to the ICHD-2, but they are not "finalised" because the HCC expects them to be "field tested" and they may undergo further revision if it is found that they are still problematic. Nevertheless, given the problems with the ICHD-2 criteria and the fact that the ICHD-2R criteria represent current thinking amongst experts in the field, it is reasonable to accept the sponsor's argument that the ICHD-2R criteria for CM should be the reference standard to which the Botox pivotal study inclusion criteria are compared.

The sponsor has acknowledged that the ICHD-2R criteria for CM still do not match the entry criteria for the Botox pivotal trials, 191622-038 and 191622-039. To be randomised in the Botox pivotal studies, patients had to have ≥15 headache days during the previous 28 days, with ≥4 h continuous headache on each of these headache days, and ≥ 50% of the headache days being probable migraine. Medication overuse was allowed.

There are four main points of difference between these entry criteria and the ICHD-2R criteria for CM:

The ICHD-2R criteria require that headaches must have occurred on ≥15 days per month for at least 3 months, with a corresponding 3 month minimum history requirement for migraine-type headaches. The entry criteria for the Botox pivotal studies included the "≥15 days per month" frequency element (actually ≥15 days over the 28 day screening period), but not the "at least 3 months" history element. Instead, the Botox pivotal study entry criteria required an effective minimum history of only one month (the duration of the screening period). Presumably, investigators would only have entered patients in the screening period who had already had headaches on ≥15 days per month at the start of screening, thus extending to 2 months the effective minimum history of frequent headaches prior to randomisation. However, it is likely that most of the patients in the Botox studies actually had a history of frequent headaches extending well beyond the three month minimum specified by the ICHD-2R, as discussed below.

The ICHD-2R criteria exclude patients with medication overuse, whereas the Botox trials included patients with medication overuse (based on medication usage during the screening period).

The ICHD-2R criteria do not specify how long the headaches must last on each headache day, whereas the Botox trials required that headaches be continuous for at least 4 hours on each headache day during the screening period.

The ICHD-2R criteria require that the headaches be migraine or medication-modified migraine on ≥8 days per month, whereas the Botox trials required that the headaches be "probable migraine" on ≥50% of the headache days during the screening period (that is, the minimum required number of probable migraine days could be as low as 8 or as high as 14, depending on whether the patient had the minimum allowed (15) or maximum possible (28) number of headache days during the screening period).

In respect of the first point of difference, the sponsor stated that "at baseline, the enrolled population had a 20 year mean duration of CM". No information about the duration of migraine in the pivotal study population was included. However, Table 28 shows that the mean duration of "frequent migraine" in the pivotal studies was 19.4 and 19.1 years in the Botox and placebo groups, respectively. The duration of "frequent migraine" was <10 years in 26.5% and 28.3% of the Botox and placebo groups, respectively. No data were provided regarding the percentage of patients who actually fulfilled the ICHD-2R frequency and history criteria for CM (criteria A and C), but given the available information the percentage is likely to be very high.

Table 28. Baseline disease characteristics (Phase III Chronic Migraine Population; DBPC Exposure).

Disease Characteristic	BOTOX® (N = 687)	Placebo (N = 692)
Time since onset of frequent migraine (years)[a], mean ± SD	19.4 ± 12.44	19.1 ± 12.70
Time since onset of frequent migraine, n (%)		
< 10 years	182 (26.5%)	196 (28.3%)
10 to 20 years	199 (29.0%)	208 (30.1%)
> 20 years	306 (44.5%)	288 (41.6%)
Age of onset of frequent migraine (years)[b], mean ± SD	21.2 ± 10.95	21.9 ± 11.94
Age of onset of frequent migraine, n (%)		
< 12 years	131 (19.1%)	130 (18.8%)
12 to 17 years	176 (25.6%)	174 (25.1%)
18 to 40 years	339 (49.3%)	334 (48.3%)
> 40 years	41 (6.0%)	54 (7.8%)
Baseline use of acute headache pain medications, (yes), n (%)	671 (97.7%)	675 (97.5%)
Baseline overuse of acute headache pain medications[c] (yes), n (%) [a]	445 (64.8%)	458 (66.2%)
Pretrial headache prophylactic medication use (yes), n (%)	427 (62.2%)	452 (65.3%)

SD = standard deviation; Baseline is the 28 day screening period preceding the first injection on Day 0. a. Time since onset of frequent migraine was calculated from date of onset to day of patient's first injection (Day 0).

b. Age of onset of frequent migraine was calculated from birth date to date of onset. c. To qualify, a patient had to take this type of medication at least twice per week in any week with at least 5 diary days during the baseline period and at least 10 to 15 days (varying with medication category).

With respect to the second point of difference, the sponsor pointed out that although the ICHD-2R diagnostic criteria for CM specifically exclude patients with medication overuse, guidelines produced by the same organisation regarding clinical trials of prophylactic

treatments for CM nevertheless recommend the *inclusion* of patients with medication overuse, provided that randomisation is stratified according to the presence/absence of medication overuse (Silberstein *et al* 2008[12]). The apparent justification for this recommendation is that the high prevalence of medication overuse in CM patients would make it difficult to enrol sufficient patients if medication overusers were excluded.

However, the inclusion of patients with medication overuse, without first determining if the headaches resolve with medication withdrawal, means that a proportion of the enrolled patients could have MOH rather than, or in addition to, CM. This means that any observed effect of the test drug in the trial might be due to an effect on CM, or an effect on MOH, or an effect on both.

This problem can potentially be addressed, provided that:

a) randomisation is stratified according to the presence or absence of medication overuse (to avoid baseline differences between the test drug and placebo recipients within the 'medication overuse' and 'no medication overuse' subgroups);

and

b) the 'medication overuse' and 'no medication overuse' subgroups are large enough to either show statistical superiority of the test drug over placebo *within* each subgroup or to demonstrate with adequate confidence that the effect of the study treatment did not vary according to the presence or absence of medication overuse.

In Studies 191622-038 and 191622-039, randomisation was indeed stratified according to the presence or absence of medication overuse. The 'no medication overuse' subgroup in each study was too small to show a statistically significant effect of Botox on the frequency of headache days (the most important endpoint). However, when the two studies were pooled (which was acceptable given the identical study designs), Botox did produce a statistically significant reduction in the frequency of headache days in the 'no medication overuse' subgroup, as well as in the 'medication overuse' subgroup (27). In addition, the effect of Botox was significantly superior to placebo in both the 'no medication overuse' and 'medication overuse' subgroups of the pooled trials for the endpoints of migraine/probable migraine days, moderate/severe headache days, total cumulative hours of headache occurring on headache days and proportion of patients with severe HIT-6 category scores (Tables 29 and 30). Compared to placebo, Botox did not significantly reduce the frequency of headache episodes in the 'no medication overuse' subgroup, but the clinical relevance of that endpoint is questionable.

For all of the endpoints except the proportion of patients with severe HIT-6 category scores, the placebo-subtracted effect of Botox was smaller in the 'no medication overuse' subgroup than in the 'medication overuse' subgroup. However, mean baseline values were also lower in the 'no medication overuse' group and this could explain at least some of the difference in the apparent effect size between the 'no medication overuse' and 'medication overuse' subgroups (a lower baseline value leaves less room for improvement).

[12] Silberstein S, Tfelt-Hansen P, Dodick DW, Limmroth V, Lipton RB, Pascual J, *et al*. Guidelines for controlled studies of prophylactic treatment of chronic migraine in adults. *Cephalalgia* 2008; 28:484-495.

Table 29. Pooled Studies 079 and 080: Baseline mean and mean change from baseline at Week 24 in various headache measures, according to medication overuse stratum and in the overall ITT population.

Endpoint / Stratum	Baseline		Week 24			P-value
	Botox	Placebo	Botox	Placebo	Botox - Placebo †	
HA days						
Medication overuse	20.1	19.8	-8.2	-6.2	-2.0	<0.001
No medication overuse	19.6	19.7	-8.8	-7.3	-1.5	0.013
Overall	19.9	19.8	-8.4	-6.6	-1.8	<0.001
HA episodes						
Medication overuse	12.8	13.8	-5.4	-4.9	-0.5	0.028
No medication overuse	10.9	11.4	-5.0	-4.6	-0.4	0.146 (NS)
Overall	12.2	13.0	-5.2	-4.9	-0.3	0.009
Migraine/probable migraine days						
Medication overuse	19.3	19.1	-8.1	-6.0	-2.1	<0.001
No medication overuse	18.8	18.5	-8.4	-6.6	-1.8	0.004
Overall	19.1	18.9	-8.2	-6.2	-2.0	<0.001
Moderate/severe HA days						
Medication overuse	18.5	18.4	-7.7	-5.7	-2.0	<0.001
No medication overuse	17.4	17.3	-7.8	-6.0	-1.8	0.005
Overall	18.1	18.0	-7.7	-5.8	-1.9	<0.001
Cum. hrs of HA on HA days						
Medication overuse	291.31	270.46	-114.46	-70.80	-43.66	<0.001
No medication overuse	304.37	302.05	-129.21	-99.26	-29.95	0.023
Overall	295.93	281.22	-119.67	-80.49	-39.18	<0.001

HA = headache. NS = not significant. † Calculated by the evaluator. P-value for between-group comparison at week 24 from ANCOVA with baseline value as covariate.

Table 30. Pooled Studies 079 and 080: Percentage of patients with severe category HIT-6 scores at baseline and Week 24, according to medication overuse stratum and in the overall ITT population.

% patients with HIT-6 score ≥60 (Severe)	Baseline		Week 24					P-value
	Btx	Pbo	Btx	Pbo	Change from baseline †			
					Btx	Pbo	Btx - Pbo	
Medication overuse	94.8	94.6	71.0	81.9	-23.8	-12.7	-11.1	<0.001
No medication overuse	90.9	89.0	61.3	70.9	-29.6	-18.1	-11.5	0.027
Overall (mean)	93.5	92.7	67.6	78.2	-25.9	-14.5	-11.4	<0.001

Btx - Botox. Pbo = placebo. † Calculated by the clinical evaluator. P-value for between-group comparison at Week 24 by Pearson's chi-square.

In responding to the differences between the pivotal study entry criteria and the ICHD-R criteria for CM, the sponsor also compared the baseline demographics and key disease characteristics of three overlapping subsets of the patients who were screened for the Botox pivotal studies. All three subsets required patients to have begun screening (which implied that the treating physicians regarded them as having CM) and completed enough of the screening period to have 20 days of headache diary data. A total of 2736 patients satisfied these initial conditions. The three subsets drawn from these 2736 were:

1383 patients who met the inclusion criteria for the pivotal trials and went on to be randomised (referred to as the PREEMPT=yes group).[13] These patients fulfilled the Botox pivotal study entry criteria as previously described.

1912 patients who "met the ICHD-2R criteria for chronic migraine", referred to as the "ICHD-2R=yes" subset. In fact, the definition used in the analysis ignored two elements of the ICHD-2R CM criteria, namely the requirement that headaches must have been present on ≥15 days per month *for at least 3 months*, and the requirement that medication overuse *not* be present. The first omission is not likely to be important, given the previously-made point that a high percentage of the trial patients probably met the "≥ 3 months" ICHD-2RN duration criterion. The second omission is addressed by the next subset.

673 patients from the "ICHD-2R=yes" subset who did not have medication overuse, designated the "ICHD-2RN=yes" subset.

The demographics, main baseline headache characteristics and headache medication history of the three subsets were broadly similar, as shown in Table 31 (with the obvious exception that 0% of the patients in the "ICHD-2RN=yes" subset had medication overuse).

[13]. The name reflects the acronym of the pivotal trials (**P**hase II **RE**search **E**valuating **M**igraine **P**rophylaxis **T**herapy). It is not clear why one of the 1384 patients who made up the combined ITT population of the two trials was excluded, but this is of no real importance.

Table 31. Baseline characteristics of the three migraine diagnostic group subsets.

Characteristic	ICHD2-RN=yes (N=763)	ICHD-2R=yes (N=1912)	PREEMPT=yes (N=1383)
Age, mean (SD)	38.1 (10.94)	41.9 (10.78)	41.3 (10.53)
Age, median	38.1	42.0	42.0
Female	85.9%	86.1%	86.4%
Caucasian	84.7%	89.2%	90.1%
BMI, mean (SD)	27.9 (6.87)	27.2 (6.53)	27.0 (6.38)
Beck depression score, mean (SD)	6.5 (6.00)	6.5 (6.21)	6.3 (6.09)
Frequency headache days, mean (SD)	18.4 (5.08)	18.2 (5.31)	19.9 (3.67)
Frequency headache episodes, mean (SD)	10.0 (5.00)	11.3 (5.38)	12.6 (5.40)
Frequency migraine days, mean (SD)	15.6 (6.06)	15.3 (6.34)	16.4 (5.76)
Age of onset of chronic migraine, mean (SD)	20.8 (11.11)	21.9 (11.61)	21.6 (11.48)
Medication overuse	0.0%	64.8%	65.4%
Ever tried headache prophylaxis medications	50.8%	60.6%	63.5%
Currently using acute headache medications	92.7%	97.4%	97.5%

SD=standard deviation

Further analyses showed that the pivotal study inclusion criteria had 94% specificity for identifying a population with CM according to partial ICHD-2R criteria (ignoring medication overuse) but only 55% specificity for identifying patients who satisfied the full ICHD-2R definition (that is, with no medication overuse).

Further analyses were conducted in two observational datasets:

1.The overlap between ICHD-2R criteria and the Botox pivotal study criteria was examined in data from Bigal *et al* 2007. This study utilised the clinical records and headache diaries of 557 patients who had been diagnosed as having transformed migraine (TM) according to the criteria proposed by Silberstein and colleagues in 1996[14]. TM was the predecessor, in definitional terms, to CM (which was not introduced until 2004). A diagnosis of TM required a combination of:

-headache on >15 days a month for >1 month; with

-an average headache duration >4 h day if untreated; and

-at least one of a history of episodic migraine (EM), or a history of increasing headache frequency with decreasing severity of migrainous features over at least 3 months, or headaches that at some time meet the IHS criteria for migraine other than duration; and

-does not meet the criteria for new daily persistent headache or hemicrania continua.

[14] Silberstein SD *et al*. Classification of daily and near-daily headaches: field trial of revised IHS criteria. *Neurology* 1996; 47:871-5.

Two subsets of the study population were defined: one with medication overuse and one without medication overuse. In the subset with medication overuse, the proportion of the patients who met the partial ICHD-2R criteria (ignoring medication overuse) was similar to the proportion who met the Botox pivotal study criteria (86.9% versus 80.9% respectively). A similar overlap was seen within the subgroup without medication overuse (92.4% met the full ICHD-2R criteria and 88.0% met the Botox pivotal study criteria). In both comparisons the differences were not statistically significant but confidence intervals were not reported.

2. Similarities between the demographic characteristics of patients meeting ICHD-2R criteria and those meeting Botox pivotal study criteria was examined in participants in the German Headache Consortium (GHC) study (Katsarava *et al* 2010[15]). The GHC study is a population-based study of headache sufferers in which questionnaires were mailed to a random sample of 18,000 18 to 65 year-olds in demographically diverse regions of Germany. Within this dataset, the demographic profiles of respondents fulfilling ICHD-2R criteria for CM ignoring medication overuse (N=45) and those fulfilling the Botox pivotal study criteria (N=37) were compared. The two groups were found to be similar in respect of gender distribution, mean age, body mass index (BMI), level of education, smoking status and level of alcohol use.

The sponsor concludes that "the chronic migraine population evaluated in the Phase III clinical studies is representative of the target population of patients who would be receiving Botox for the treatment of chronic migraine as currently defined by ICHD-2R". This is simply not true if the drug were to be prescribed only to patients who strictly match the ICHD-2R definition, because that definition unequivocally excludes patients with medication overuse, whereas the pivotal study populations did not. However, a significant effect of Botox was demonstrated in a subgroup of patients that *does* match the ICHD-2R definition of CM, namely the 'no medication overuse' subgroup of the pooled pivotal studies.

Justification of the Phase II population in support of the Phase III studies

The CER observed that the populations studied in the Phase II studies (Studies 191622-038 and 191622-039) were dissimilar to those of the pivotal studies and that in neither of these studies was the effect of Botox on the primary efficacy endpoint significantly greater than that of placebo. Accordingly, the CER questioned the value of these trials as "supporting" studies.

In their response, the sponsor pointed out that the differences between the entry criteria for the Phase II and Phase III studies were the result of evolving diagnostic criteria for CM over the period that the trials were designed and conducted. At the time of Studies 191622-038 and 191622-039, patients with frequent migraine occurring over a prolonged period fell under the ICHD classification "chronic daily headache" (CDH), defined as headache on >15 days per month. The use of the CDH criteria for study enrolment thus meant that patients were enrolled who would not have qualified as CM under the definition used for the Botox pivotal studies (and, for that matter, under the ICHD-2 or ICHD-2R definitions of CM).

[15] Katsarava Z, Manack A, Yoon M-S, Obermann M, Becker H, Dommes P, Turkel C, Lipton RB, Diener HC. Chronic Migraine: Classification, Complications, and Comparisons. *Cephalalgia* 2010; accepted for publication.

The sponsor has also pointed out that in the original submission, and in recognition of these differences in entry criteria, a subgroup of patients from Studies 191622-038 and 191622-039 was identified who met the pivotal study inclusion criteria in respect of headache frequency and duration and who were not taking concurrent headache prophylaxis. Data from this pooled subgroup of 181 Botox and 141 placebo treated patients were analysed for the diary derived primary and secondary efficacy parameters evaluated in the Phase III studies (headache days and so on).

A statistically significant between group difference for headache days, migraine/probable migraine days and acute headache pain medication days favouring Botox over placebo was observed for this Phase II subgroup of patients. Analyses of other efficacy parameters did not show statistically significant between group differences. However, the mean changes from baseline were directionally aligned with results observed in the Phase III population and were always greater in the Botox-treated patients than the placebo-treated patients. The sponsor argues that the efficacy demonstrated in this subpopulation with chronic migraine in the Phase II studies is consistent with efficacy shown in the Phase III studies, hence it is supportive of the Phase III results.

A problem with this pooled analysis is that Studies 191622-038 and 191622-039 had slightly different designs (in particular, they used different Botox dose regimens), and this raises questions about the validity of the simple pooling of results that was undertaken by the sponsor. A more appropriate approach would have been to combine the studies in a meta-analysis.

Overall, Studies 191622-038 and 191622-039 provide some supporting evidence of efficacy, but the evidence is weak, deriving as it does from a *post hoc* analysis of data that were pooled using a potentially inappropriate method. In addition, the patients in the analysis were selected on the basis of satisfying the Botox pivotal study entry criteria rather than the ICHD-2R definition of CM, which further complicates the interpretation of their clinical significance.

Issues Regarding the Phase III Study Design and the Strength of the Evidence of Efficacy Demonstrated in the Phase III Studies

Justification for use of placebo comparator in the context of the EMEA Guideline

The CER noted that the pivotal studies were two-armed (Botox and placebo) and that "the advice to include an active control, contained in the relevant guideline (EMEA, 2003) was not followed".

The sponsor has responded that an active control was not required on two grounds:

The sponsor considers that the guideline pertains to trials in episodic rather than chronic migraine because the guideline states that "attacks should occur at least 2 times per month, usually 2-6 times per month", whereas CM requires ≥15 attacks per month.

No suitable active control is available because the trials of treatments that are approved for migraine prophylaxis have generally excluded CM patients and no product is approved specifically for the prophylaxis of CM.

The distinction between episodic and chronic migraine is not relevant in this context because the relevant guideline (EMEA/CPMP/EWP/2158/99. Guideline on the choice of the non-inferiority margin) is espousing a general principle that when there is a high placebo response rate, trials intended to demonstrate that a test drug is non-inferior to an active control should also have a placebo arm. The purpose of the placebo arm is to show that any apparent non-inferiority of the test drug to the active control is not just due to a lack of sensitivity of the trial design.

However, the pivotal studies in the Botox application were intended to show superiority of Botox over placebo, so an active control was not required.

There are a number of older treatments (for example, beta blockers and pizotifen) that are approved for migraine prophylaxis in Australia, without specification as to whether the migraines are "chronic" or "recurrent". The use of one or more of them as controls would have provided information on the relative efficacy of Botox and these currently-used treatments. However, while that information may be relevant to making an informed choice between the available treatment alternatives, it is not required for the purposes of registration under the Therapeutic Goods Act. The use of a placebo control is ethically acceptable even though there are approved treatments that potentially cover the proposed indication, because (a) therapeutic failure in the placebo arm was not life-threatening and was handled by allowing rescue medication, and (b) even if an active control had been used, a placebo group would still have been required to demonstrate sensitivity, as noted above.

Overall, neither the point made in the CER nor the arguments of the sponsor are relevant. The reliance on placebo-controlled trials without an active comparator is acceptable.

Rationale for the dose used in the Phase III studies

In response to the CER's criticism that the selection of doses for the pivotal studies (and hence for the product information) was arbitrary and not evidence-based, the sponsor provided a pre-publication copy of a paper that discussed the design of the Botox pivotal studies (Blumenfeld *et al* 2010). The paper included the following justification for the dose regimen used in the pivotal studies:

> ***Dose***
>
> *Between 1997 and 2000, five exploratory, randomized, double-blind, placebo-controlled, parallel group design studies of episodic migraine were conducted. In these studies, each treatment arm used a fixed-site, fixed-dose IM injection paradigm with the intent of determining which muscle(s) and dose(s) were effective. Doses ranged from 6 U to 75 U, and the number of injection sites ranged from three to eleven, administered IM in up to 4 muscle groups, all in the front of the head (corrugator, procerus, frontalis, and temporalis) with no posterior head or neck injections. Two of these studies evaluated a single treatment cycle and patients were followed for approximately 16 weeks. The other three studies evaluated multiple treatment cycles repeated at 120-day intervals in sequential follow-on studies.*
>
> *In 2001, four additional larger, exploratory, randomized, double-blind, placebo-controlled, parallel group design studies were initiated: 2 in patients with episodic migraine and two in patients with CDH. All four studies utilized a fixed-site, fixed-dose treatment paradigm. In two of the studies, additional treatments were allowed in predefined head and neck muscles where patients had predominant pain. Doses evaluated in these studies ranged from 75 U in 20 injection sites across seven specific head and neck muscles, 24 to 260 U in 58 injection sites across seven specific head and neck muscles. In one of these Phase II studies in CDH, the dose included 225 U, 150 U, and 75 U groups and provided insight with regard to the optimally safe and effective dosage per injection cycle. However, in this trial a dose response was observed for tolerability, with the 225 U dose group having more AEs (for example, muscle weakness, neck pain) than the other two treatment groups. With regard to efficacy, the two higher dose groups were both different from the 75 U group, but there was no difference in efficacy between the 225 U and 150 U groups. Therefore, it was determined that the optimal total dose to maximize efficacy and tolerability was*

within the range of >150 U and <200 U. PREEMPT confirmed that 155 U to195 U of onabotulinumtoxin A is efficacious for treating patients with CM.

Injection Sites and Techniques

Dilution volume used for each 100 U vial of onabotulinumtoxin A varied across the early studies, which could have also contributed to varied findings across these studies, and this is another important factor to consider for this injectable treatment. Early exploratory studies diluted each vial with 1.33 to 10 mL, which resulted in onabotulinumtoxin A concentrations that ranged from 7.5 U/0.1 mL to 0.1 U/0.1 mL. The occurrence of eyelid ptosis, which may be influenced by the dose and dilution administered to the frontal muscles (corrugator, procerus, and frontalis muscles), was seen in up to 17.5% patients injected with a total maximum dose of 57 U (75 U group) (dilution 1.33 mL/vial) to these muscles. In another study, despite a maximum dose of only 19 U in these muscles (25 U total dose group), ptosis was reported at a rate of 14.3% when using a dilution of 4 mL/vial. In the double-blind, placebo-controlled phase of the pivotal Phase III PREEMPT trials, ptosis was reported at low rates (3.6% of onabotulinumtoxin A-treated and 0.3% of placebo-treated patients) with a total dose of 35 U to the frontalis, corrugator, and procerus muscles...

... In the development of a treatment paradigm for onabotulinumtoxin A injections, perhaps the greatest evolution has been in the selection of sites for the injections. As mentioned above, two approaches have been widely used: fixed-site/fixed-dose and follow-the-pain. It was previously believed that the type of approach depended on the type of headache, but whether one approach should be preferred over the other has not previously been firmly established. Early headache studies generally used a fixed-site approach, identifying sites in the forehead and glabellar region while generally avoiding the occipital and neck regions. The fixed-site approach distributes onabotulinumtoxin A to muscles that align with the peripheral nerve distribution of the cervical and trigeminal sensory system, which is believed to be the target-end organ for onabotulinumtoxin A in treating CM. These sites remain unchanged regardless of where the patient's pain is located. The PREEMPT injection paradigm, which uses a combination of fixed and follow-the-pain injection sites, provides optimal distribution of onabotulinumtoxin A based on individual patient symptoms.

The muscle groups chosen in PREEMPT were based on in-depth analysis of the interaction effects of muscle group dose on efficacy variables in patients who were not using prophylactic headache medication during baseline, and in-depth analyses of the safety and tolerability of the dose and dosage paradigm used in the two Allergan sponsored Phase II studies of patients with CDH. The findings from these analyses, which are discussed further below, serve as the 223 foundation for the choice of muscles, dose, and dilution used in the PREEMPT studies.

<u>Frontalis, Corrugator and Procerus (Frontal/Glabellar Region)</u>

In the Phase II trials, patients reported that the frontal/glabellar region was the most frequent location where their head pain started and ended. In the first trial, doses for the frontal/glabellar region were not specified; only a total dose was specified for the overall region, which was administered across the frontalis, corrugator, and procerus muscles. In the second trial, the frontalis and corrugator muscles of the forehead were injected, but not the procerus muscle. Overall, the first trial had better signals for efficacy than the second trial. Thus, to ensure the best chance for efficacy as well as ensure consistency and standardization of treatment,

the PREEMPT paradigm used the muscles that were injected in the first trial: the frontalis, corrugator, and procerus.

The AE rate of eyelid ptosis was 7.5% in the onabotulinumtoxinA-treated group in the first trial, and 4.8% and 6.6% in the 150 U and 225 U dose groups, respectively, in the second trial. To reduce the potential for focal adverse events such as eyelid ptosis, a slightly lower total dose (35 U) than the average dose administered to the frontal muscles in the second trial (40 U) was chosen for evaluation in the Phase III PREEMPT studies. Furthermore, in the PREEMPT trials the exact number of injections and location for injection to these muscles was specified in the protocol and injection training to ensure optimal tolerability and to specifically reduce the eyelid ptosis AE rates observed in the Phase II trials. Indeed, the PREEMPT injection method in these muscles appears to have achieved these goals, because the PREEMPT clinical program had statistically significant separation from placebo across multiple headache symptom measures, with an overall eyelid ptosis rate of 3.6% for onabotulinumtoxinA-treated patients in the double blind, placebo-controlled phase of the pooled Phase III trials.

Temporalis

In the Phase II trials, patients reported that the temporalis area was the second most frequent location where their head pain started and ended. The fixed-site, fixed-dose for this muscle in the Phase III trials was determined based on the fact that the mean dose administered to the temporalis muscle in the first trial was ~40 U (~20 U per side) and the maximum dose was 50 U. There were no emerging tolerability issues from injecting this muscle at these doses in the Phase II trials. Because this muscle was a very common location of predominant pain for many patients in the Phase II trials, it was decided that for the PREEMPT paradigm the total dose of 40 U (20 U per side) would be required as a minimum dose, and an allowance for an additional 10 U to this muscle area could be given using the follow-the-pain regimen.

Cervical Paraspinal Muscle Group (Neck Muscles)

In the Phase II trials, patients indicated that their headache pain frequently started and/or stopped in the back of the head (either in the occipitalis and/or the neck). The splenius capitis and semispinalis muscles were the neck muscles injected in both Phase II trials. The protocols allowed investigators some discretion as to specific injection location in these muscles, and many of the investigators administered the treatment to the mid-neck region and often injected these muscles using longer needles to ensure that they reached the semispinalis muscle. In the second trial, which was a dose-ranging, fixed-site, fixed-dose regimen trial, patients in the middle- and high-dose groups showed a relatively high incidence of neck pain (~25%). In some instances, neck muscle weakness resulted in patients needing temporary soft collars to support their head. In this trial, patients in the middle- and high-dose groups received 20 U and 30 U, respectively, to each side of the splenius capitis and semispinalis neck muscles, for total doses of 40 U and 60 U, respectively, across these two muscle groups. The incidence of neck pain (13.3%) in patients treated in first trial (which had variable neck dose that could range from 20 U to 40 U total across the semispinalis and splenius capitis muscles) was not as high; these patients received average doses of ~18 U in each muscle group for a total mean dose in the mid-neck region of ~36 U.

Upon review of the tolerability data, the PREEMPT injection paradigm for the neck was revised. Injections were to be given to the upper neck (cervical paraspinal muscles) at the base of the skull, rather than to the mid-neck region. The follow-the-pain injection regimen was not allowed in the neck region and injections were to be more superficial rather than deep into the neck muscles. Hence, the injection needle length and gauge were standardized to 0.5 inch and 30 gauge, respectively, which is shorter and smaller bevel than what had been allowed in the second Phase II trial (that trial had allowed use of up to 1.5 inch and/or larger 27 gauge needle). Furthermore, it was decided to reduce the total dose injected into the neck region. The overall dose was reduced to a fixed-site, fixed-dose of 20 U for this muscle group (10 U to each side of the head). It was anticipated that this dose would be sufficient from an efficacy perspective and that the lower neck dose would result in less neck pain and neck rigidity, and also decrease the risk of excessive neck muscle weakness, which would improve the overall tolerability profile while maintaining efficacy. The overall adverse event rates in the pooled analysis of the double blind, placebo-controlled phase of the PREEMPT studies was less than what was observed in the Phase II studies, with neck pain occurring in 8.7% of the onabotulinumtoxin A-treated patients versus 2.7% of the placebo-treated patients. There was only one patient in PREEMPT who required a soft collar due to excessive weakness, compared to 10 patients in the Phase II studies, confirming that a reduction in the dose and needle length was appropriate.

<u>Occipitalis</u>

In the Phase II trials, patients reported that occipitalis was the third most frequent location where their head pain started and ended. The Phase II data was also evaluated to ascertain the frequency of follow-the-pain paradigm actually used by clinicians in the first trial, because variation in the dosage was allowed for all muscle groups in that protocol except for the occipitalis. The mean and median doses for each muscle group showed that the dosages for the temporalis and trapezius muscles were the muscle groups with the most variation across patients, which indicated follow-the-pain was most frequently used for these muscle groups. Most patients have predominant pain either on one side of the head, in the back of the head, or in the shoulders that may warrant additional treatment to those areas. Because a decision had been made to reduce the overall dose administered to the neck and to not allow follow-the-pain regimen in the neck muscles (as described above), there was concern that there would be insufficient "back of the head" dose to ensure efficacy, especially since so many patients complain of pain in that area. Thus, the minimum dose administered to the occipitalis was increased from the Phase II dose, and, to reduce risk of neck weakness, the sites for injection into the occipitalis were located primarily above the occipital ridge, which would also reduce the risk of neck weakness. Furthermore, if patients had a complaint of a predominant pain in the back of the head, additional follow-the-pain dosing would be allowed in this muscle.

<u>Trapezius</u>

In the Phase II trials, approximately 20%-30% of patients reported that their headache pain started and/or ended in the trapezius muscles. In the second trial, the total doses administered to the trapezius muscles were 20 U, 40 U, and 60 U in the 75 U, 150 U, and 225 U dose groups, respectively. The incidence of arm (shoulder) pain, which was felt to be related to injections into the trapezius muscle due to the close location and the thinness of the muscle at the proximal location near the shoulder muscle, was higher for the two higher dose groups: 8.2% in the 225 U group and

8.9% in the 150 U group compared to 6.3% in the 75 U group. In the first trial, the mean dose administered to the trapezius was ~48 U and the incidence of arm (shoulder) pain was 5.8%, which is lower than that observed in the second trial. The incidence of arm (shoulder) pain in the patients who received the maximum 60 U dose was not felt to be a general safety concern, but at the same time there was a desire to minimize patient discomfort while ensuring optimum efficacy from this treatment. Thus, the dosage regimen for the trapezius muscle in the PREEMPT clinical program was standardized to a minimum dose of 30 U (15 U on each side), with the option for additional follow-the-pain treatment to a maximum dose of 50 U (up to 20 U additional administered as 5 U per injection site divided across 1 or both sides) if clinically needed. This standardization was appropriate, as demonstrated by the reduction in the incidence of arm (shoulder) pain for onabotulinumtoxinA-treated patients (2.9%) in the double-blind phase of PREEMPT.

Masseter Muscle

The masseter muscle, which was an optional muscle that could have been injected in the first Phase II trial, was not included as a muscle to be injected in PREEMPT. The masseter muscle was injected in only 24% (84/355) of patients in that trial, and clinical data analyses suggested that patients who received masseter injections did not benefit from onabotulinumtoxinA treatment to the same extent as those who did not receive masseter injections. It was unclear from this finding whether patients who were manifesting pain in the masseter region represent a subgroup of chronic migraineurs and/or whether comorbid chronic pain conditions of temporomandibular disorder or chronic pain in or around the temporomandibular joint were potentially confounding the results. Although there was no indication of specific adverse events resulting from masseter injection, neither was there evidence that including the masseter muscle enhanced the efficacy; hence it was not included as a target muscle group for injection in the Phase III PREEMPT trials.

In the above rationale, references to dose-related efficacy differences refer to secondary efficacy endpoints and/or non-significant trends (no statistically significant dose-related differences were seen for the primary efficacy endpoints in the Phase II studies). Nevertheless, the sponsor has provided acceptable evidence that the dosage regimen used in the pivotal clinical trials was not arbitrary but instead represented a considered, evidence-based attempt to achieve an optimal balance between efficacy and adverse effects.

In the Botox pivotal trials, very specific instructions were provided regarding the placement of each injection and were presumably followed by the investigators. These instructions and the rationale for them were explained in Blumenfeld *et al* 2010[16]. The particular balance of benefits and risks that was seen in the pivotal trials is contingent upon the use of these specific injection placements. Accordingly, if the submission is approved, it will be important for the PI to reproduce the injection placement instructions that were used in the pivotal trials. As it stands, the draft PI does not do this.

[16] Blumenfeld AM, Silberstein SD, Dodick DW, Aurora SK, Turkel CT, Binder WJ. Method of injection of onabotulinumtoxina for chronic migraine: A safe, well-tolerated, and effective treatment paradigm based on the PREEMPT clinical program. *Headache* 2010; accepted for publication.

Clinical significance of the efficacy results for chronic migraine

The CER acknowledged the statistical significance of the differences between Botox and placebo in the pivotal trials, but questioned whether these differences were clinically meaningful, particularly given the likelihood that inadvertent unblinding of treatment assignment would presumably have led to an overestimate of the effect of Botox.

The sponsor has responded with a discussion of the efficacy results, mostly in accordance with a framework recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT; Dworkin *et al* 2009[17]). In brief, the IMMPACT paper argues that group mean differences in an efficacy measure should not be confused with the reduction that an individual patient would consider worthwhile. For example, a number of studies have shown that for individuals experiencing chronic pain, a 20 mm reduction or a 30% reduction from baseline on a 100 mm pain intensity scale is regarded as "moderately important" and a 50% reduction is regarded as "substantial improvement". However, it does not follow that a medication has exerted a clinically meaningful effect only if it produces a *mean* reduction in pain intensity of this magnitude compared to placebo. If this criterion were applied, few of the currently-available analgesics would be regarded as having a clinically worthwhile effect on chronic pain (the placebo-subtracted mean reduction for a range of analgesics including paracetamol, Non-steroidal Anti-inflammatory Drugs (NSAIDs), opioids, pregabalin, is typically in the range of 4 to 15 mm on a 100 mm scale). Instead, IMMPACT argues that one should first define what is a clinically meaningful change from baseline in an individual (for example, the 20 mm or 30% reduction in pain intensity mentioned above). Next, one should use this criterion to categorise patients in the test and placebo groups as responders or non-responders. One should then calculate the percentage of responders in the test and placebo groups, and determine the number-needed-to-treat (NNT) to produce each *additional* responder in the test group. Finally this NNT should be compared with the NNTs for established therapies that are regarded as worthwhile. In doing so, one should take into account other factors such as adverse effects of the drug that might offset the beneficial effect, the rapidity of onset of treatment benefit, durability of treatment benefit, improvements in secondary endpoints such as physical and/or emotional functioning, convenience, patient adherence, cost, mechanism of action (for example, a drug with a mechanism of action different to that of existing treatments offers the prospect of usage in combination with existing treatments to achieve a greater effect), and other benefits (for example, few or no drug interactions).

In relation to the IMMPACT framework, the sponsor performed the first step of defining a clinically meaningful change from baseline in an individual patient, namely a reduction of ≥50% in the number of headache days. This is a reasonable criterion because it corresponds to the ≥50% reduction used to define a response in the EU guideline for studies of episodic migraine and accords with the criterion of "substantial improvement" in chronic pain.

However, when comparing the proportion of responders to Botox with the proportion of responders to other treatments, the sponsor merely compared the response rates in the active treatment arms, without taking into account the response rates in the placebo arms of the corresponding studies. This is inappropriate because it does not compare the treatment effect of the different drugs (which by definition is the incremental effect over that of placebo).

[17] Dworkin RH, Turk DC, McDermott MP, Pierce-Sandner S, Burke LB, Cowan P, *et al*. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. Pain 2009;146:238-244.

The sponsor did, however, perform an analysis to determine whether the percentage of patients with a *clinically meaningful* response was *significantly* higher in the Botox group, compared to placebo. This was found to be the case for most of the headache endpoints, including the most important endpoint of headache days and the migraine-specific endpoint of migraine/probable migraine days.

NNTs for the various endpoints were not determined by the sponsor but were calculated by the evaluator to be 8.3 for a 50% reduction in headache days and 8.5 for a 50% reduction in migraine/probable migraine days, based on the pooled data. Cochrane systematic reviews of anticonvulsants and propranolol for migraine prophylaxis (Chronicle and Mulleners 2004[18]; Linde and Rossnagel 2004[19]) found that to produce a 50% reduction in migraine frequency, mean NNTs were in the range of 2 to 5 (Table **3**32, below).

Table 32. NNT to produce a 50% reduction in migraine frequency (Cochrane systematic reviews of anticonvulsant drugs and propranolol for migraine prophylaxis).

Drug	NNT	95% CI for NNT	
Sodium valproate	3.1	(1.9 - 8.9)	* The NNT for propranolol was not reported but was calculated by the evaluator, based on the primary analysis of data from parallel-group trials and the first period of crossover studies, in which the response rate was 30.9% in the combined placebo groups with a relative risk of 1.72 (95% CI 1.23-2.40) for response in the combined propranolol groups.
Divalproex sodium	4.8	(3.5 - 7.5)	
Gabapentin	3.3	(2.1 - 8.4)	
Carbamazepine	2.1	(1.6 - 3.3)	
Topiramate	3.9	(3.4 - 5.1)	
Propranolol	4.5*	(2.3 - 6.6)*	

Thus, the NNTs for Botox do not compare favourably with NNTs for anticonvulsants and propranolol in the prophylaxis of migraine. However, the patients in the anticonvulsant and propranolol studies had less frequent, episodic migraine (generally from 2 to 12 migraine days/month) compared to the chronic migraine sufferers in the Botox pivotal studies (who had headaches on ≥15 days with group means of 19 to 20 days). It is reasonable to assume that when migraine is more frequent it is harder to produce a 50% reduction, and this could explain the higher NNTs in the Botox studies. Also, the methodological quality of the anticonvulsant and propranolol studies was not always satisfactory, which would tend to increase the apparent treatment effect and lower the NNT for those treatments.

Further evidence of the clinical value of the effects of Botox was provided by the observation of statistically significant and clinically meaningful (as defined in the literature) superiority of Botox over placebo for two validated measures of the impact of headache on daily activities and quality of life: the Headache Impact Test (HIT-6) and the Migraine-Specific Quality of Life Questionnaire (MSQ).

The sponsor also referred to two published studies that compared Botox directly with other treatments; topiramate and divalproex sodium (sodium valproate). Topiramate is approved in Australia for migraine prophylaxis (but not specifically for chronic migraine,

[18] Chronicle EP, Mulleners WM. Anticonvulsant drugs for migraine prophylaxis. Cochrane Database of Systematic Reviews 2004, Issue 3. Art. No.: CD003226.

[19] Linde K, Rossnagel K. Propranolol for migraine prophylaxis. Cochrane Database of Systematic Reviews 2004, Issue 2. Art. No.: CD003225.

and on the basis of studies that enrolled patients with an average of 6 to 7 migraine days/month). Sodium valproate is used for migraine prophylaxis but is not approved in Australia for that indication. Both studies were small (60 patients in the topiramate study and 59 in the valproate study, of whom only 14 had chronic migraine) and neither study included a placebo group to test assay sensitivity. Because of these shortcomings, the lack of a significant difference between Botox and the comparator treatments in these two studies is clinically meaningless.

The sponsor addressed other aspects of the IMPACCT criteria for assessing the clinical relevance of a statistically significant effect as follows:

Rapidity of onset: Treatment effects of Botox were assessed on a 28-day cycle with the first assessment at Week 4. Significant differences favouring Botox were seen at this first assessment for a range of endpoints, and at most subsequent assessments through to the end of the double-blind treatment period.

Duration of effect: A significant difference in the proportion of responders (in this case defined as ≥50% reduction from baseline) in respect of the most important endpoint, headache days, was still present at Week 56, even though the placebo patients had been switched to Botox from Week 24 onwards. The effect of Botox on other endpoints also persisted throughout the 56 week treatment period, although the between-group difference waned over time once the placebo patients were switched to Botox. This information also addresses one of the concerns raised in the CER, relating to the demonstration of continued efficacy during repeated courses of Botox.

Convenience and patient adherence to treatment: The sponsor contends that as Botox is administered by a doctor once every 12 weeks, "the treating physician can ensure compliance and accurate dosing". The sponsor also argued that the withdrawal rate due to adverse events in the Botox arms of the pivotal studies, while higher than the rate in the placebo group, was relatively low (3.2% in Study 191622-079 and 2.3% in Study 191622-080). However, this percentage does not actually reflect adherence in the clinical trials, because patients also ceased treatment for other reasons. In the 24 week double-blind period of the combined pivotal trials, of the 688 patients who received the first Botox treatment, 592 remained under treatment at Week 24 giving an adherence rate of 86%. At Week 56, 513 patients in the Botox group remained under treatment, giving an adherence rate of 75% (see Figures 1 and 2 in the CER). These figures are quite good, although adherence would presumably be lower in actual clinical practice (that is, without the intensive follow-up and other efforts to retain patients and promote adherence that are associated with a clinical trial).

Uniqueness of mechanism of action: Botox exerts its effect locally and has minimal systemic effects, provided the dosage instructions are carefully followed. This is a potential advantage over orally administered treatments. The sponsor also argues that as the mechanism of action of Botox differs from that of currently-available therapies, it is of use in patients with migraine that is refractory to other treatments. As evidence for this, the sponsor cited the beneficial effects that were seen in the subgroup of patients with medication overuse, on the assumption that this group represents a population with migraine that had not responded to those medications and was therefore refractory to treatment. However, this is not necessarily true for all of the subgroup, since a proportion of them probably had MOH (that is, instead of having migraine that was refractory to treatment, the medications were the *cause* of their frequent headaches).

Limitations of other treatments: The sponsor has noted that there are currently no treatments specifically approved for the prophylaxis of chronic migraine; that studies

of other treatments for the prophylaxis of chronic migraine are limited; and that the treatments which are currently used (antiepileptic drugs, antihypertensive agents, etc) have not been evaluated in large controlled trials and are associated with significant systemic adverse effects leading to high discontinuation rates.

Other benefits: The sponsor has pointed out that patients with chronic migraine have complex comorbidities (depression, anxiety, other types of chronic pain, etc) and as a result are often taking a range of medicines. These are less likely to interact with Botox than with systemic migraine therapies. Patients using Botox are also not restricted from taking other headache treatments such as acute treatments for breakthrough headache. Finally, if a patient does not receive adequate headache relief from other prophylactic therapies, Botox can be started without the need for a washout period.

In summary, the sponsor has identified a number of reasons why the use of Botox may be preferable to other treatments that are currently employed for the prophylaxis of chronic migraine. The NNT for Botox is higher than the NNTs for these other treatments, but Botox was studied in patients with more frequent and presumably more treatment-resistant migraine. In any case, and notwithstanding the IMPACCT recommendations, superiority or non-inferiority to other therapies is not a requirement for registration under the Therapeutic Goods Act if a drug can be shown to produce a clinically meaningful treatment effect compared to placebo. In the case of Botox, the sponsor's studies - if they were unbiased - showed that that the percentage of patients who experienced *clinically* meaningful reductions (that is, ≥50% improvement from baseline) in a range of headache measures was *significantly* higher with Botox than placebo, which amounts to the same thing. The clinical relevance of these findings is further supported by significant improvements in the Botox group, compared to placebo, relating to the impact of headaches on daily activities and quality of life.

These clinically meaningful effects were demonstrated in the overall pivotal study population, which included patients with medication overuse (who therefore did not comply with the ICHD-2R definition of CM). No corresponding analysis was performed in the subgroup that matched the ICHD-2R definition of CM, i.e. the 'no medication overuse' subgroup. For most endpoints (except the proportion of patients with HIT-6 scores in the severe category), the placebo-subtracted effect of Botox was smaller in the 'no medication overuse' subgroup than in the overall study population. This raises the question of whether the statistically significant effects in the important 'no medication overuse' subgroup, being smaller than those in the overall population, were clinically meaningful. Importantly, the effect of Botox on the proportion of patients with severe HIT-6 scores was not only statistically significant in the 'no medication overuse' subgroup, but slightly higher than in the overall study population. The HIT-6 is a measure of the effect of headaches on the ability to function in daily life, and thus may be regarded as a direct measure of the clinical relevance of the effect of Botox. It is therefore reasonable to conclude that although the effects of Botox on other endpoints were slightly lower in the 'no medication overuse' subgroup than in the overall population, they nevertheless led to a clinically meaningful improvement in patients' daily function, as evidenced by the HIT-6.

An important caveat on the conclusion that the effect of Botox was clinically meaningful is that it assumes that the magnitude of the benefit in the pivotal studies was not materially exaggerated due to bias (specifically, reporting bias due to unblinding of treatment allocation). This issue is discussed in the next section.

Adequacy of blinding during the Phase III studies

Data from Phase II 'double-blind' trials showed that unblinding definitely occurred in those studies: about 85% of Botox recipients and 60% of placebo recipients were able to accurately identify their treatment assignment, instead of the expected 50% in each group

that should have been observed if blinding had been successful. It is reasonable to expect that the same occurred in the pivotal trials, and it was a distinct deficiency of the pivotal study designs that the adequacy of blinding was not similarly assessed.

The sponsor argues that unintentional unblinding of patients in the Phase III studies was unlikely because 'potentially unblinding adverse events' (a list of AEs relating to paralysis or hypaesthesia at and around the injection sites) were reported by only 16.5% of the study participants with no "excessive" reporting in the Botox group. Although the difference was not statistically significant (p=0.145), such potentially unblinding AEs were in fact reported in two-and-a-half times as many patients in the Botox group (165 Botox, 64 placebo).

Of more relevance, the mean reduction in the most important efficacy endpoint (number of headache days) was the same in Botox recipients who reported a potentially unblinding AE and Botox recipients who did not report such an AE (-8.4 days in each case). The same pattern was seen in the placebo group (-6.6 days in each case). In other words, the presence of potentially unblinding AEs did not alter the patients' assessment of efficacy for the most important efficacy endpoint.

The sponsor also argued that the injection paradigm for Botox in the migraine studies targeted administration to the trigeminal sensory system and would have led to less muscle paralysis and other local evidence of treatment assignment than the injection paradigm that is used for cosmetic indications.

The sponsor asserted that the lack of influence of potentially unblinding AEs on patients' assessment of efficacy in the pivotal trials showed that blinding was maintained in those studies. This is one potential interpretation of the data, but perhaps not the correct one given the clear evidence of unblinding in the Phase II studies. An alternative interpretation is that blinding was not maintained, but that even when patients were unblinded by the presence of potentially unblinding AEs, this did not bias their assessment of efficacy (as a group).

Given this second possibility, it is relevant to note that that the 'potentially unblinding adverse events' nominated by the sponsor are probably not the only source of unblinding. This can be inferred from the observation that the excess percentage of Botox recipients who correctly guessed their treatment in the Phase II studies (85% - 50% = 35%) was higher than the percentage of Botox recipients who presumably had potentially unblinding AEs in those studies (which was not reported but would have been about 25%, based on the Phase III trial experience). Apparently, something else in addition to potentially unblinding AEs was contributing to unblinding (for example, less severe local effects that were not reported as AEs) [20]. The question therefore arises as to whether unblinding by this other means (whatever it was) also had no effect on the assessment of efficacy.

In summary, the sponsor's assertion that the blind was maintained in the pivotal studies represents one interpretation of the data, but not the only one. If blinding was not maintained (as was definitely shown for the Phase II studies), the sponsor has demonstrated that one potential source of unblinding did not bias the efficacy assessment. However that source apparently does not account for all of the unblinding and residual bias due to unblinding by other means has not been excluded. One could postulate that if unblinding by AEs did not influence the efficacy assessment, then unblinding by other means also would not influence the efficacy assessment. This sounds reasonable but

[20] Data were presented to show that "potentially unblinding cosmetic effects" of Botox did not materially affect the assessment of efficacy, but the analysis relied only on cosmetic effects that were reported as AEs.

remains unconfirmed, which in turn means that there is still some doubt about whether the study results are completely unbiased.

Additional Concerns Raised by the Clinical Evaluator Relationship between Botox and the reported AEs of constipation and dyspnoea

The CER noted that reports of constipation and dyspnoea were more common in Botox recipients than placebo recipients. The sponsor had reviewed the individual cases and concluded that the reports were related to underlying medical conditions or concurrent medications rather than Botox. The clinical evaluator did not consider that this had completely resolved the question of a possible relationship to Botox.

In the response to the CER, the sponsor provided information to the following effect:

Constipation is a common complaint in the general population. The incidence rate of constipation in Botox recipients in the migraine studies was only 5/1000 person-years, which compares favourably to published rates of up to 50/1000 years in the general population.

Dyspnoea is also a relatively common complaint (but the incidence rate in the general population was not provided).

The frequency of constipation or dyspnoea, although numerically higher than in the placebo group was nevertheless very low; only 0.3% for each AE in the combined Botox groups, compared to 0.1% in the combined placebo groups.

There was no evident relationship between Botox dosage or number of treatments and the occurrence of constipation or dyspnoea. The cumulative incidence of these AEs increased with follow-up duration, but this would be expected even if the AEs are not treatment related.

With one exception, there was no evident relationship between the timing of Botox injections and the onset of constipation or dyspnoea. The exception was a patient who reported dyspnoea on three occasions, with each episode occurring two days after Botox injection. The sponsor acknowledged that this is likely to represent a causal relationship, but also argued that the dyspnoea was due to weakening of Botox-injected neck muscles acting as accessory muscles of inspiration, rather than systemic spread of toxin. This is not a convincing argument given that Botox was injected only into posterior neck muscles in the migraine studies, whereas it is mostly the anterior neck muscles that function as accessory muscles of inspiration. Furthermore, accessory muscles of inspiration only play a significant role in individuals with respiratory disease (which this patient was not stated to have) or during maximal ventilation during exercise (also not documented in this case).

No other AEs that might confirm distant spread of botulinum toxin were present at the same time as the constipation or dyspnoea.

Either a relevant medical history or concomitant medications that could have contributed to the occurrence of constipation were identified in all but one Botox recipient who reported that AE. In the remaining patient, constipation occurred 60 days after the second Botox treatment and did not worsen after a subsequent Botox treatment, which is not suggestive of a causal relationship.

Dyspnoea was mild or moderate in all but one patient. In all but one case (described above), Botox recipients who reported dyspnoea had concomitant conditions that could have caused the AE, or the timing of dyspnoea was inconsistent with the pharmacology of Botox.

Overall, constipation and dyspnoea were infrequent and in most cases probably not related to Botox. However in one case, the timing of dyspnoea indicates that this AE was probably caused by Botox in that particular patient. The sponsor's argument that this was a "local" effect due to neck muscle weakness is not convincing.

Use of the term "Complicated migraine"

The CER noted that implementation of the exclusion criterion of "complicated migraine" was unclear, given that it would seem to exclude patients with CM (which, under the ICHD-2 definition is listed as one of the "complications of migraine").

The sponsor clarified that the exclusion criterion was worded so as to exclude specific migraine diagnoses (hemiplegic migraine, basilar migraine, ophthalmoplegic migraine and migrainous infarction) that are clinically complex and thus "complicated". Investigators were trained to exclude patients who had these specific diagnoses, not patients with chronic migraine. This response is satisfactory.

Validation of the HIT-6 questionnaire

The CER questioned the method used for validation of the HIT-6 questionnaire, stating that the validation process used data from the Phase III studies, and therefore cannot properly be used in qualifying the questionnaire for use in analysing these same studies.

The sponsor responded that the validation of the HIT-6 actually occurred in two samples, both of which were independent of the Botox Phase III studies. The two samples were the National Survey of Headache Impact study and the HIT-6 Validation study. The cited publications confirmed this and the response is regarded as satisfactory.

Clarification on the source data for Table 1-7 of the original submission

The CER requested clarification on the source of the baseline data for Study 191622-038 in Table 1-7 in the original submission. The sponsor responded that there was a protocol change during the study and that the data were not collected in the case report forms (CRFs) until after the protocol change. This meant that the CRFs did not include the relevant data for 49.3% of the patients, which in turn meant that the information was not included in the baseline data tabulations in the Study 191622-038 report (which were based on the CRFs). However, when the Integrated Summary of Efficacy (ISE) was being prepared and it became evident that the sponsor needed to identify a subgroup of patients within the Phase II trials whose migraine characteristics corresponded to those of the patients in the pivotal trials, it was found that the data required to identify this subgroup could be derived from the baseline diary records. This response is satisfactory.

Other Matters

Mechanism of action

In their response, the sponsor has modified a proposed statement in the *Pharmacology* section of the Botox PI as follows:

> "*The presumed mechanism for headache prophylaxis is by blocking the peripheral signals to the central nervous system, which inhibits central sensitisation, as confirmed by ~~preclinical and~~ clinical studies."*

The sponsor states that the claim regarding confirmation of this mechanism in *clinical* studies is supported by Gazerani *et al* 2006[21] and Gazerani *et al* 2009[22] in the original submission.

[21] Gazerani P, Staahl C, Drewes AM, Arendt-Nielsen L. The effects of Botulinum toxin type A on capsaicin-evoked pain, flare, and secondary hyperalgesia in an experimental human model of

These studies were not discussed in the CER because they were supplied as "supporting references" rather than data for evaluation.

Examination of the two published papers reveals that Botox suppressed the pain, flare and hyperalgesia associated with intradermal capsaicin injection and reduced cutaneous heat, electrical and pressure pain thresholds. However, the studies did not actually confirm the mechanism of action of this effect. As stated in the abstracts of the two studies: "The effects are *suggested* to be caused by a local peripheral effect of BoNT-A [Botulinum Toxin A] on cutaneous nociceptors" (Gazerani *et al* 2006) and "Findings from the present study *suggest* that BoNT/A *appears* to preferentially target C fibers and probably TRPV1-receptors, block neurotransmitter release and subsequently reduce pain, neurogenic inflammation and cutaneous heat pain threshold" [emphasis added].

Thus, the proposed phrase "as confirmed by clinical studies" overstates the strength of the evidence and should not be approved. Furthermore, as the sponsor's editing indicates that the postulated mechanism of action was not confirmed by nonclinical studies either, it is debatable whether any reference to it should be allowed.

Safety data from published studies

Safety information from company-sponsored studies of Botox in episodic migraine (EM) was covered in the CER. However, the ISS provides additional information regarding the safety of Botox in published studies that included patients with CM, EM, episodic TTH (ETTH) and chronic TTH (CTTH). This information is relevant to the safety of Botox in the treatment of CM but was not specifically mentioned in the CER. The safety profile of Botox in these studies was similar to what was seen in the company-sponsored CM trials, and the studies did not raise any additional safety concerns.

Clinical aspects of the Safety Specification in the Risk Management Plan

A Risk Management Plan (RMP; designated Version 3.1 and dated 26 October 2009) was included in the original submission. The CER did not include any comments on the accuracy or completeness of the Safety Specification (SS) in the RMP.

The RMP was not Australian-specific and covered all presentations and indications approved for Botox worldwide. The clinical evaluator commented only on clinical aspects of the SS that relate directly to the proposed CM indication. Information relating to other indications has not been assessed, as the relevant data were not available to the evaluator.

Clinical Summary and Conclusion (2)

Recommendation Regarding Authorisation

In patients with CM corresponding to the ICHD-2R definition (the 'no medication overuse' subgroup of the pooled pivotal trials), Botox produced a *statistically* significant reduction (compared to placebo) in the most important endpoint of headache days, the migraine-specific endpoint of migraine/probable migraine days, and the supporting endpoints of moderate/severe headache days, total headache hours on headache days and the proportion of patients with HIT-6 scores in the severe category. The fact that the effect on HIT-6 was not only statistically significant but slightly higher in the 'no medication overuse' subgroup than the overall study population, combined with other analyses

trigeminal sensitization. (2006). *Pain* 122:315–25.

[22] Gazerani P, Pedersen NS, Staahl C, Drewes AM, Arendt-Nielsen L. (2009). Subcutaneous Botulinum toxin type A reduces capsaicin-induced trigeminal pain and vasomotor reactions in human skin. Pain. 141(1-2):60-9

showing that the effects on HIT-6 and other endpoints in the overall population were clinically meaningful, provides reassurance that the effects of Botox in the 'no medication overuse' subgroup were also clinically meaningful.

Botox also had statistically significant and clinically meaningful effects in the 'medication overuse' subgroup. This population did not strictly correspond to the ICHD-2R definition of CM because they were overusing headache medications, but it is likely that although some of the subgroup may have had MOH, a large proportion of them would have had treatment-resistant CM.

The conclusion that Botox had clinically meaningful effects is weakened if the magnitude of the effect size was materially exaggerated due to bias in the pivotal studies. In regard to this question of bias, there are reasonable grounds to suspect that blinding was not fully maintained in the pivotal studies, and one would normally expect such unblinding to lead to an overestimate of the treatment effect. However, analyses presented by the sponsor showed that the presence or absence of the most obvious potential source of unblinding (so-called 'potentially unblinding adverse effects') did not alter the estimate of treatment effect for the most important efficacy endpoint (headache days). Data from the Phase II trials indicate that 'potentially unblinding adverse effects' probably did not account for all of the unblinding, so there is some residual doubt as to whether the pivotal studies were completely unbiased. However, most of the potential unblinding has been accounted for and it may be reasonably be argued that if unblinding by AEs did not influence the efficacy assessment, then unblinding by other means (for example, cosmetic effects that were not recorded as AEs) also would not influence the efficacy assessment (although this remains unconfirmed).

In regard to safety, AEs seen in the migraine studies were consistent with the safety profile of Botox as demonstrated in other indications and documented in the PI. In the pooled pivotal trials, SAEs were reported in 33/687 (4.80%) of the Botox recipients and 16/692 (2.31%) of the placebo recipients. This gives a number-needed-to-harm (NNH) of 40.2 for each additional patient affected by an SAE in the Botox group, which balances favourably against the NNTs of 8.3 for each additional patient with a 50% reduction in headache days and 8.5 for each additional patient with a 50% reduction in migraine/probable migraine days.

Overall, there is some residual doubt as to whether the study results were entirely unbiased. On balance however, the benefits of Botox demonstrated in patients with CM according to the ICHD-2R definition (the 'no medication overuse' subgroup) and also in patients with CM and medication overuse (some of whom may have had MOH, but the majority of whom probably had treatment-resistant CM) are sufficient in comparison to its risks to recommend approval of the submission.

V. Pharmacovigilance Findings

Risk Management Plan (RMP)

The RMP for Botox was evaluated by the Office of Product Review at TGA. It was noted that the sponsor did not identified any new safety concerns with respect to use in chronic migraine. Following review of the product safety specification, the following table (Table 33) summaries the safety issues.

Table 33.

Important identified risks	• Hypersensitivity reaction including anaphylaxis and serum sickness • Pre-existing neuromuscular disorders
Important Potential Risks	• Possible distant spread of toxin including dysphagia • Seizure • Cardiovascular events • Guillain-Barré syndrome • Medication Error resulting from interchanging botulinum toxin units from one product to another • The effect of botulinum toxin may be potentiated by agents interfering with neuromuscular transmission, such as curare-like compounds, aminoglycosides, and spectinomycin.
Important missing information	• The effect of administering different botulinum toxin serotypes at the same time or within several months is unknown • Use in pregnancy and lactation • Drug utilisation/current treatment practices

The sponsor proposed routine pharmacovigilance and risk minimisations activities[23] for all risks and areas of missing information. In addition, enhanced pharmacovigilance to monitor the risk of distant spread of toxin and Guillain Barré syndrome, and additional risk minimisation activities for distant spread of toxin were proposed.

Overall the Pharmacovigilance Plan and Risk Minimisation activities were accepted by the TGA after consideration of the recommendations made in the evaluation.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

No new data were submitted with this application.

[23] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Nonclinical

Three nonclinical pharmacological studies describing rat models of nociception involving peripheral sensitisation were submitted. In these models allodynia or hyperalgesia was inhibited by intraplantar injection of Botox; other analgesics administered systemically were also effective. Acute nociception was unaffected by Botox. The nonclinical evaluator considered that while these results may be explained by botulinum toxin-mediated inhibition of release of compounds from the peripheral primary afferent terminals, direct evidence is lacking. The nonclinical evaluator considered that extrapolation of such a mechanism of action to a similar inhibitory effect in the pathogenesis of migraine is tenuous.

These studies were submitted to support proposed words in the PI regarding the mechanism of action of Botox in the treatment of chronic migraine. The nonclinical evaluator supported amended PI statements that did not claim a known mechanism of action for the effect of Botox in chronic migraine.

Clinical

There were two CERs for this submission. Following receipt of the first CER the sponsor submitted supplementary data that was evaluated in a second CER, referred to below as the supplementary CER. The supplementary CER evaluated justifications, literature and additional analysis of the studies evaluated in the initial CER. There were no clinical pharmacology studies.

Efficacy:

There were two Phase II studies and two Phase III studies relevant to the proposed indication. These were double-blind, randomised, placebo-controlled studies evaluating up to three treatment regimens of Botox for the prophylaxis of chronic headache. Study 191622-038 used Botox doses from 105 U to 260 U and Study 039 used doses of 75, 150 and 225 U. Neither study showed a statistically significant difference for its primary efficacy endpoint of change from baseline in the number of headache-free days. These studies also included an assessment of the effectiveness of blinding. Patients were asked to guess which treatment they were receiving. In both studies ~14% of patients considered they were receiving placebo.

The pivotal efficacy endpoints were intended to evaluate efficacy and safety of Botox as headache prophylaxis in migraine patients with ≥ 15 headache days per 4-week period. Each study included a 4-week baseline phase followed by a 24-week, double-blind, randomised, placebo-controlled phase and then a 32-week open-label extension phase. Subjects received 2 x 12-week treatment cycles during the double-blind phase and 3 treatment cycles during the extension phase. Subjects received from 155 – 195 U Botox or placebo via intramuscular injection to 31 to 39 injection sites across seven head and neck muscle groups in each cycle. Some 679 subjects were randomised in Study 191622-079 and 705 in Study 191622-080.

These studies enrolled subjects with a history of migraine; long lasting headache (≥ 4 hours) that occurred on 15 or more days per 28 days; an indication that most headache days were migraine in origin (that is, ≥ 50% were required to be migraine or probable migraine according to ICHD-II definition) and to have had four or more intermittent, long-lasting headaches in the 4-week baseline period. Subjects were excluded if they had received prophylaxis for migraine within 28 days prior to the start of the baseline period. Patients with medical conditions that may have confounded the results including moderate and severe depression (Beck Depression Inventory score > 24), fibromyalgia,

temporomandibular disorder, unremitting headache, chronic tension-type headache and headache attributed to another disorder were excluded from study.

Patients meeting the criteria for medication overuse headache were included and composed the majority of patients. Medications for acute treatment of migraine included: ergotamine, triptans, simple analgesics, opioids and combination analgesic medication. These medications could also be taken during the studies as prescribed.

The primary efficacy endpoint in Study 191622-079 was change from baseline to Week-24 in frequency of headache episodes per 28-day period. In Study 191622-080 the primary endpoint was change from baseline in the number of headache days per 28-day period. Key secondary efficacy endpoints in these studies included the change from baseline in frequency of headache episodes/ days (whichever was not the primary endpoint); migraine/ probable migraine days; migraine/ probable migraine headache episodes and acute headache pain medication intakes. Effect of treatment on quality of life was measured by 5 questionnaires and these were also secondary endpoints. Amendments to the protocol added other variables including proportion of patients with 50% reduction in headache days and 50% reduction in headache episodes.

The primary comparison was of the ITT population by ANCOVA with baseline headache as the covariate. For a patient who reported any diary data in less than 10 days of a 28 day period, the score of the period was imputed by a modified last observation carried forward (mLOCF) in which the patients previous 28-day score (that is, the last observation) was adjusted in proportion to the change in the mean overall treatment groups from that 28-day period to the missing data 28-day period and rounded to the nearest whole number. The initial analysis did not adjust for multiplicity effects. A subsequent analysis for this adjustment was then performed.

In both the Botox and placebo groups overuse of acute headache pain medications was reported in the majority of patients (64.8% Botox and 66.2% placebo) at baseline. Use of medication for acute treatment of migraine occurred during both studies. Both studies included subjects who had medication overuse headache and a subgroup analysis for subjects with analgesia overuse for mean change from baseline at Week 24 in frequency of headache days and frequency of headache episodes was performed. Other efficacy endpoints were not provided for this subgroup.

In Study 191622-079, the mean number of headaches in the preceding 28 day period was 12.3 at baseline and reduced to7.1 at Week 24 for subjects given Botox and from 13.4 at baseline to 8.1 at Week 24 in subjects given placebo. The difference in mean reduction in headache frequency Botox versus, placebo was -0.1 and this difference was not statistically significant. The frequency of headache days reduced from 20.0 at baseline to 12.2 at week 24 in subjects given Botox and from 19.8 at baseline to 13.4 at Week 24 in subjects given placebo (difference 1.4 days; $p = 0.006$).

In Study 191622-080 the mean number of headaches in the preceding 28 day period was 19.9 at baseline and reduced to 10.9 by Week 24 for subjects given Botox and from 19.7 at baseline to 13.0 after 24 weeks in subjects given placebo. The difference in mean reduction in headache frequency Botox versus, placebo was 2.3 ($p < 0.001$). The frequency of migraine/ probable migraine days per 28-day period reduced from 19.2 at baseline to 10.5 at week 24 in subjects given Botox and from 18.7 at baseline to 12.4 at Week 24 in subjects given placebo (difference 2.4 days; $p< 0.001$).

A post-hoc analysis of pooled results from the pivotal Phase III studies (Studies 191622-079 and 191622-080) was performed. This analysis is described in the supplementary CER with key efficacy results tabulated below (Table 34). It includes assessment of

number of migraine/ probable migraine days. The subgroup analysis for subjects with analgesia overuse was also presented.

Table 34.

Endpoint / Stratum	Baseline		Week 24			P-value
	Botox	Placebo	Botox	Placebo	Botox - Placebo †	
HA days						
Medication overuse	20.1	19.8	-8.2	-6.2	-2.0	<0.001
No medication overuse	19.6	19.7	-8.8	-7.3	-1.5	0.013
Overall	19.9	19.8	-8.4	-6.6	-1.8	<0.001
HA episodes						
Medication overuse	12.8	13.8	-5.4	-4.9	-0.5	0.028
No medication overuse	10.9	11.4	-5.0	-4.6	-0.4	0.146 (NS)
Overall	12.2	13.0	-5.2	-4.9	-0.3	0.009
Migraine/probable migraine days						
Medication overuse	19.3	19.1	-8.1	-6.0	-2.1	<0.001
No medication overuse	18.8	18.5	-8.4	-6.6	-1.8	0.004
Overall	19.1	18.9	-8.2	-6.2	-2.0	<0.001
Moderate/severe HA days						
Medication overuse	18.5	18.4	-7.7	-5.7	-2.0	<0.001
No medication overuse	17.4	17.3	-7.8	-6.0	-1.8	0.005
Overall	18.1	18.0	-7.7	-5.8	-1.9	<0.001
Cumulative hrs of HA on HA days						
Medication overuse	291.31	270.46	-114.46	-70.80	-43.66	<0.001
No medication overuse	304.37	302.05	-129.21	-99.26	-29.95	0.023
Overall	295.93	281.22	-119.67	-80.49	-39.18	<0.001

This analysis showed statistically significant efficacy assessed using various endpoints as shown above. Statistically significant differences in the proportion of patients with ≥50% reduction in headache days was also shown in the pooled Phase III studies (47.1% reduction for Botox versus 35.1% for placebo; p= 0.001). The differences for 50% reduction in headache frequency were not statistically significant (48.6% for Botox versus 43.1% for placebo; p= 0.065).

Baseline, headache pain medication was taken on a mean (standard deviation (SD)) of 26.9 (19.13) occasions per 28-day period in the Botox group and on 27.8 (20.73) occasions in the placebo group. By week 24 this was reduced by a mean (SD) of 10.1 (17.15) in the Botox group and by 9.4 (16.79) in the placebo group.

In addition to describing results of the pooled analysis of pivotal studies the supplementary CER discussed the difficulties in development of diagnostic criteria for

chronic migraine and the relevance of the pivotal study entry criteria to the proposed patient population.

There were four main points of difference between the entry criteria used in the pivotal trials and the ICHD-2R criteria for chronic migraine. The major differences are summarised as:

- ICHD-2R specifies that headaches occur on at least 15 days per month for 3 months whereas this could not be confirmed in the clinical trial group, though it was probable;
- patients with medication overuse headache are not included as having chronic migraine by ICHD-2R but these patients were included in the clinical trial group;
- ICHD-2R does not specify a daily duration of headache, however the clinical trial group were required to have continuous headache for at least 4 hours on each headache day;
- ICHD-2R requires headaches to be migraine or medication-modified migraine on at least 8 days per month, whereas the clinical trial group were required to have probable migraine on at least 50% of the headache days.

Analysis by the sponsor, discussed in the supplementary CER, showed that the pivotal study inclusion criteria had 94% specificity for identifying a population with chronic migraine according to partial ICHD-2R (ignoring medication overuse) but only 55% specificity for identifying patients who satisfied the full ICHD-2R definition (i.e. with no medication overuse). The clinical evaluator has noted the difficulty in separating a population with analgesia overuse headache from those with treatment-resistant chronic migraine.

The supplementary CER also includes discussion of the initial clinical evaluator's observation that there should have been an active control in the pivotal studies and that there was insufficient rationale for the dose used in the pivotal trials. This response was considered in the supplementary CER. The sponsor's case can be summarised as: there is no approved treatment for "chronic migraine" in Australia; therapeutic failure is not life-threatening; rescue medication was permitted; and a placebo arm would have been required in any case to demonstrate sensitivity of the trial. These points were accepted.

The sponsor also argued that the percentage of subjects with a 30% or 50% reduction in headache days is a better measure of efficacy. The supplementary CER presented percentages of subjects in the pivotal studies with ≥ 50% reduction from baseline to week 24 for key headache efficacy variables. From these results the clinical evaluator has calculated the NNT of 8.3 to obtain a ≥ 50% reduction in headache days and 8.5 for a ≥ 50% reduction in migraine/ probable migraine days, based on pooled data. The clinical evaluator then compared this with data from a Cochrane review of NNT for a 50% reduction in migraine frequency for various medications used as migraine prophylaxis. Each of these was better than the result for Botox. Of the medicines assessed in the Cochrane review, only topiramate and propranolol have indications for migraine prophylaxis. None of these medicines is indicated for prophylaxis of chronic migraine.

Other points raised by the sponsor to support use of Botox in prophylaxis of chronic migraine are discussed in the supplementary CER. These concerned primarily why Botox may be preferable to other treatments. Various secondary endpoint results and concerns raised by the initial clinical evaluator were also discussed.

Safety:

Assessment of adverse events and clinical laboratory monitoring was presented from the pivotal and supportive efficacy studies and also from seven studies of patients with acute

migraine. A total of 3235 subjects received Botox in these studies, of these 1384 received Botox in studies of chronic migraine.

Adverse events occurring during the double-blind period in the pooled population for all these studies are shown in the CER. An analysis of this data set was also performed for 17 preferred terms pertinent to toxicity associated with botulinum toxin including: dyspnoea, pneumonia aspiration, respiratory failure, hypotonia, muscular weakness, diplopia, extraocular muscle paresis, eyelid ptosis, vision blurred, facial palsy, facial paresis, bradycardia, constipation, dry mouth, urinary retention, dysarthria, and dysphagia. The events were disproportionately reported in subjects given Botox with 658 reports versus, 34 in subjects given placebo. There were no deaths in that dataset. Muscular weakness was reported in 228 subjects given Botox compared to seven given placebo. In 223 of the Botox cases these events were isolated to the head, neck, shoulders and/ or arms as would be anticipated from the treatment.

Very few serious adverse events were reported across the Phase II and III studies. In each of the studies more serious events were reported in subjects given Botox than placebo during the double-blind period. However in Studies 191622-079 and 191622-080 only one serious adverse event in each study was considered to be treatment-related (intractable migraine in a subject given Botox in each study). One death occurred in Study 191622-038 and it was due to cardiovascular disorder in a subject given placebo.

No meaningful changes in clinical laboratory data were reported across the studies.

Risk Management Plan

The Risk Management Plan (RMP) was evaluated and a supplementary review of a revised plan was also conducted. The RMP reviewer has accepted the sponsor's updated RMP.

In its response to the RMP review the sponsor has noted that prescribers of Botox for chronic migraine are expected to be neurologists and pain specialists.

Risk-Benefit Analysis

Delegate Considerations

Chronic migraine is a difficult condition to diagnose and to treat and no medicines are currently approved specifically to manage this condition. Current migraine prophylaxis treatments are for migraine prophylaxis in general with the majority of patients receiving them likely to have presented with episodic migraine. Efficacy of Botox in the prophylaxis of episodic migraine was not been assessed by the clinical evaluators and this indication has not been requested by the sponsor.

The initial CER raised the following concerns with the submission:

- limited evidence to base the proposed dose regimen;
- blinding of patients may not have been not fully effective;
- the lack of an active control;
- the patient group proposed for the indication was only a minority subgroup of subjects in each of the pivotal studies;
- a limited analysis of efficacy criteria for the proposed patient group was supplied;
- it was unclear if this limited analysis allowed for multiplicity effects which may be considerable given the large number of secondary endpoints measured in the studies; and
- lack of evidence of ongoing efficacy against placebo after two treatment cycles.

Each of these concerns has been addressed by the sponsor and that response has been evaluated in the supplementary CER. The major concerns with the pivotal studies are that they did not include only subjects meeting the ICHD-R2 criteria for chronic migraine and that the pooled analysis was *post-hoc*. To a large extent the subjects enrolled in these studies met the ICHD-R2 criteria, with the exception of inclusion of subjects with analgesia overuse. Patients with treatment-resistant chronic migraine may be difficult to differentiate from patients with analgesia overuse headache, given that these patients may present with similar symptoms and be reluctant to forego use of analgesics. The subgroup analysis of pooled study results has given assurance that Botox shows efficacy in patients likely to have treatment-resistant chronic migraine but who are also taking excessive analgesics. Statistically significant efficacy was less well demonstrated for subjects without analgesia overuse, but this is likely to have been due to the lower number of these subjects enrolled in the studies.

The mean benefit from use of Botox seems quite small, though it was statistically significant. There were modest mean reductions in acute analgesia use, headache days and headache frequency. The 50% responder analysis of key efficacy parameters provided assurance that clinically meaningful efficacy occurred for a substantial minority of patients. The use of 50% or 30% responder rates is often used in the assessment of medicines for treatment of psychiatric conditions and was also used as a secondary efficacy endpoint in the assessment of topiramate for migraine prophylaxis.

The injection of Botox to multiple muscle groups over the head and neck is not without side effects, particularly muscle weakness. This would be anticipated given that is a well established effect of Botox. Other side effects associated with exposure to botulinum toxin such have not been considered as serious however they occur more frequently in subjects given Botox than in those given placebo. The proposed dose does not exceed the current maximum dose of Botox for other conditions.

Conclusion and recommendation

The Delegate considered that there was sufficient evidence that Botox is effective in the treatment of chronic migraine to approve its use for this condition. The indications approved in the USA and in the UK have included different descriptors of chronic migraine which are reflective of some of the inclusion criteria in the pivotal clinical trials and/ or the ICHD-2R definition of chronic migraine. The US PI also includes a statement regarding lack of efficacy in the prophylaxis of episodic migraine.

Any indication for use in chronic migraine should take into account the difficulty in distinguishing between patients with analgesia overuse headache and treatment-resistant chronic migraine. However if this distinction is not made then the patient does not meet the ICHD-2R definition of chronic migraine. A working definition of chronic migraine is required to be included in the indication.

The Delegate proposed the indication of:

> *Prophylaxis of headaches in adults with a history of chronic migraine (at least 3 months of headaches on at least 15 days per month of which at least 8 days are with migraine).*

The Delegate proposed to include statements on the lack of assessment of efficacy in episodic migraine and tension headache in the *Precautions* section of the PI. Published reports of use of Botox for tension type headache and the episodic migraine studies in the submission did not demonstrate efficacy, though a formal evaluation of these studies has not been undertaken. The Delegate also proposed to include in the PI a statement that patients having experienced chronic migraine and responded to Botox should not continue

injections indefinitely but should have treatment interruptions to determine if ongoing injections are required.

The advice of the ACPM is requested regarding:

- the wording of the indication;
- location within the PI of a statement on the lack of evidence of efficacy of Botox in other headache conditions; and
- whether the PI should include a statement that use of Botox for treatment of chronic migraine should be restricted to neurologists and pain specialists as is anticipated by the sponsor.

Response from Sponsor

Allergan Australia Pty. Ltd. referred to the pre-ACPM report and concurred with the recommendation of the Delegate to approve the extension of indication for Botox (Botulinum Toxin Type A) to include prophylaxis of headaches in adults with chronic migraine.

Allergan took the opportunity to respond to some of the comments made by the Delegate. The following areas were discussed in detail:

1. Wording of Indication

2. Statement in PI relating to lack of evidence of efficacy in other headache conditions

3. Statement in PI regarding restriction to neurologists and pain specialists

4. Statement in PI relating to treatment interruptions

5. Other changes to the Product Information document

The Delegate had stated that any indication for use in chronic migraine should take into account the difficulty in distinguishing between patients with analgesia overuse headache and treatment resistant chronic migraine and believes a working definition of chronic migraine is required to be included in the indication.

Allergan proposed the following wording for the indication, which adds the working definition for chronic migraine approved in the UK SmPC:

"prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine)"

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM) having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended rejection of the submission from Allergan Australia Pty Ltd to register Botulinum toxin type A (Botox) for prophylaxis of headaches in adults with a history of chronic migraine (at least 3 months of headaches on at least 15 days per month of which at least 8 days are with migraine).
In making this recommendation, the ACPM considered the data provided and concluded that the evidence was insufficient to demonstrate clear clinical efficacy for the proposed population.
Despite demonstration of statistically significant efficacy, clinical significance is questionable in view of the large placebo effective of the multiple injections. While there was a 10% response rate in the pooled data from the submitted studies, the ACPM advised that the studies were inadequately designed as they did not include the critical parameters of appropriate blinding, use of active comparators or the exploration of minimum effective

dosing and did not differentiate between the population groups (overuse versus chronic migraine populations).

Outcome

The Delegate did not accept the advice of the ACPM in relation to this submission because the Delegate considered that the ACPM did not give sufficient weight to the following issues:

- Chronic migraine is a difficult condition to diagnose and to treat and no medicines are currently approved specifically to manage this condition;
- Complete blinding of patients and treating doctors in a clinical trial would not be possible given the effect of botulinum toxin type A on muscles;
- Current migraine prophylaxis treatments are for migraine prophylaxis in general, with the majority of patients receiving them likely to have presented with episodic migraine, therefore no active control could reasonably be considered as an acceptable comparator;
- There is clinical trial evidence of statistically and clinically significant differences between Botox and placebo for key efficacy measures for prophylaxis of headaches including reductions in the frequency of headache days, migraine/ probable migraine days, moderate/ severe headache days, and in measures of the impact of headaches on patients' daily life such as the Headache Impact Test (HIT-6) and the Migraine-Specific Quality of Life (MSQ) questionnaires;
- There are no new safety concerns associated with this new indication and the maximum recommended dose for this new indication is less than the maximum recommended dose for the approved indications of focal spasticity in adults and cervical dystonia (spasmodic torticollis).

The Delegate was of the opinion that due to the difficulties in diagnosing and managing patients with chronic migraine that these patients should be reviewed by either a neurologist or a pain management specialist prior to receiving Botox for prophylaxis of headaches and considered that treatment with Botox in patients with chronic migraine should not be ongoing. There has been no assessment of whether Botox will continue to be effective or if continued treatment with Botox will be required in those patients who have an initial response to treatment. This is reflected in the PI.

The TGA Delegate recommended amendments to the PI that were accepted by the sponsor and included in the final PI.

Based on a review of safety and efficacy, TGA approved the registration of Botulinum Toxin, Type A Purified Neurotoxin Complex 100U Injection vial and Botulinum Toxin, Type A Purified Neurotoxin Complex 200U Injection vial for the following new indication:

> *"Prophylaxis of headaches in adults with chronic migraine (headache on at least 15 days per month of which at least 8 days are with migraine)"*

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

NAME OF THE MEDICINE

BOTOX® purified neurotoxin complex injection (100 U or 200U)
(botulinum toxin, type A)

DESCRIPTION

Composition

Active ingredient:
Each vial of BOTOX® contains either 100 units (U) or 200 units (U) of botulinum toxin, type A, as a haemagglutinin complex.

Excipients:
Human albumin: 0.5 mg for 100 U or 1.0 mg for 200 U
Sodium chloride: 0.9 mg for 100 U or 1.8 mg for 200 U

One unit (U) corresponds to the calculated median lethal intraperitoneal dose (LD_{50}) in mice of the reconstituted BOTOX® injected intraperitoneally. The units by which the potency of the preparation of BOTOX® purified neurotoxin complex are measured are not interchangeable with other commercial preparations of botulinum toxin.

BOTOX® (botulinum toxin, type A) purified neurotoxin complex is a sterile, vacuum-dried injection of purified botulinum toxin, type A produced from a culture of the Hall strain of *Clostridium botulinum* grown in a medium containing casein hydrolysate, glucose and yeast extract. It is purified from the culture solution by a series of acid precipitations to a crystalline complex consisting of the haemagglutinin protein and the active high molecular weight toxin protein. The complex is re-dissolved in a solution containing sodium chloride and human albumin and sterile filtered (0.2 microns) prior to lyophilisation. BOTOX® is to be reconstituted with sterile non-preserved saline prior to injection.

PHARMACOLOGY

Pharmacological action

Therapeutic class: neuromuscular blocking agent.

BOTOX® (botulinum toxin, type A) purified neurotoxin complex blocks neuromuscular conduction by binding to receptor sites on motor or parasympathetic nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. When injected intramuscularly at therapeutic doses, BOTOX® produces a localised partial but reversible chemical denervation of the muscle, and localised muscle paralysis. When the muscle is chemically denervated, it atrophies and may develop extrajunctional acetylcholine receptors. There is evidence that the nerve can sprout and reinnervate the muscle, with the weakness thus being reversible.

When injected intradermally, BOTOX® produces temporary chemical denervation of the sweat gland resulting in local reduction of sweating.

In vitro studies of isolated rat synaptosome fragments indicated that botulinum toxin has a high affinity for cholinergic terminals where it binds to the pre-synaptic membrane.

Chronic Migraine

Limited nonclinical data suggest that BOTOX® may reduce sensitisation processes, but the actual mechanism of action for headache prophylaxis is not known.

Blepharospasm

The paralytic effect on muscles injected with BOTOX® is useful in reducing the excessive, abnormal contractions associated with blepharospasm. Following peri-ocular injection of BOTOX®, distant muscles show electrophysiological changes but no clinical weakness or other clinical change for a period of several weeks or months, parallel to the duration of local clinical paralysis.

Typically, patients with blepharospasm show improvement lasting an average of 12.5 weeks prior to the need for re-treatment.

Strabismus

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

Focal Spasticity in adults and children two years and older

BOTOX® treatment reduces both the objective signs and subjective symptoms of spasticity. Improvements include reduction in muscle tone, increase in range of motion, reduction in pain and a reduction of spasticity-related functional disability.

Cervical Dystonia (spasmodic torticollis)

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

Primary Hyperhidrosis of the Axillae

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

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

Spasmodic Dysphonia
Spasmodic dysphonia is a focal laryngeal dystonia with task specific spasms of the vocal cords seriously interfering with communication. Approximately 90% of the patients have adductor spasmodic dysphonia with spasms of the adductor muscles including thyroarytenoid, lateral cricoarytenoid and interarytenoid muscles. About 10% of patients have abductor spasmodic dysphonia with spasms of the abductors of the vocal cords, in particular the posterior cricoarytenoid muscles. Many studies have shown that at least 90% of patients with adductor spasmodic dysphonia obtain a satisfactory or better result with BOTOX® injections. Treatment of abductor spasmodic dysphonia is more technically difficult and results are less satisfactory, but with a tailored approach most patients still obtain satisfactory improvement with BOTOX® injections.

Glabellar Lines
Glabellar lines are secondary to relative overactivity (or hyperfunctioning) of the muscles associated with frowning. When injected into the corrugator and/or procerus muscles, BOTOX® weakens the overactive underlying muscle contraction, decreasing the severity of the glabellar lines and improving appearance. In controlled clinical trials, onset of action was rapid (effect of BOTOX® was apparent at the first assessment timepoint of 7 days) and lasted at least 4 months for many subjects.

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

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

CLINICAL TRIALS – Therapeutic Indications

Chronic Migraine
BOTOX® was evaluated in two multi-national, multi-centre 56-week studies that included a 24-week, 2 injection cycle, double-blind phase comparing BOTOX® to placebo (saline), followed by a 32-week, 3 injection cycle, open-label phase. A total of 1,384 chronic migraine adults who had either never received or were not using any concurrent headache prophylaxis during a 28-day baseline, had ≥ 15 headache days, with 50% being migraine/probable migraine, and ≥ 4 headache episodes were studied

in two phase 3 clinical trials. These patients had a mean duration of chronic migraine for 19.2 ± 12.56 years, and during the 28-day baseline 906 (65.5%) patients were and 478 (34.5%) patients were not overusing acute headache pain medications. These patients were randomised to placebo (saline) or to 155 U - 195 U BOTOX® injections every 12 weeks; maximum 5 injection cycles. During the trial, patients were allowed to use acute headache treatments. BOTOX® treatment demonstrated statistically significant (p<0.001) and clinically meaningful improvements from baseline compared to placebo (saline) for 50% reduction in headache days, mean frequency of moderate/severe headache days and total cumulative hours of headache on headache days (see Tables 1, 2, 3 and 4). Results of the Headache Impact Test (HIT-6) and Migraine-Specific Quality of Life (MSQ) questionnaires indicated BOTOX® had a sustained duration of action and improved functioning, vitality, psychological distress and overall quality of life (refer to Tables 1, 2, 3 and 4).

Table 1: Week 24 (Primary Timepoint) Key Efficacy Variables for Pooled Phase 3 Studies

Efficacy per 28 days	Pooled Studies 191622-079 & 191622-080		
	BOTOX® (N=688)	Placebo (saline) (N=696)	p- value
Mean change from baseline in frequency of headache days [a]	-8.4	-6.6	<0.001
Mean change from baseline in frequency of migraine/probable migraine days [a]	-8.2	-6.2	<0.001
Mean change from baseline in number of moderate/severe headache days [a]	-7.7	-5.8	<0.001
Mean change from baseline in total cumulative hours of headache on headache days [a]	-119.73	-80.49	<0.001
Mean change from baseline in frequency of headache episodes [a]	-5.2	-4.9	0.009
Decrease from baseline in 50% or more headache days [a]	47.1%	35.1%	<0.001
Proportion of patients with severe HIT-6 category scores [b]	67.6%	78.2%	<0.001
Total HIT-6 scores [b]	-4.8	-2.4	<0.001
Mean change from baseline in MSQ scores [b]			
Role function- Restrictive	-17.0	-8.6	<0.001
Role function- Preventative	-13.1	-6.4	<0.001
Role function- Emotional Function	-17.9	-9.5	<0.001

[a] Evaluated over a 28 day pre-randomisation baseline period and a 28 day period leading up to Week 24

[b] Administered once at baseline and once at Week 24, and designed to collect data based on patient's one month recall

Table 2: Week 24 (Primary Timepoint) Key Efficacy Variables for Pooled Phase 3 Studies in Medication Overuse Subgroup

Efficacy per 28 days	Pooled Studies 191622-079 & 191622-080		
	BOTOX® (N=445)	Placebo (saline) (N=459)	p- value
Mean change from baseline in frequency of headache days[a]	-8.2	-6.2	<0.001
Mean change from baseline in frequency of migraine/probable migraine days[a]	-8.1	-6.0	<0.001
Mean change from baseline in number of moderate/severe headache days[a]	-7.7	-5.7	<0.001
Mean change from baseline in total cumulative hours of headache on headache days[a]	-111.91	-73.26	<0.001
Mean change from baseline in frequency of headache episodes[a]	-5.6	-4.9	0.028
Proportion of patients with severe HIT-6[b] category scores	71.0%	81.9%	<0.001
Total HIT-6 scores[b]	-4.7	-2.2	<0.001
Mean change from baseline in MSQ scores[b]			
Role function- Restrictive	-16.9	-7.6	<0.001
Role function- Preventative	-13.9	-5.8	<0.001
Role function- Emotional Function	-18.3	-8.7	<0.001

[a] Evaluated over a 28 day pre-randomisation baseline period and a 28 day period leading up to Week 24
[b] Administered once at baseline and once at Week 24, and designed to collect data based on patient's one month recall

Table 3: Week 24 (Primary Timepoint) Key Efficacy Variables for Pooled Phase 3 Studies in No Medication Overuse Subgroup

Efficacy per 28 days	Pooled Studies 191622-079 & 191622-080		
	BOTOX® (N=445)	Placebo (saline) (N=459)	p- value
Mean change from baseline in frequency of headache days[a]	-8.8	-7.3	0.013
Mean change from baseline in frequency of migraine/probable migraine days[a]	-8.4	-6.6	0.004
Mean change from baseline in number of moderate/severe headache days[a]	-7.7	-6.1	0.005
Mean change from baseline in total cumulative hours of headache on headache days[a]	-128.75	-99.73	0.023
Mean change from baseline in frequency of headache episodes[a]	-5.1	-4.5	0.146
Proportion of patients with severe HIT-6[b] category scores	61.3%	70.9%	0.027
Total HIT-6 scores[b]	-5.1	-2.7	<0.001
Mean change from baseline in MSQ scores[b]			
Role function- Restrictive	-17.2	-10.6	0.001
Role function- Preventative	-11.7	-7.7	0.032
Role function- Emotional Function	-17.4	-11.0	0.017

[a] Evaluated over a 28 day pre-randomisation baseline period and a 28 day period leading up to Week 24

[b] Administered once at baseline and once at Week 24, and designed to collect data based on patient's one month recall

Table 4: Week 24 (Primary Timepoint) Key Efficacy Variables for Phase 3 Studies

Efficacy per 28 days	Study 191622-079			Study 191622-080		
	BOTOX® (N=341)	Placebo (saline) (N=338)	p- value	BOTOX® (N=347)	Placebo (saline) (N=358)	p- value
Mean change from baseline in frequency of headache days [a]	-7.8	-6.4	0.006	-9.0	-6.7	<0.001
Mean change from baseline in frequency of migraine/probable migraine days [a]	-7.6	-6.1	0.002	-8.7	-6.3	<0.001
Mean change from baseline in number of moderate/severe headache days [a]	-7.2	-5.8	0.004	-8.3	-5.8	<0.001
Mean change from baseline in total cumulative hours of headache on headache days [a]	-106.70	-70.40	0.003	-132.41	-90.01	<0.001
Mean change from baseline in frequency of headache episodes [a]	-5.2	-5.3	0.344	-5.3	-4.6	0.003
Proportion of patients with severe HIT-6 category scores [b]	68.9%	79.9%	0.001	66.3%	76.5%	0.003
Total HIT-6 scores [b]	-4.7	-2.4	<0.001	-4.9	-2.4	<0.001
Mean change from baseline in MSQ scores [b]						
Role function- Restrictive	-16.8	-8.8	<0.001	-17.2	-8.4	<0.001
Role function- Preventative	-12.6	-7.6	0.005	-13.5	-5.4	<0.001
Role function- Emotional Function	-16.9	-10.0	0.001	-19.0	-9.1	<0.001

[a] Evaluated over a 28 day pre-randomisation baseline period and a 28 day period leading up to Week 24
[b] Administered once at baseline and once at Week 24, and designed to collect data based on patient's one month recall

Blepharospasm

In one study, botulinum toxin was evaluated in 27 patients with essential blepharospasm. Twenty-six of the patients had previously undergone drug treatment utilising benztropine mesylate, clonazepam and/or baclofen without adequate clinical results. Three of these patients then underwent muscle stripping surgery still without an adequate outcome. One patient of the 27 was previously untreated. Upon using botulinum toxin, 25 of the 27 patients reported improvement within 48 hours. One of the other patients was later controlled with a higher dosage. The remaining patient reported only mild improvement but remained functionally impaired.

In another study, twelve patients with blepharospasm were evaluated in a double-blind, placebo-controlled study. All patients receiving botulinum toxin (n=8) were improved compared with no improvements in the placebo group (n=4). The mean dystonia score improved by 72%, the self-assessment score rating improved by 61%

and a videotape evaluation rating improved by 39%. The effects of the treatment lasted a mean of 12.5 weeks.

In a separate study, blepharospasm patients received an average dose per eye of 33 U of BOTOX® injected at 3 to 15 sites. The most frequently reported treatment-related adverse events were ptosis (20.8%), superficial punctate keratitis and eye dryness (6.3% each).

Strabismus
Six hundred and seventy-seven adult patients with strabismus treated with one or more injections of BOTOX® were evaluated in a large retrospective case review. Fifty-five percent of these patients improved to an alignment of 10 prism diopters or less when evaluated six months or more following injection (1). Large strabismus angles tended to return to pre-injection position and required re-injection more frequently than smaller angles. Thirty-five percent of adults with horizontal strabismus were corrected by one injection to within 10 prism diopters of orthoposition.

Focal spasticity in children 2 years and older

Upper limb spasticity
Two randomised, evaluator-blinded studies compared BOTOX® plus standard care with standard care alone in a total of 72 children with hemiplegic cerebral palsy and upper limb spasticity. In these studies the muscles in the arm and hand that were injected included the biceps brachii, brachialis, brachioradialis, flexor carpi ulnaris and radialis, pronator teres, pronator quadratus, flexor digitorum profundus and sublimis, flexor pollicis longus and brevis, thumb adductor, short flexor of the thumb and interossei.

In the 6-month study (n = 42; 2 to 8 years) spasticity as measured by the Modified Ashworth Scale (MAS) was significantly reduced in children treated with BOTOX® (1-2 U/kg/muscle, maximum dose 240 units, mean 137 units) at months 1 and 3, but returned to baseline values at month 6. Quality of upper limb movement as measured by the Quality of Upper Extremity Skills Test (QUEST) improved significantly from baseline in both groups but to a greater extent in BOTOX®–treated children at months 1 (61% vs. 19%, p=0.004) and 3 (71% vs 33%, p=0.03), but not at month 6 (p=1.0). Children treated with BOTOX® had a significantly greater improvement in function as measured by Goal Attainment Scaling (GAS). Children treated with BOTOX® improved more quickly than those treated with standard care alone. No treatment-related adverse effects were reported.

In the three month study (n = 30, 5-15 years) upper limb function was measured using the Melbourne Assessment of Unilateral Upper Limb Function. Children in the BOTOX® group (0.5 to 2.0 U/kg/muscle) had a 14% improvement in function compared with no change in children in the control group at month 3 (p = 0.002). In this study, there was no difference between treatment groups on the GAS. Three treatment-related adverse effects were reported, 2 localised weakness and one increased frequency of micturition.

Lower limb spasticity – Equinus
A three-month, double-blind, placebo-controlled parallel study was conducted in , cerebral palsy children, aged 2 to 16 years with equinus ankle position. Seventy-two were administered 4U/kg body weight of BOTOX® into the medial and lateral heads of the gastrocnemius at baseline (2 U/kg/muscle), for hemiplegic patients and 1 U/kg/muscle for diplegic patients) and again at 4 weeks. The cumulative dose of BOTOX® over 4 weeks was 2-4 U/kg/muscle and overall 8 U/kg body weight up to a maximum of 200 units during a 30 day period. BOTOX® was significantly more effective than placebo (as assessed by improvement of 3 or more grades on the composite score of Rating Scale (PRS) of dynamic gait (gait pattern, ankle position, hindfoot position during foot strike, knee position during gait, degree of crouch and speed of gait). Improvement was reported by 53%, 50%, 60% and 54% of BOTOX® patients versus 25%, 27%, 25% and 32% of placebo patients at weeks 2, 4, 8 and 12, respectively. Of the individual assessments included on the PRS, a significantly greater number of BOTOX® patients versus placebo patients had improvements in gait pattern (weeks 2, 8 and 12) and ankle position (weeks 2, 6 and 12).

In the 39 month long-term, open-label follow-up of these patients, the medial and lateral gastrocnemius muscles were injected at a dose of 2 U/kg/muscle with a maximum total dose of 200 U of BOTOX® into the medial and lateral heads of the gastrocnemius, and then as needed thereafter. Of the 207 patients evaluated; 115 patients were followed for 12 months, 100 for 18 months, 45 for 2 years and 6 for up to 3 years. The percent of patients who showed an improvement based on the PRS ranged from 41% to 67% over the 3-year period. Of the individual assessments which were included in the PRS, significant improvements were seen at every visit over the 3-year period.

Lower limb spasticity – hip adductor
Published studies showed that BOTOX® is effective in reducing pain and spasticity and improving function. A double-blind placebo-controlled study[8] (n=16) in children aged 2 to 10 years found that 4U/kg body weight to each adductor muscle group (total dose 8 units/kg total body weight) administered 5 -10 days before scheduled isolated adductor surgery significantly reduced mean pain scores (74% reduction, p=0.003), analgesic requirements (50% reduction, p=0.005) and length of hospital stay (33% reduction, p=0.003) compared with placebo.

A second study[9] (n = 43, mean age 8.2 ± 2.5 years) compared the efficacy of BOTOX® (300U injected into the adductor and medial hamstring muscles) with a pressure splint against hip adductor muscle spasticity. Both groups improved during the study period, however, at the 3 month visit, BOTOX® was significantly more effective than pressure splints for spasticity and motor performance as measured by the MAS (p=0.002) and knee distance (p=0.02).

Adverse events were not reported in these studies.

Focal spasticity in adults
Three double-blind placebo-controlled studies involving 256 post-stroke patients with upper limb spasticity showed clinically and statistically significant improvements in wrist, elbow and finger flexor muscle tone. The Ashworth scale was used to measure

clinically significant changes in muscle tone which was assessed from a score of zero (no increase in muscle tone) to 4 (limb rigid in flexion or extension).

In one study, 126 patients were treated with 200 U to 240 U of BOTOX® into the wrist, finger and thumb flexor muscles. A clinically and statistically significantly greater reduction in muscle tone was observed in BOTOX®-treated patients compared to placebo as measured on the Ashworth scale ($p<0.001$) at 1, 4, 6, 8, and 12 weeks post-treatment. The Physician Global Assessment also showed statistically significant improvements at all post-treatment visits for these patients ($p < 0.001$). Furthermore, patients treated with BOTOX® had significant improvement for a pre-determined, targeted disability item associated with upper limb spasticity at 4, 6, 8 and 12 weeks post-treatment ($p\leq0.05$).

In two studies, patients treated with a total dose of either 300 U or 360 U of BOTOX® had significantly greater reduction in wrist and elbow flexor tone compared to placebo. Additionally, the Physician Global Assessment also showed significant benefit from BOTOX® at doses of 75, 180 and 360 U.

In a double-blind, placebo-controlled study of 85 patients with moderate to severe lower limb spasticity, injections of up to 300 U of BOTOX® into the soleus, posterior tibialis and either gastrocnemius or flexor digitorum longus muscles resulted in a reduction of spasm frequency, a reduction in pain, an improvement in spasticity as rated by the physician and increase in range of motion of the ankle as measured by goniometry. All of these changes were clinically and statistically significant. In addition, treatment with BOTOX® in patients with severe spasticity (Ashworth score of 3) resulted in a clinically and statistically significant reduction in muscle tone. In an open-label follow-up to this study, a second injection of BOTOX® clinically and statistically significantly reduced muscle tone in both moderate and severe patients at 4, 8 and 12 weeks post 2nd injection.

Cervical Dystonia (spasmodic torticollis)

In a multicentre study, 170 cervical dystonia patients who had responded to an open-label run-in period (out of 214 patients) were randomised to receive BOTOX® (n=88) or placebo (n=82) in a double-blind, parallel-group evaluation for 10 weeks. Physicians determined the muscles and doses injected for each patient and used a mean total body BOTOX® dose of 236 U (Range: 95 to 360 U). BOTOX® was significantly better compared with placebo by measures of improvement in the Cervical Dystonia Severity Scale (head position rating), physician global assessment, patient global assessment, frequency and intensity of pain, and functional disability by week 6, with sustained benefit for up to 10 weeks. Improvement, as measured by physician global assessment, was 50.6% for the BOTOX® group and 31.1% for the placebo group, a difference of 19.5% ($p=0.009$), which was essentially the same as the pre-defined value of 20% set for a clinically meaningful difference.

In a separate multicentre study, a total of 135 patients were treated. Patients received a single 100-300 U injection of one formulation followed by the other, 8-16 weeks later. Physicians determined the muscles and doses to be injected for each patient and used a mean total body BOTOX® dose of approximately 155 U for all treatment periods. Maximum clinical improvement was observed at 6 weeks, with over 80% of

patients achieving a treatment success by week 6. In relation to time-to-retreatment, at week 6 (42 days) post-injection, 67% of the BOTOX® group had not yet worsened since baseline compared to 45% of the placebo group. At week 10 (70 days) post-injection, 60% of the BOTOX® group remained improved compared to 30% in the placebo group. These differences were statistically significant (p=0.0002).

Primary Hyperhidrosis of the Axillae

In a double-blind, parallel-group, multicentre study, 320 patients with bilateral axillary primary hyperhidrosis were randomised to receive BOTOX® (n=242) or placebo (n=78). Subjects were eligible for enrolment in the study if their baseline spontaneous axillary, as measured by gravimetric assessment over 5 minutes at room temperature and at rest, was ≥ 50 mg. Baseline axillary sweat production was similar in the two treatment groups (216 mg in the BOTOX® group and 236 mg in the placebo group). Treatment responders were defined as subjects showing at least a 50% reduction from baseline in axillary sweating measured by gravimetric assessment.

The incidence of responders among BOTOX®-treated patients was significantly higher (p<0.001) than placebo-treated patients at all post-treatment time points for up to 16 weeks. The incidence of responders among BOTOX®-treated patients ranged from 95% at week 1 to 82% at week 16 compared to 32% at week 1 to 21% at week 16 for placebo-treated patients. The mean percentage reduction in the BOTOX®-treated group ranged from 83% at week 1 to 69% at week 16 compared to 22% at week 1 to 4% at week 16 in the placebo-treated group. The corresponding mean amounts of sweat production at these timepoints were 29 mg and 54 mg in the BOTOX®-treated patients compared to 166 mg and 190 mg in the placebo-treated patients.

Subject's global assessment of treatment satisfaction was significantly higher (p<0.001) in BOTOX®-treated than placebo-treated patients at all post-treatment timepoints.

Spasmodic Dysphonia

In the largest series reported 639 patients with adductor spasmodic dysphonia and 108 patients with abductor spasmodic dysphonia were injected with a mean dose of 3.1 ± 3.1 units and 2.16 ± 1.07 units of BOTOX® respectively. The patients recorded the responses in a diary, including their percentage of normal function, on a global visual analogue scale where 100% was a normal voice and 0% was inability to phonate. For adductor spasmodic dysphonia the mean onset of effect was 2.4 ± 4.3 days with a mean peak effect of 9 ± 12.7 days. The mean duration of benefit was 15.1 ± 12.3 weeks, the percent of normal function rose from 52.4% ± 22% to 89.71% ± 13%. For abductor spasmodic dysphonia mean onset of effect was 4.1 ± 5.5 days with a mean peak effect of 10 ± 12.5 days. The mean duration of benefit was 10.5 ± 12.2 weeks. The percentage of normal function rose from 54.8% ± 21.9% to 66.7% ± 23.4% respectively.

In another large series of 169 patients (adductor spasmodic dysphonia 88.8%, abductor spasmodic dysphonia 1.8% and mixed spasmodic dysphonia 4.1%) the median treatment outcome score was excellent in 63.9% of patients, very good in 18%, satisfactory in 14.5% and unsatisfactory in 3.5%, as judged by a subjective self-rating scale which patients recorded in a diary. Speech rate increased after

BOTOX® therapy by approximately 12 syllables per minute. Nasendoscopy, before and after treatment in many patients, confirmed the weakening of the vocal cords and abolition of the spasms.

CLINICAL TRIALS – Cosmetic Indications

Glabellar Lines

In two multicentre, double-blind, placebo-controlled, parallel-group studies of identical design, patients with moderate to severe glabellar lines evaluated at maximum frown were randomised to receive BOTOX® (n=405) or placebo (n=132). In these studies, the severity of glabellar lines was significantly reduced for up to 120 days in the BOTOX® group compared to the placebo group as measured by investigator rating of glabellar line severity at maximum frown and at rest, and by subjects global assessment of change in appearance of glabellar lines. Thirty days after injection, 80% of BOTOX®-treated patients were considered by investigators as treatment responders (glabellar line severity score of mild or none), and 89% of patients felt they had moderate or better improvement, compared to 3.0% and 6.8% of placebo-treated patients respectively.

A third, open-label study was also conducted to support the continued efficacy of repeat BOTOX® injections. At the completion of the double-blind studies, patients were able to enter this open-label phase with repeat treatments given at 120 day intervals. Therapeutic effect was maintained over the three injection cycles assessed with results showing increased efficacy following multiple injection sessions.

Crow's Feet

Two multicentre, double-blind, placebo-controlled, parallel-group studies were performed to examine the safety and efficacy of BOTOX® for the treatment of crow's feet. In one study, patients with bilaterally symmetrical, moderate or severe crow's feet at maximum smile were randomised to receive BOTOX® (n=130) [age range 27 to 64 years (mean = 47 years)], injected bilaterally at three sites per side, for a dose of 3 U, 6 U, 12 U or 18 U per side or placebo (n=32). Treatment with BOTOX® showed a dose-related response up to 12 U; although the response was similar in the two highest dose groups, 12 U and 18 U. The duration of response was dose-related, with significant mean reductions from baseline in crow's feet severity to day 180 for the 12 U ($p \leq 0.032$) and 18 U ($p \leq 0.003$) groups, day 150 for the 6 U group ($p \leq 0.017$) and day 120 for the 3 U group ($p \leq 0.006$). No significant changes were seen within the placebo group at any post-treatment timepoint. Maximum responder rates were observed at day 30 for all treatment groups. The safety profile in the active treatment groups was similar to placebo.

The second study examined the safety and efficacy of treatment of crow's feet with 1 of 3 dosages of BOTOX® (n=148) or placebo (n=49) [age range 27 to 65 years (mean = 47 years)], and the effect on the severity of forehead lines and glabellar lines. In this study, patients with bilaterally symmetrical, moderate or severe crow's feet at maximum smile; forehead line severity of mild, moderate or severe at maximum eyebrow elevation and glabellar line severity of mild, moderate or severe at maximum frown were treated with BOTOX®, injected bilaterally at three sites per side, for a dose of 6 U, 12 U or 18 U per side or placebo. Although significant improvements in crow's feet were seen with all BOTOX® doses when compared to placebo, the

treatment of crow's feet did not affect the severity of either horizontal forehead lines or glabellar lines. Thus it appears that the treatment of crow's feet at doses of 18 U, 12 U and 6 U does not affect adjacent areas and as such dose modification is not considered necessary. No safety concerns were seen at any dose of BOTOX® treatment.

The safety and efficacy of BOTOX® for the treatment of crow's feet has been described in published clinical studies. In one study (5), 60 patients were treated with 6 U, 12 U or 18 U of BOTOX® in the orbicularis oculi muscle on one side of the face and placebo contralaterally. At 16 weeks after injection, patients were treated with 12 U or 18 U of BOTOX® bilaterally. BOTOX® was associated with significantly higher success rates than placebo at all dose levels, as determined by both trained observers and patients. At 4 weeks post-injection, 89-95% of patients on the BOTOX®-treated side were considered by investigators as treatment responders and 60-80% of patients felt they had treatment success, compared to approximately 5-15% and 15-45%, respectively on the placebo treated side. No clear dose response relationship was observed. Benefits of the second injection lasted longer than the first, with success rates for the second injection reaching 100% for the 12 U and 18 U groups at week 4. BOTOX® was well tolerated. No serious or severe adverse events were reported.

Forehead Lines

The safety and efficacy of BOTOX® for the treatment of horizontal forehead lines has been described in published clinical studies. In one study (7), BOTOX® was administered to 59 patients with horizontal forehead lines scoring 2 (moderate) or 3 (severe) on the facial wrinkle scale (FWS). Patients were randomly assigned to receive 8 U, 16 U and 24 U of BOTOX® injected into the frontalis muscle with additional brow depressor injections. Approximately 90% of subjects responded to treatment as rated by investigators and up to 75-80% by self-assessment at week four. There was a reduction in horizontal rhytide severity in all three BOTOX® treatment groups at both contraction and repose. There was a significant dose-response trend ($p \leq 0.019$) for sustained duration of improvement: 53% in the 24 U group versus 15% in the 8 U group at 16 weeks ($p \leq 0.023$ for difference between groups), by trained observer. There was a significant dose-response trend ($p \leq 0.011$) for rate of relapse to baseline: 35% in the 24 U group versus 75% in the 8 U group at 16 weeks ($p \leq 0.038$ for difference between groups), by trained observer. BOTOX® was well tolerated. No serious adverse events were reported.

Pharmacokinetics

Pharmacokinetic studies in humans are not practicable with BOTOX®.

Distribution studies in rats indicate slow muscular diffusion of ^{125}I-botulinum neurotoxin A complex in the gastrocnemius muscle after injection, followed by rapid systemic metabolism and urinary excretion. The amount of radiolabelled material in the muscle declined at a half-life of approximately 10 hours. At the injection site the radioactivity was bound to large protein molecules, whereas in plasma it was mostly bound to small molecules, suggesting rapid systemic metabolism of the substrate. Within 24 hours of dosing, 60% of the radioactivity was excreted in the urine. Autoradiographic results after intramuscular injection of ^{125}I-botulinum neurotoxin A complex into the proximal inner surface of the upper eyelids of rabbits also indicate slow muscular diffusion.

INDICATIONS

BOTOX® (botulinum toxin type A) purified neurotoxin complex is indicated for the following therapeutic indications:

- prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine)
- treatment of strabismus in children and adults
- treatment of blepharospasm associated with dystonia, including benign blepharospasm and VIIth nerve disorders (specifically hemifacial spasm) in patients twelve years and over
- treatment of cervical dystonia (spasmodic torticollis)
- treatment of focal spasticity of the upper and lower limbs, including dynamic equinus foot deformity, due to juvenile cerebral palsy in patients two years and older
- treatment of severe primary hyperhidrosis of the axillae
- treatment of focal spasticity in adults
- treatment of spasmodic dysphonia.

BOTOX® (botulinum toxin type A) purified neurotoxin complex is indicated for the following cosmetic indications:

- temporary improvement in the appearance of upper facial rhytides (glabellar lines, crow's feet and forehead lines) in adults.

CONTRAINDICATIONS

BOTOX® (botulinum toxin type A) purified neurotoxin complex is contraindicated in individuals with known hypersensitivity to any ingredient in the formulation.

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

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

PRECAUTIONS

Lack of interchangeability between botulinum toxin products
DUE TO THE LACK OF AN INTERNATIONAL UNIT, BOTOX® IS NOT THERAPEUTICALLY EQUIVALENT TO THE OTHER BOTULINUM TOXIN TYPE A PREPARATION CURRENTLY AVAILABLE ON THE AUSTRALIAN MARKET. THE POTENCIES OF BOTOX® AND THE OTHER BOTULINUM TOXIN TYPE A PREPARATION ARE BASED ON DIFFERENT ASSAY METHODS. IN VIEW OF THIS LACK OF HARMONISATION OF UNIT SYSTEMS FOR THE BOTULINUM TOXINS TYPE A ON THE MARKET, EXTREME CAUTION IS REQUIRED IF IT SHOULD PROVE NECESSARY TO SUBSTITUTE THE BOTULINUM TYPE A TOXIN OF ONE PHARMACEUTICAL COMPANY BY ANOTHER. THE EFFECT OF ADMINISTERING DIFFERENT BOTULINUM NEUROTOXIN SEROTYPES AT THE SAME TIME OR WITHIN SEVERAL MONTHS OF EACH OTHER IS UNKNOWN. EXCESSIVE NEUROMUSCULAR WEAKNESS MAY BE EXACERBATED BY ADMINISTRATION OF ANOTHER BOTULINUM TOXIN PRIOR TO THE RESOLUTION OF THE EFFECTS OF A PREVIOUSLY ADMINISTERED BOTULINUM TOXIN.

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

Pre-existing neuromuscular disorders
Individuals with peripheral motor neuropathic diseases (e.g., amotrophic lateral sclerosis, or motor neuropathy) or neuromuscular junctional disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should only receive BOTOX® with caution: Patients with neuromuscular disorders may be at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of BOTOX®. Published medical literature has reported rare cases of administration of a botulinum toxin to patients with known or unrecognized neuromuscular disorders where the patients have shown extreme sensitivity to the products. In some cases, dysphagia has lasted several months and required placement of a gastric feeding tube.

Hypersensitivity reactions
Serious and/or immediate hypersensitivity reactions have been rarely reported. As

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

General
The recommended dosages and frequencies of administration for BOTOX® should not be exceeded (see Dosage and Administration).

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

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

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

As with any injection, procedure-related injury could occur. An injection could result in localized infection, pain, inflammation, paresthesia, hypesthesia, tenderness, swelling, erythema, and/or bleeding/bruising. Needle-related pain and/or anxiety may result in vasovagal responses, e.g. syncope, hypotension, etc. Care should be taken when injecting near vulnerable anatomic structures.

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

Blepharospasm
Reduced blinking from BOTOX® injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defect and corneal ulceration, especially in patients with VIIth nerve disorders. One case of corneal perforation in an aphakic eye requiring corneal grafting has occurred because of this effect. Careful testing of corneal sensation in eyes previously operated upon, avoidance of injection into the lower lid area to avoid ectropion, and vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.

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

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

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

Spasticity
BOTOX® is a treatment of focal spasticity that has only been studied in association with usual standard of care regimens. BOTOX® treatment is not likely to be effective in improving range of motion at a joint affected by a known fixed contracture. Identification of the goals for which BOTOX® treatment is being instituted must be undertaken prior to injection. Clinical examination to identify the specific muscles causing spasticity is necessary, and use of electromyography, muscle ultrasound or electrical stimulation may facilitate the accuracy of the BOTOX® injections

Cervical Dystonia (spasmodic torticollis)
Dysphagia and Breathing Difficulties
Treatment with BOTOX and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with preexisting swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or swallowing. When distant effects occur, additional respiratory muscles may be involved. Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin. Dysphagia may persist for several months, and require use of a feeding tube to maintain adequate nutrition and hydration. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised.

Treatment of cervical dystonia with botulinum toxins may weaken neck muscles that serve as accessory muscles of ventilation. This may result in a critical loss of breathing capacity in patients with respiratory disorders who may have become dependent upon these accessory muscles. There have been postmarketing reports of serious breathing difficulties, including respiratory failure, in cervical dystonia patients. Patients with smaller neck muscle mass and patients who require bilateral injections into the sternocleidomastoid muscle have been reported to be at greater risk for dysphagia. Limiting the dose injected into the sternocleidomastoid muscle may reduce the occurrence of dysphagia. Injections into the levator scapulae may be associated with an increased risk of upper respiratory infection and dysphagia.

Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin.

Primary Hyperhidrosis of the Axillae
Causes of secondary hyperhidrosis (e.g. hyperthyroidism, pheochromocytoma) should be considered to avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of the underlying disease.

Spasmodic Dysphonia
The diagnosis of spasmodic dysphonia should also be established by a multidisciplinary approach including neurological, ENT and speech pathology assessment. Laryngoscopy (preferably by a nasendoscope) is mandatory during the diagnostic evaluation to exclude other structural disorders of the larynx causing any form of dysphonia and to observe the nature of the hyperadductive or hyperabductive movements.

In general, treatment of spasmodic dysphonia with BOTOX® injections should not be administered in pregnant or breastfeeding women. It should be avoided in patients who are due to have elective surgery requiring general anaesthetic as BOTOX® relaxes the vocal cords, potentially increasing the risk of peri-operative aspiration etc. It is recommended that this procedure be carried out by appropriately trained physicians in facilities prepared to manage reflex stridor should it occur in association with the procedure.

Chronic migraine
Due to the difficulties in establishing a diagnosis of chronic migraine, patients being considered for prophylaxis of headaches with BOTOX® should be evaluated by a neurologist or pain management specialist prior to receiving treatment with BOTOX®. The use of BOTOX® for prophylaxis of headaches in adults with chronic migraine has been assessed for 3 cycles over 32 weeks. No long term safety or efficacy data for this indication are available. Patients who do not have an adequate response after 2 treatment cycles should not continue treatment. Patients should not receive more than 3 cycles of treatment prior to an assessment of the need for further treatment.

The safety and effectiveness of BOTOX® have not been established for the prophylaxis of headaches in adults with episodic migraine (14 headache days or fewer per month) or tension type headache.

Carcinogenicity
Long-term studies in animals have not been performed to evaluate the carcinogenic potential of BOTOX® injection. BOTOX® is not structurally related to any known carcinogens.

Genotoxicity
BOTOX® was inactive in *in vitro* tests for gene mutation and in *in vitro* and *in vivo* tests for clastogenicity.

Effects on Fertility
Intramuscular BOTOX® doses of 4 U/kg (males) and 8 U/kg (females) did not affect rat fertility. Decreased fertility occurred with higher doses, which also resulted in signs of toxicity. The relevance of these findings to human fertility is not known.

Use in Pregnancy: Pregnancy Category B3.
Category B3 drugs are those that have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

There are no adequate data regarding the use of botulinum toxin type A in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. BOTOX® should not be used during pregnancy unless the benefits clearly outweigh the potential risks. If the use of BOTOX® is determined to be warranted during pregnancy, or if the patient becomes pregnant whilst taking BOTOX®, the patient should be apprised of the potential risks.

There was no evidence of teratogenicity in animal studies. Intramuscular administration of BOTOX® to mice and rats during the period of organogenesis reduced dam weight gain and fetal ossification (4 U/kg); higher doses (8 or 16 U/kg) were associated with reductions in foetal body weights and/or delayed ossification. Intramuscular administration to rabbits twice during the period of organogenesis resulted in abortions (2 U/kg) and maternal deaths (4 and 6 U/kg), while daily intramuscular administration during organogenesis resulted in reduced fetal weights (0.25 and 0.5 U/kg) and increased resorptions (0.5 U/kg); the no-effect dose was 0.125 U/kg, although all doses were maternotoxic. Intramuscular treatment of rats with a maternotoxic dose of BOTOX® (16 U/kg) twice during gestation and once during lactation resulted in increased post-implantation loss and reduced pup weights, but post-weaning pup development was unaffected. The significance of the adverse findings in animals for clinical risk is uncertain.

Use in Lactation
There is no information on whether BOTOX® is excreted in human milk. The use of BOTOX® during lactation is not recommended.

Paediatric Use
Safety and effectiveness in paediatric patients below the age of 18 years have not been established for the indication of chronic migraine.

Safety and effectiveness in children below the age of 12 years have not been established for the indications of blepharospasm, hemifacial spasm, cervical dystonia, hyperhidrosis, spasmodic dysphonia or upper facial lines (forehead, crow's feet and glabellar lines). The safety and effectiveness of BOTOX® in the treatment of focal spasticity has not been investigated in children under two years of age.

There have been rare spontaneous reports of death in children after treatment with BOTOX®. Some of these patients had risk factors including significant

neuromuscular debility, dysphagia, aspiration pneumonia, seizures and cardiovascular disease. Caution should be exercised when treating patients who are significantly debilitated such as those children who are quadriplegic, require a gastrointestinal feeding tube or have a history of aspiration pneumonia or lung disease.

New onset or recurrent seizures have also been reported, typically in children who are predisposed to experiencing these events. The exact relationship of these events to the BOTOX® injection has not been established.

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

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

If BOTOX® is used during pregnancy, or if the patient becomes pregnant while being treated with BOTOX®, the patient should be apprised of the potential risks, including abortion or foetal malformations seen in animals.

Patients should be advised of the potential for experiencing malaise lasting up to six weeks after injection with BOTOX®.

Patients with cervical dystonia (spasmodic torticollis) 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 and/or dyspnoea. In rare cases, tube feeding, aspiration pneumonia and death have been reported. Dysphagia may persist for two to three weeks after injection, but has been reported to last up to five months post-injection. Patients or caregivers should be advised to seek immediate medical consultation if swallowing, speech or respiratory disorders arise.

Effects on Laboratory Tests
There were no significant differences in routine laboratory variables between the placebo and BOTOX® groups in patients receiving doses up to 360 U, for the treatment of cervical dystonia.

ADVERSE EFFECTS

General

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

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

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

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

New onset or recurrent seizures have also been reported, typically in patients who are predisposed to experiencing these events. The exact relationship of these events to the botulinum toxin injection has not been established.

Chronic Migraine
Safety data were compiled from two Chronic Migraine double-blind, placebo-controlled studies involving 687 patients treated with BOTOX®. The following adverse reactions were reported.

Adverse Reactions Reported by ≥1% of BOTOX treated Patients and More Frequent than in Placebo-treated Patients in **Two Chronic Migraine Double-blind, Placebo-controlled Clinical Trials**

Adverse Reactions	BOTOX® N=687	Placebo N=692
Nervous system disorders		
Headache	32 (4.7%)	22 (3.2%)
Migraine	26 (3.8%)	18 (2.6%)
Facial paresis	15 (2.2%)	0 (0.0%)
Eye disorders		
Eyelid ptosis	25 (3.6%)	2 (0.3%)
Musculoskeletal and connective tissue disorders		
Neck pain	60 (8.7%)	19 (2.7%)
Musculoskeletal stiffness	25 (3.6%)	6 (0.9%)
Muscular weakness	24 (3.5%)	2 (0.3%)
Myalgia	21 (3.1%)	6 (0.9%)
Musculoskeletal pain	18 (2.6%)	10 (1.4%)
Muscle spasms	13 (1.9%)	6 (0.9%)
Muscle tightness	9 (1.3%)	3 (0.4%)
General disorders and administration site conditions		
Injection site pain	23 (3.3%)	14 (2.0%)
Skin and subcutaneous tissue disorders		
Pruritus	7 (1.0%)	2 (0.3%)
Rash	7 (1.0%)	6 (0.9%)

Migraine, including worsening migraine, was reported in 3.8% of BOTOX® and 2.6% of placebo (saline) patients, typically occurring within the first month after treatment. These reactions did not consistently reoccur with subsequent treatment cycles, and the overall incidence decreased with repeated treatments.

Other adverse reactions reported more frequently in the BOTOX® group compared to the placebo group at a frequency less than 1% include: dysphagia, pain in jaw, and pain of skin.

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

Blepharospasm

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

Ptosis	11.0%
Irritation/tearing (includes dry eye, lagophthalmos and photophobia)	10.0%
Ectropion, keratitis, diplopia and entropion were reported rarely	<1.0%

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

Diffuse skin rash and local swelling of the eyelid skin lasting for several days following eyelid injection were reported infrequently in clinical studies.

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

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

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

Strabismus
In a clinical investigation of botulinum toxin use in strabismus over a 9-year period, the incidence rates (% injections) of adverse events from 8,300 injections are reported (1). The total number of patients who received the injections is not reported.

Effects on adjacent muscles: the incidence of partial ptosis and vertical deviation were 16% and 17% respectively. Complete ptosis was rare. In one series, slight residual ptosis (0.16%) and induced vertical deviation of greater than two prism dioptres (2%) persisted for 6 months or longer.

Retrobulbar haemorrhage (0.2%) occurred without visual loss. Decompression of the orbit after five minutes was performed to restore retinal circulation in one case.

Scleral perforation (0.11%): these tended to occur in myopic eyes and at a prior surgical site. A vitreous haemorrhage occurred in one patient which reduced vision for several months before clearing. In another patient, a reduction in vision from 20/25 to 20/30 was reported.

Pupillary dilation (0.06%): at least two of these were consistent with ciliary ganglion damage (Adie's pupil).

Past pointing and spatial disorientation may result from inducing paralysis in one or more extraocular muscles. Covering the affected eye may alleviate these symptoms.

Diplopia is common after treatment in patients with good vision in both eyes. Diplopia in adults can be managed by patching. In one case, diplopia appeared to be permanent due to loss of suppression.

No systemic paralytic effect has been seen or suspected in any patient treated with the small doses used for strabismus.

Variation in incidence rates of the most frequently observed effects, ptosis and vertical deviation per patient, have also been reported in other retrospective observational studies. There is no obvious explanation for the substantial variation.

In the literature, 3 different studies (2-4) evaluating BOTOX® for the treatment of strabismus (n=266) indicated percent incidence of ptosis occurred in a range of 30% to 37% of injections or 37% of patients. Vertical deviation was reported in 42% of injections or from 10% to 34% of patients.

Other studies have shown side effects such as sub-conjunctival and conjunctival haemorrhages to be fairly common. There have also been infrequent reports of headache, cycloplegia, ocular vertigo and corneal irritation. In one study, 5/45 (11.1%) patients were shown to exhibit an increase in intra-ocular pressure which was reversible.

VIIth Nerve Disorders (hemifacial spasm)
Adverse effects reported after injection of BOTOX® have included blurring of vision, facial droop, dizziness and tiredness, in addition to those listed above.

Focal spasticity in children two years and older
The safety of BOTOX® used for the treatment of focal spasticity was evaluated, from clinical studies for the treatment of dynamic equinus foot deformity, upper limb spasticity and lower limb spasticity. As is expected for any intramuscular injection procedure, localised pain, discomfort, bruising and oedema was associated with the injection in these patients. All treatment-related adverse events were mild to moderate in severity and were self-limiting.

In children treated for upper limb spasticity, the most frequently reported treatment related adverse events included local and general weakness, trigger finger, clumsiness, hypokinesia, falling and increased frequency of micturition, joint dislocation and muscle spasms. The percent of patients who experienced these events at least once during the study are summarised below:

	BOTOX® (n=74)
Muscular weakness, local	5.4%
Muscular weakness, general	2.7%
Trigger finger	2.7%
Clumsiness	1.4%
Falling	1.4%
Hypokinesia	1.4%
Increased frequency of micturition	1.4%
Joint dislocation	1.4%
Muscle spasms	1.4%

Other adverse events reported commonly or very commonly in these studies were convulsions, nasopharyngitis, pneumonia, vomiting and contusion.

In children treated for dynamic equinus foot deformity due to spasticity in juvenile cerebral palsy, the adverse events most frequently reported treatment-related included falling, leg pain, leg (local) weakness and general weakness. The percent of patients who experienced these events at least once during the study are summarised below:

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

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

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

In children treated for spasticity of the hip adductor muscles, there were no adverse events reported in the studies evaluated.

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

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

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

The safety of BOTOX® was evaluated in 82 patients who received a single treatment for lower limb spasticity associated with stroke in either a double-blind or an open-label study. The following treatment related adverse events were reported: accidental injury (1.2%), incoordination (1.2%) and paresthesia (1.2%). Adverse events reported were mild to moderate in severity.

Of the 56 patients who received BOTOX® in the double-blind phase of the study, 44 went on to receive a second injection in the open-label study. Additional treatment related adverse reactions reported were: hypertonia (4.5%), asthenia (2.3%), headache (2.3%) and hyperkinesia (2.3%).

Cervical Dystonia (spasmodic torticollis)
The following adverse events were reported following BOTOX® treatment for cervical dystonia. Patients received an average dose of 155 U (range 100 – 300 U).

ADVERSE EVENT	BOTOX® (n = 131)
Body as a whole:	
- neck pain	5.3%
- asthenia	3.1%
- headache	1.5%
- pain at injection site	1.5%
Digestive system	
- dysphagia	12.2%
Muscular system	
- muscle weakness	0.8%

Dysphagia was the most commonly reported adverse event after treatment with BOTOX®. Dysphagia and symptomatic general weakness may be attributable to an extension of the pharmacology of BOTOX® resulting from the spread of the toxin outside the injected muscles. Dysphagia is usually reported as mild to moderate severity in most patients. However, in an occasional patient it may be associated with more severe problems. Limiting the dose injected into the sternocleidomastoid muscle to less than 100 U may decrease the occurrence of dysphagia. (See Precautions).

Neck pain due to BOTOX® injection may be due to a change in resting tone for the contralateral muscles, or other muscles not previously affected by dystonia. In rare instances, neck pain has been severe. Dysphonia has also been reported in the literature for patients who have been treated for cervical dystonia. Rhinitis has also been reported.

Primary Hyperhidrosis of the Axillae

The safety of BOTOX® was evaluated in 287 patients who received at least 1 treatment exposure of primary hyperhidrosis of the axillae in double-blind and open-label studies. Adverse events reported as treatment related in greater than 1% of BOTOX®-treated patients are listed in decreasing order of incidence: perceived increase in non-axillary sweating (4.5%), injection site pain (1.7%), pain (1.4%) and vasodilation (hot flushes) (1.0%). Two of 207 subjects (1.0%) who received repeated injections of BOTOX® developed transient arm weakness. Body odour has also been reported.

Spasmodic Dysphonia

In the largest series reported of BOTOX® treatment for this disorder common adverse events after treatment with BOTOX® were breathy dysphonia (47.6% of all treatment sessions), dysphagia (14.9%) and aspiration (5.9%) for adductor spasmodic dysphonia and dysphagia (11.2%) and stridor (6.9%) for abductor dysphonia.

In another large trial of 169 patients with spasmodic dysphonia, the following adverse events were recorded in ≥1 of 1093 BOTOX® treatments. Paralytic dysphonia (breathy dysphonia) in 338/1093 (31%) treatments (mild 139, moderate 114, severe 73, very severe 12), technical failure in 90/1093 (8%) treatments, dysphagia in 38/1093 (3%) treatments (mild 17, moderate 15, severe 4, very severe 2), pain in 13/1093 (1%) treatments (mild 5, moderate 6, severe 2), gagging in 6/1093 (0.5%) treatments (mild 3, moderate 3), diplophonia in 3/1093 treatments, flu-like symptoms in 2/1093 treatments of moderate severity, and persistent cough in 2/1093 treatments.

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

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

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

Other studies have reported the incidence of injection site bruising to be between 4-25% of BOTOX®-treated patients, with similar rates noted for placebo (5-6). Other adverse events related to BOTOX® treatment included temporary droop of the lateral portion of the lower eyelid (5%), which is consistent with the pharmacologic action of BOTOX® and may be injection technique-related (6).

Forehead Lines
In a clinical study where BOTOX® was administered to 59 patients with horizontal forehead lines (8 U to 24 U into frontalis), the following treatment related adverse events were reported: headache (22.0%), bruising (10.2%), eyebrow ptosis (10.2%), eyelid swelling (20.3%), aching/itching forehead (5.1%), nausea (3.4%), feeling of tension (1.7%), flu-like symptoms/cold (1.7%) and other (6.8%). All adverse events were mild or moderate in severity and no serious adverse events were reported (7).

Passive Adverse Event Surveillance
The following other adverse events have been reported since the drug has been marketed: abdominal pain; blurred vision; brachial plexopathy; decreased hearing; diarrhea; ear noise; erythema multiforme; fever; focal facial paralysis; localized

numbness; loss of appetite; malaise; myalgia; myasthenia gravis; pruritus; psoriasiform eruption; radiculopathy; sweating; syncope; vomiting and alopecia including madarosis.

DOSAGE AND ADMINISTRATION

Route of Administration

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

General

Medical practitioners administering treatment should be appropriately trained in injecting BOTOX®.

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

In general, dosing of BOTOX® should be individualised for each patient and always start with the minimal effective dose. The dosing interval should typically not be more frequent than every three months.

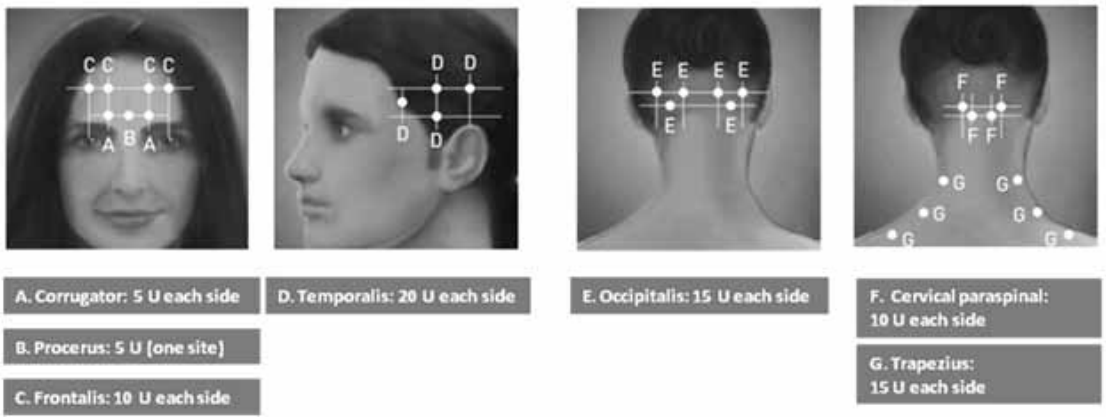
Chronic Migraine

The recommended dose for treating chronic migraine is 155 U to 195 U administered intramuscularly (IM) using a 30-gauge, 0.5 inch needle as 0.1 ml (5 U) injections per each site. Injections should be divided across 7 specific head/neck muscle areas as specified in the table below. A 1-inch needle may be needed in the neck region for patients with extremely thick neck muscles. With the exception of the procerus muscle, which should be injected at 1 site (midline), all muscles should be injected bilaterally with the minimum dose per muscle as indicated below, with half the number of injections sites administered to the left, and half to the right side of the head and neck. If there is a predominant pain location(s), additional injections to one or both sides may be administered in up to 3 specific muscle groups (occipitalis, temporalis and trapezius), up to the maximum dose per muscle as indicated in the table below.

The recommended re-treatment schedule is every 12 weeks.

Due to the difficulties in establishing a diagnosis of chronic migraine, patients being considered for prophylaxis of headaches with BOTOX® should be evaluated by a neurologist or pain management specialist prior to receiving treatment with BOTOX®. The use of BOTOX® for prophylaxis of headaches in adults with chronic migraine has been assessed for 3 cycles over 32 weeks. No long term safety or efficacy data for this indication are available. Patients who do not have an adequate response after 2 treatment cycles should not continue treatment. Patients should not receive more than 3 cycles of treatment prior to an assessment of the need for further treatment.

Recommended injection sites for chronic migraine:



BOTOX® Dosing By Muscle for Chronic Migraine

	Recommended Dose
Head/Neck Area	**Total Number of Units (U) (number of IM injection sites[a])**
Frontalis[b]	20 U (4 sites)
Corrugator[b]	10 U (2 sites)
Procerus	5 U (1 site)
Occipitalis[b]	30 U (6 sites) up to 40 U (up to 8 sites)
Temporalis[b]	40 U (8 sites) up to 50 U (up to 10 sites)
Trapezius[b]	30 U (6 sites) up to 50 U (up to 10 sites)
Cervical Paraspinal Muscle Group[b]	20 U (4 sites)
Total Dose Range:	**155 U to 195 U**

[a] 1 IM injection site = 0.1 mL = 5 U BOTOX®
[b] Dose distributed bilaterally for minimum dose

Blepharospasm
An injection of BOTOX® (botulinum toxin type A) purified neurotoxin complex is prepared by drawing into a sterile 1.0 mL tuberculin syringe an amount of the properly diluted toxin (see Dilution Table) slightly greater than the intended dose. Air bubbles in the syringe barrel are expelled and the syringe is attached to the injection needle, preferably a 1½", 27-30 gauge needle. Injection volume in excess of the intended dose is expelled through the needle into an appropriate waste container to assure patency of the needle and to confirm that there is no syringe-needle leakage. A new, sterile needle and syringe should be used to enter the vial on each occasion for dilution or removal of BOTOX®.

For blepharospasm, diluted BOTOX® injection (see Dilution Table) is injected using a sterile, 27-30 gauge needle with or without electromyographic guidance. 1.25 U to 2.5 U (0.05 mL to 0.1 mL volume at each site) injected into the medial and lateral pre-tarsal orbicularis oculi of the upper lid and into the lateral pre-tarsal orbicularis oculi of the lower lid is the initial recommended dose. Pre-tarsal injections are often

appropriate and may vary based on the patient's presentation. In the upper lid, maximising the distance of the injection from the levator palpebrae superioris may reduce the complication of ptosis. Avoiding medial lower lid injections, and thereby reducing diffusion into the inferior oblique, may reduce the complication of diplopia.

In general, the initial effect of the injections is seen within three days and reaches a peak at one to two weeks post-treatment. Each treatment lasts approximately three months, following which the procedure can be repeated indefinitely. At repeat treatment sessions, the dose may be increased up to two-fold if the response from the initial treatment is considered insufficient – usually defined as an effect that does not last longer than two months. However there appears to be little benefit obtainable from injecting more than 5.0 U per site. Some tolerance may be found when BOTOX® is used in treating blepharospasm if treatments are given any more frequently than every three months. The effect is rarely permanent.

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

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

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

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

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

I. Initial doses in units. Use the lower listed doses for treatment of small deviations. Use the larger doses only for large deviations.
   A. For vertical muscles, and for horizontal strabismus of less than 20 prism dioptres: 1.25 – 2.5 U in any one muscle.
   B. For horizontal strabismus of 20 prism dioptres to 50 prism dioptres: 2.5 – 5.0 U in any one muscle.
   C. For persistent sixth nerve palsy of one month or longer duration: 1.25 – 2.5 U in the medial rectus muscle.

II. Subsequent doses for residual or recurrent strabismus.

A. It is recommended that patients be re-examined 7-14 days after each injection to assess the effect of that dose.
B. Patients experiencing adequate paralysis of the target muscle that require subsequent injections should receive a dose comparable to the initial dose.
C. Subsequent doses for patients experiencing incomplete paralysis of the target muscle may be increased up to two-fold compared to the previously administered dose.
D. Subsequent injections should not be administered until the effects of the previous dose have dissipated as evidenced by substantial function in the injected and adjacent muscles.
E. The maximum recommended dose as a single injection for any one muscle is 25 U.

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

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

Treatment of focal spasticity of the upper limb and lower limbs, including dynamic equinus foot deformity, due to juvenile cerebral palsy in patients two years and older
The exact dosage and number of injection sites should be tailored to the child's needs based on the size, number and location of muscles involved, the severity of spasticity, presence of local muscle weakness, and the patient response to previous treatment. In clinical trials the dose per muscle ranged from 0.5-2.0 U/kg body weight in the upper limb and 2.0 -4.0 U/kg/body weight in the lower limb per treatment session. For the treatment of equinus foot deformity the total dose is up to 4 U/kg or 200 U (whichever is the lesser amount) divided into two sites in each medial and lateral head of the gastrocnemius muscle. In other muscles the dose per muscle ranged from 3.0-8.0 U/kg body weight and did not exceed 300U divided among selected muscles at any treatment session. Following initial injection to the gastrocnemius muscle, further involvement of the anterior or posterior tibialis may need to be considered for additional improvement in the foot position at heel strike and during standing.

A 27 or 30 gauge needle should be used with an appropriate needle length to reach the targeted muscles. For focal spasticity, localisation techniques include electromyography, muscle ultrasound or electrical stimulation.

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 typically not more frequently than every three months. The degree of muscle spasticity at the time of reinjection may necessitate alterations in the dose of BOTOX® and muscles to be injected.

The table below is intended to give dosing guidelines for injection of BOTOX® in the treatment of focal spasticity in children aged 2 years and older. The maximum total

dose is 8.0 units/kg body weight and 300 units divided among selected muscles at any treatment session:

Muscles in upper limb	**Dosage in U/kg/muscle**
Biceps brachii	0.5 - 2.0 U
Brachialis	0.5 - 2.0 U
Brachioradialis	0.5 - 2.0 U
Flexor carpi ulnaris	0.5 - 2.0 U
Flexor carpi radialis	0.5 - 2.0 U
Pronator teres	0.5 - 2.0 U
Pronator quadratus	0.5 - 2.0 U
Flexor digitorum profundus	0.5 - 2.0 U
Flexor digitorum sublimis	0.5 - 2.0 U
Flexor pollicis longus	0.5- 2.0 U
Flexor pollicis brevis	0.5 - 2.0 U
Opponens pollicis	0.5 - 2.0 U
Adductor pollicis	0.5 - 2.0 U

Muscles in lower limb	**Dosage in U/kg/muscle**
Hip adductor group (adductor longus, adductor brevis, adductor magnus, medial hamstrings)	4.0 U
Gastrocnemius	2.0-4.0 U

Focal Spasticity in Adults

The exact dosage and number of injection sites should be tailored to the individual based on the size, number and location of muscles involved, the severity of spasticity, presence of local muscle weakness, and the patient response to previous treatment. In clinical trials, the doses did not exceed 360 U divided among selected muscles (typically in the flexor muscles of the elbow, wrist and fingers) at any treatment session. Clinical improvement in muscle tone generally occurs within two weeks following treatment with the peak effect seen four to six weeks following treatment. In clinical studies, patients were reinjected at 12- to 16-week intervals. The degree of muscle spasticity at the time of reinjection may necessitate alterations in the dose of BOTOX® and muscles to be injected.

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

Muscle	**Total Dosage; Number of Sites**
Biceps brachii	100 – 200 U; up to 4 sites
Flexor digitorum profundus	15 - 50 U; 1-2 sites
Flexor digitorum sublimis	15 - 50 U; 1-2 sites
Flexor carpi radialis	15 - 60 U; 1-2 sites
Flexor carpi ulnaris	10 - 50 U; 1-2 sites
Adductor pollicis	20 U; 1-2 sites
Flexor pollicis longus	20 U; 1-2 sites
Posterior tibialis	70 – 100 U; 1-2 sites
Soleus	80 – 125 U; 1-2 sites
Flexor digitorum longus/brevis	50 – 100 U; 2-4 sites
Gastrocnemius medial/lateral	50 – 200 U; 2-4 sites

A 27 or 30 gauge needle should be used with an appropriate needle length to reach the targeted muscles. For focal spasticity, localisation techniques include electromyography, muscle ultrasound or electrical stimulation.

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

Cervical Dystonia (spasmodic torticollis)

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

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

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

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

Dosage Guide

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

This information is provided as guidance for the initial injection. The extent of muscle hypertrophy and the muscle groups involved in the dystonic posture may change with time necessitating alterations in the dose of toxin and muscles to be injected. The exact dosage and sites injected must be individualised for each patient. Clinical improvement generally occurs within the first two weeks after injection. The maximum clinical benefit generally occurs approximately six weeks post-injection. The duration of therapeutic effect reported in the clinical trials showed substantial variation (from 2 to 32 weeks), with a typical duration of approximately 12 to 16 weeks, depending on the patient's individual disease and response.

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

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

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

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

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

In general, a total dose of 360 U every two months should not be exceeded for the treatment of cervical dystonia. The time-to-retreatment will vary between patients, however data from controlled clinical studies indicates that symptoms may start to re-emerge at approximately 8-10 weeks post-injection (see Pharmacology – Clinical Trials).

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

Primary Hyperhidrosis of the Axillae

For the treatment of hyperhidrosis, 100 U of BOTOX® should be reconstituted with 4.0 mLs of sterile 0.9% sodium chloride for injection. For each axilla, 50 U of BOTOX® (2.0 mL) should be injected intradermally and evenly distributed in 10-15 sites approximately 1-2 cm apart within the hyperhidrotic area. For the treatment of hyperhidrosis, a 30 gauge needle should be used. The hyperhidrotic area may be defined using standard staining techniques (e.g Minor's iodine starch test). Repeat injections for axillary hyperhidrosis should be administered when the effects from the previous injection subside. However, repeat injections at intervals of less than four months are not recommended.

Spasmodic Dysphonia

Patients with spasmodic dysphonia should be treated by physicians skilled in the anatomy and physiology of the larynx, and have facility with nasal endoscopy and also electromyographically guided injections. The procedure should be carried out in a facility equipped to manage potential acute complications such as reflex stridor. The treatment program should be individualised for each patient at each treatment session. Peak effect is generally seen within 7 days following an injection

BOTOX® (100 U/vial) should be reconstituted with 4.0 to 5.0 mL of 0.9% sterile non-preserved saline, giving a final concentration of 2.0–2.5 units per 0.1 mL. It is usual to commence with a standard dose of 1.0–2.5 units in 0.1 mL of BOTOX® to each thyroarytenoid muscle in adductor spasmodic dysphonia and subsequently vary the dose by altering the concentration according to patient requirements and response to therapy. An occasional patient will require 3 units per vocal cord and many patients over the years have reduced their dose, down to even 0.2 units per vocal cord. Bilateral injections are generally recommended but an occasional patient will benefit from unilateral injections, sometimes alternating between sides with each subsequent treatment.

In abductor spasmodic dysphonia 2-5 units of BOTOX® are usually injected unilaterally into one posterior cricoarytenoid muscle via a lateral retrocricoid, supracricoid or transcricoid approach.

The injection is usually performed in the supine position with a small pillow under the shoulders to improve laryngeal exposure. For adductor spasmodic dysphonia, the laryngeal surface landmarks are identified, including the thyroid and cricoid cartilage, and in particular the small gap between the cricothyroid space and membrane. Identification of the landmarks is a critical part of this procedure and sometimes this can be difficult in individuals with thick necks.

In adductor spasmodic dysphonia the EMG recording needle is advanced in the midline through the cricothyroid membrane, directing the needle rostral, and approximately 30^{o} lateral towards a thyroarytenoid muscle. For a bilateral procedure, the needle is redirected towards the opposing muscle. Once within the muscle, EMG insertional activity is audible and placement can be confirmed by phonating /e/. Having confirmed needle placement, the desired amount of BOTOX® in 0.1 mL is injected.

In all cases of abductor spasmodic dysphonia, endoscopy should be performed prior to each treatment to assess the dynamic activity of each vocal cord and the size of the glottal airway. Typically, the posterior cricoarytenoid (PCA) muscle on the more active side is chosen for therapy. A retrocricoid approach should be used whereby the injection needle, containing 2-5 units of BOTOX® in 0.1 mL, is directed towards the PCA muscle in a curving fashion at the level of the cricoid cartilage to lie behind the larynx. The larynx may be rotated laterally on the appropriate side to improve access. To confirm needle placement, the patient sniffs sharply to activate the posterior cricoarytenoid muscle resulting in a characteristic EMG interference pattern. BOTOX® is then injected. Only unilateral injections are recommended at each treatment session. The determination of which PCA muscle to treat at any injection session is determined by endoscopic review. Treatment sessions are performed only when the non-injected cord has sufficient motion to protect from stridor in the event that the injected cord would become immobile. An occasional patient with abductor spasmodic dysphonia will have increased activity of the cricothyroid muscle, which can also be evaluated by EMG, and may also benefit from supplemental injections into this muscle.

To date there has only been one report of a patient developing resistance to the injections, with the development of neutralising antibodies, probably because the doses used are very small compared to other indications.

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

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

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

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

Improvement of severity of glabellar lines generally occurs within one week after treatment. The effect was demonstrated for up to 4 months.

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

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

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

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

Dilution Technique
To reconstitute vacuum-dried BOTOX® injection, use sterile normal saline without a preservative; 0.9% Sodium Chloride Injection is the recommended diluent. Draw up the proper amount of diluent in the appropriate size syringe. Since BOTOX® is denatured by bubbling or similar violent agitation, inject the diluent into the vial gently. Discard the vial if a vacuum does not pull the diluent into the vial. Record the date and time of reconstitution on the space on the label. BOTOX® should be administered within 24 hours after reconstitution.

During this time period, reconstituted BOTOX® should be stored in a refrigerator (2° to 8°C). Reconstituted BOTOX® should be clear, colourless and free of particulate matter. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration and whenever the solution and the container permit.

Dilution Table for 100 U and 200 U vials:

Diluent Added (0.9% Sodium Chloride Injection)	100 U Vial	200 U Vial
	Resulting dose (U/0.1 mL)	Resulting dose (U/0.1 mL)
0.5 mL	20	40
1 mL	10	20
2 mL	5	10
4 mL	2.5	5
5 mL	2	4
8 mL	1.25	2.5
10 mL	1	2

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

Lack of Response

There are several potential explanations for a diminished or absent response to an individual treatment with BOTOX®. These may include:

- inadequate dose selection,
- selection of inappropriate muscles for injection,
- muscles inaccessible to injection,
- underlying structural abnormalities, such as muscle contractures or bone disorders,
- change in pattern of muscle involvement,
- patient perception of benefit compared with initial results,
- inappropriate storage or reconstitution,
- neutralising antibodies to botulinum toxin

A neutralising antibody is defined as an antibody that inactivates the biological activity of the toxin. In general, the proportion of patients who lose their response to botulinum toxin therapy and have demonstrable levels of neutralising antibodies is less than 5%, though in a long-term juvenile cerebral palsy study, of 117 patients treated with BOTOX®, antibodies were detected in 33/117 (28%) at either 27 or 39 months. Thirty-one of these 33 had been responders, 19/31 (6%) continued to respond, with 7/31 (2%) becoming non-responders, and no data available for 5/31.

The critical factors for neutralising antibody production are the frequency and dose of injection. Tolerance may be observed in some patients treated more frequently than every three months. The potential for neutralising antibody formation may be minimised by injecting with the lowest effective dose given at the longest feasible intervals between injections (injection intervals should typically be no more frequent than three months). The dose should not exceed 360 U in any two month period for adult spasticity patients and patients with cervical dystonia. The total dose of BOTOX® in any three month period should not exceed 8 U/kg or 300 U (whichever is the lesser amount) when used in children for the treatment of equinus foot deformity. When patients do not respond to BOTOX® injections a suggested course of action is:

(1) wait the usual treatment interval; (2) consider reasons for lack of response listed above; (3) test the patient's serum for neutralising antibody presence. More than one ineffective treatment course should occur before classification of a patient as a non-responder, because there are patients who continue to respond to therapy despite the presence of neutralising antibodies.

OVERDOSAGE

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

The entire contents of a vial is below the estimated dose (from primate studies) for toxicity in humans weighing 6 kg or greater

Should symptoms (muscular weakness, ptosis, diplopia, blurred vision, facial weakness, swallowing and speech disorders, constipation, aspiration pneumonia, difficulty breathing or respiratory depression) occur post injection or oral ingestion, the person should be medically monitored for up to several weeks. These patients should be considered for further medical evaluation and appropriate medical therapy immediately instituted, which may include hospitalisation. Advise patients or caregivers to seek immediate medical attention if any of these symptoms occur. Specific anti-toxin to botulinum toxin is only likely to be effective if given within thirty minutes of the botulinum injection.

In the event of overdosage or the injection into the wrong muscle, additional information may be obtained by contacting the poisons information centre in your State or Territory.

PRESENTATION AND STORAGE CONDITIONS

BOTOX® (botulinum toxin type A) purified neurotoxin complex is a sterile, vacuum-dried preparation. It is supplied in a clear glass vial with a rubber stopper and tamper-proof aluminium seal, containing a white powder for reconstitution. BOTOX® is available in 100 U and 200 U of vacuum-dried *Clostridium botulinum* toxin type A. Refer to description for list of excipients.

Storage

Store the vacuum-dried product in the refrigerator between 2-8°C.

Administer BOTOX® (botulinum toxin type A) purified neurotoxin complex within 24 hours after the vial is removed from the refrigerator and reconstituted. During these twenty four hours, reconstituted BOTOX® should be stored in a refrigerator (2-8 °C). Reconstituted BOTOX® should be clear, colourless and free of particulate matter.

The reconstituted product does not contain a preservative. It should be used for one patient only and any residue discarded.

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

NAME AND ADDRESS OF THE SPONSOR

Allergan Australia Pty Ltd
810 Pacific Highway
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A.B.N. 85 000 612 831

BOTOX® 100 U - AUST R 67311
BOTOX® 200 U* - AUST R 172264

*- not marketed

POISON SCHEDULE OF THE MEDICINE

S4: Prescription Only Medicine

DATE OF APPROVAL

Approved by the Therapeutic Goods Administration on 15 March 2011

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Reference/Publication #