Ref: 0059424/UK

Mr Hagen

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25th January 2013

Dear Mr Hagen

Re: BOTOX® (botulinum toxin type A)

Thank you for your enquiry regarding BOTOX® (botulinum toxin type A), which was forwarded to me by my colleague Ms Suzanne Grant.

I understand that you requested information regarding the safety and efficacy of BOTOX® in the prophylaxis of headache in chronic migraine.

In the UK BOTOX® is licensed for:

• the symptomatic relief of blepharospasm, hemifacial spasm and idiopathic cervical dystonia (spasmodic torticollis)
• the management of severe hyperhidrosis of the axillae, which does not respond to topical treatment with antiperspirants or antihidrotics
• 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)
•the management of urinary incontinence in adult patients with neurogenic detrusor overactivity due to subcervical spinal cord injury (traumatic or non-traumatic) or multiple sclerosis, who are not adequately managed with anticholinergics; patients should be already catheterising or willing and able to catheterise if required.

BOTOX® is also indicated for focal spasticity, including the treatment of:
• dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients, two years of age or older and
• wrist and hand disability due to upper limb spasticity associated with stroke in adults.

BOTOX® is also indicated for the temporary improvement in the appearance of moderate to severe vertical lines between the eyebrows seen at frown (glabellar lines), in adults <65 years old, when the severity of these lines has an important psychological impact for the patient.

Please consult the BOTOX® Summary of Product Characteristics for full prescribing information, available on www.medicines.org.uk

As stated in the Summary of Product Characteristics (SPC) for BOTOX®:

> **"Botulinum toxin units are not interchangeable from one product to another."**
>
> **"Doses recommended for BOTOX are not interchangeable with other preparations of botulinum toxin."**

Migraine headache is a complex primary headache disorder classified into the subtypes of episodic migraine (EM) (< 15 headache days/month) and chronic migraine (CM) (≥ 15 headache days/month).[1] The diagnostic criteria for migraine were first established by the International Classification of Headache Disorders (ICHD-1)[2,] which were subsequently amended in the ICHD-2 to account for the small group of patients with daily or near-daily chronic headache. In general, headache is considered a complicated disease area for clinical study and presents numerous protocol design challenges including concomitant medication usage, medication overuse, evolving headache definitions, appropriate study endpoint selections, placebo responses, and in the case of BOTOX® treatment, selection of an appropriate injection technique and patient population.[2,3]

The safety and efficacy of BOTOX® as prophylactic treatment in chronic migraine have been evaluated in the PREEMPT Clinical Trials Programme (**P**hase III **RE**search **E**valuating **M**igraine **P**rophylaxis **T**herapy). A summary of this data is provided below.

The PREEMPT programme comprised two phase III randomised, double-blind, placebo-controlled studies and included a total of 1384 patients.[4,5] Both studies included a 24 week double-blind phase with two injection cycles, followed by a 32 week open-label extension phase with three injection cycles. BOTOX® (155 U) or placebo was administered as 31 fixed-site, fixed-dose injections across seven specific head/neck muscle areas. At the investigator's discretion, an additional 40 U could be administered using a follow-the-pain strategy into the temporalis, occipitalis, and/or trapezius muscles. The maximum dose was 195 U. Patients used an interactive voice response system (IVRS) telephone diary to record their headache symptoms and acute treatments.

Randomised controlled phase

Change from baseline in frequency of headache days and headache episodes at week 24 were key efficacy measures evaluated in both trials. Six other pre-specified secondary efficacy variables based on the change from baseline in the 28 days ending with week 24 were evaluated in one or both trials: 1) migraine days, 2) migraine episodes, 3) moderate/severe headache days, 4) cumulative headache hours on headache days, 5) acute medication use, and 6) the proportion of patients with severe (≥ 60) Headache Impact Test (HIT-6) (Table I).

Table I. Phase III Clinical Trials: Study Design

Study	Study Population	N	Dose (U)	Study Duration (Weeks)	Outcome Measures
(Aurora et al., 2010)	• CM[a] • Age: 18-65	679	155-195[b]	56	*Primary:* • Change from baseline in frequency of headache episodes *Secondary;* • Change from baseline in frequency of • headache days • migraine days • migraine episodes • acute headache pain medication intakes • moderate/severe headache days • Change from baseline in cumulative total headache hours on headache days • % Patients with severe (≥60) HIT-6 score
(Diener et al., 2010)	• CM[a] • Age: 18-65	705	155-195[b]	56	*Primary:* • Change from baseline in frequency of headache days *Secondary;* • Change from baseline in frequency of • migraine days • moderate/severe headache days • headache episodes • acute headache pain medication intakes • Change from baseline in cumulative total headache hours on headache days • % Patients with severe (≥60) HIT-6 score

[a] CM as defined by ICHD-II[2]
[b] The minimum dose was 155 U distributed across 31 fixed sites across seven specified head/neck muscles (corrugators, procerus, frontalis, temporalis, occipitalis, cervical paraspinal and trapezius). An additional 40 U could be administered at the investigator's discretion on one or both sides in up to three muscle groups (occipitalis, temporalis, and trapezius)
HIT: Headache Impact Test

In both studies, a significant decrease from baseline in the frequency of headache days at week 24 was reported (BOTOX®: -7.8 to -9.0, placebo: -6.4 to -6.7; $p \leq 0.006$). In the PREEMPT 2 study, a statistically significant decrease from baseline in headache episodes at week 24 was reported in the BOTOX® group compared to placebo (BOTOX®: -5.3, placebo: -

4.6, p = 0.003), while PREEMPT 1 did not report any significant differences compared to baseline for this endpoint (BOTOX®: -5.2, placebo: -4.3, p = 0.344).

Statistically significant improvements compared to placebo were reported at week 24 for change from baseline in frequency of migraine days (p ≤ 0.002), number of moderate/severe headache days (p ≤ 0.004), cumulative headache hours on headache days (p ≤ 0.003), and proportion of patients with severe HIT-6 score (p ≤ 0.003). In regards to change from baseline in acute medication use, both studies did not report a significant difference compared to placebo at week 24; however, a post-hoc subanalysis by acute medication type resulted in significant differences compared to placebo in the change from baseline in frequency of triptan use (p ≤ 0.023).

An additional post-hoc analysis was performed on pooled results (1384 patients (BOTOX®: 688; placebo: 696) from the two studies and reported on between-group differences in efficacy, safety and tolerability that may not have been evident in individual trials.[6] The primary endpoint for the pooled analysis was mean change from baseline in frequency of headache days after 24 weeks. Secondary endpoints included mean change from baseline to week 24 in frequency of migraine/probable migraine days, frequency of moderate/severe headache days, total cumulative hours of headache on headache days, frequency of headache episodes, frequency of migraine/probable migraine episodes, frequency of acute headache pain medication intakes and the proportion of patients with severe (≥60) HIT-6 scores a week 24.

Pooled analyses demonstrated a large mean decrease in frequency of headache days, favouring BOTOX® over placebo at week 24 (-8.4 vs.-6.6; p<0.001) and at all other time points. Significant differences favoring BOTOX® were also observed for all secondary efficacy variables at all time points (weeks 4 through 24 post treatment; p<0.01) with the exception of frequency of acute headache pain medication intakes which demonstrated an overall mean reduction without significant between-group differences at all time points (p=0.247). (Table II)

Table II. Pooled Efficacy of BOTOX® at Week 24

Endpoint, Mean Change From Baseline	BOTOX® (n=688)	Placebo (n=696)	*p* Value
Frequency of HA days	-8.4	-6.6	<0.001
Frequency of migraine days	-8.2	-6.2	<0.001
Frequency of moderate/severe HA days	-7.7	-5.8	<0.001
Total cumulative HA hours on HA days	-119.7	-80.5	<0.001
% Patients with severe (≥ 60) HIT-6 score	67.6	78.2	<0.001
Total HIT-6 score	-4.8	-2.4	<0.001
Frequency of HA episodes	-5.2	-4.9	0.009
Frequency of migraine episodes	-4.9	-4.5	0.004
Frequency of acute HA pain medication intake (all categories)	-10.1	-9.4	0.247
Frequency of triptan use	-3.2	-2.1	<0.001

HA = headache; HIT = Headache Impact Test.

In regards to safety, the nature and frequency of adverse events (AEs) were similar across both trials. In both studies, the treatment-related AEs reported at a rate ≥ 5% were neck pain (5.9%-7.5%) and muscular weakness (5.2%-5.9%) (Table IV). In one study, eyelid ptosis, myalgia and musculoskeletal stiffness were reported at a higher rate in the BOTOX®-treated group than in the placebo group (specific AE rates not reported). In both studies, most AEs were mild or moderate in severity and resolved without sequelae. Across studies, there were 33 (4.8%) serious AEs reported by the BOTOX®-treated group and 16 (2.3%) reported by the placebo group. Of these serious AEs, one was treatment-related (migraine requiring hospitalisation) and reported by a patient in the BOTOX® group. Discontinuation rates due to AEs in the double-blind phase of the trial were low in both studies (BOTOX®: 3.5%-4.1%, placebo: 0.9%-1.4%).

Open label extension[7]

Following completion of the 24 week double-blind phase all patients were eligible for the 32-week open label phase in which all patients received BOTOX® over three treatment cycles. Six hundred and seven patients continued in the BOTOX®:BOTOX® (B/B) group and 629 in the placebo:BOTOX® (P/B) group.

Pooled analyses of the 56 week data demonstrated statistically significant within-group improvements from baseline at week 56 for both groups (Table III). Changes from baseline continued to increase during the extension phase, demonstrating continued improvements after each treatment cycle. There were statistically significant between group differences at week 56 favouring early use of BOTOX® over late treatment for frequency of headache and migraine days, moderate to severe headache days and total cumulative headache hours on headache days.

Table III. Pooled Efficacy of BOTOX® at Week 56

Endpoint, Mean Change From Baseline	BOTOX®:BOTOX® (n=688)	Placebo: BOTOX® (n=696)	*p* Value
Frequency of HA days	-11.7	-10.8	0.019
Frequency of migraine days	-11.2	-10.3	0.018
Frequency of moderate/severe HA days	-10.7	-9.9	0.027
Total cumulative HA hours on HA days	-169.1	-145.7	0.018
% Patients with severe (≥ 60) HIT-6 score	50.6	51.9	0.632
Total HIT-6 score	-7.7	-7.0	0.069
Frequency of HA episodes	-7.4	-7.5	0.075
Frequency of migraine episodes	-6.8	-7.0	0.117
Frequency of acute HA pain medication intake (all categories)	-15.4	-15.7	0.760
Frequency of triptan use	-4.2	-3.8	0.080

The proportion of patients from the pooled PREEMPT cohorts that completed both phases of the 56-week studies were high (74.6% B/B group and 70.7% P/B group). Only 4.6% of patients discontinued due to an AE and the proportion who experienced a serious AE during the open label phase was 3.8%. Treatment related AEs were consistent with the known tolerability profile of BOTOX® and no new events were reported. Side effects decreased progressively over the 56-week study period. Table IV summarises the treatment-related AEs reported by ≥2% of patients

Table IV. Treatment-related adverse events reported by ≥2% of patients

Treatment-related adverse events	24 weeks double-blind phase		32 weeks extension phase
	BOTOX® (n=687)	Placebo (n=692)	TOTAL (n=1205)
Neck pain	46 (6.7%)	15 (2.2%)	55 (4.6%)
Muscular weakness	38 (5.5%)	2 (0.3%)	47 (3.9%)
Eyelid ptosis	23 (3.3%)	2 (0.3%)	30 (2.5%)
Musculoskeletal pain	15 (2.2%)	5 (0.7%)	13 (1.1%)
Injection-site pain	22 (3.2%)	14 (2.0%)	24 (2.0%)
Headache	20 (2.9%)	11 (1.6%)	17 (1.4%)
Myalgia	18 (2.6%)	2 (0.3%)	15 (1.2%)
Musculoskeletal stiffness	16 (2.3%)	5 (0.7%)	20 (1.7%)
Muscle tightness	9 (1.3%)	1 (0.1%)	26 (2.2%)

The authors concluded that the PREEMPT clinical programme demonstrated the efficacy, safety and tolerability of BOTOX® in the prophylaxis of chronic migraine.

I enclose a copy of the PREEMPT 24-week and 56-week pooled data for your reference. If you would like any of the other references please provide the citation and I will be happy to send these to you.

For full prescribing information please refer to BOTOX® - Summary of Product Characteristics – available on www.medicines.org.uk

Yours sincerely

Dee Parmar
Medical Information Consultant
Healthcare Compliance & Medical Information

All personal or sensitive data submitted to Allergan is processed exclusively for responding to your enquiry and for internal medical information quality and training purposes in accordance with Allergan's Data Protection policy

Enclosures*/References

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[2] Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. Cephalagia 2004; 24(Suppl 1): 9-160
[3] Aurora, S. Botulinum toxin type A for the treatment of migraine. Expert Opin Pharmacother 2006;7(8):1085-1095
[4] Aurora SK, Dodick WD, Turkel CC et al. OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. Cephalalgia 2010; 30(7): 793–803
[5] Diener H-C, Dodick DW, Aurora SK et al. OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. Cephalalgia 2010; 30(7): 804-814
[6] **Dodick DW, Turkel CC, DeGryse RE et al. OnabotulinumtoxinA for treatment of chronic migraine: Pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Headache 2010; 50(6): 921-936
[7] **Aurora SK, Winner P, Freeman MC et al. OnabotulinumtoxinA for treatment of chronic migraine: Pooled analyses of the 56-week PREEMPT Clinical Program. Headache 2011; 51(9): 1358-1573