ALLERGAN

Level 4, 810 Pacific Highway, Gordon NSW 2072, Locked Bag 1514, Pymble NSW 2073, Australia, Phone (612) 9498 0100, Fax (612) 9498 0290

18 July 2011

Committee Secretary
Senate Finance and Public Administration Committees
PO Box 6100
Parliament House
Canberra ACT 2600

Dear Committee Secretary,

Re: Submission to the Senate Committee Inquiry on the Government's administration of the Pharmaceutical Benefits Scheme (PBS)

Allergan Australia Pty Ltd would like to provide the attached submission to the Committee as a part of the inquiry on the Government's administration of the Pharmaceutical Benefits Scheme (PBS). The submission summarises the circumstances surrounding the deferral of the PBS listing of BOTOX® (botulinum toxin type A) for severe primary axillary (underarm) hyperhidrosis following a positive recommendation by the Pharmaceutical Benefits Advisory Committee (PBAC) in March 2010.

A key conclusion arising from this review is that the deferred listing is specific to patients with severe disease who do not have alternative treatment options. Therefore in the absence of a PBS listing for BOTOX® for hyperhidrosis, patients with severe, refractory disease will not have access to subsidised treatment.

Allergan believes that the Government's deferrals policy, in general, will limit access by Australian patients to new medicines and does not sit well with the intent of the Memorandum of Understanding (MOU) signed with Medicines Australia in May 2010.

Allergan therefore requests that the Government make BOTOX® available on the PBS for patients with severe primary axillary hyperhidrosis.

If I can be any further assistance with our response please do not hesitate to contact me.

Yours sincerely,

Mark Glover

VP and Managing Director
Allergan Australia and New Zealand

ALLERGAN

Level 4, 810 Pacific Highway, Gordon NSW 2072, Locked Bag 1514, Pymble NSW 2073, Australia, Phone (612) 9498 0100, Fax (612) 9498 0290

Submission to the Senate Committee Inquiry on the Government's administration of the Pharmaceutical Benefits Scheme (PBS)

By Allergan Australia Pty Ltd

Contents

Executive Summary

On 23 June 2011 the Senate referred the following matter to the Finance and Public Administration References Committee for inquiry and report by 18 August 2011: The Government's administration of the Pharmaceutical Benefits Scheme (PBS).

The following submission by Allergan Australia Pty Ltd summarises the circumstances surrounding the deferral of the PBS listing of BOTOX® (botulinum toxin type A) for severe primary axillary (underarm) hyperhidrosis following a positive recommendation by the Pharmaceutical Benefits Advisory Committee (PBAC) in March 2010. The format of the submission is aligned to the Terms of Reference provided for the inquiry.

BOTOX® was approved by the TGA for the treatment of severe primary axillary hyperhidrosis in 2001. Registration of BOTOX® for this indication was supported by the efficacy and safety demonstrated in two large Phase III randomised controlled trials. As recognised in treatment guidelines, BOTOX® is a unique second-line therapy for patients failing prescription topical aluminium chloride antiperspirants but prior to consideration of surgical procedures that are only undertaken in a minority of patients due varied effectiveness and associated risks.

Following a petition submitted to the House of Representatives on 1 September 2008 by hyperhidrosis sufferers, Allergan submitted to the PBAC and received a positive recommendation for listing of BOTOX® for hyperhidrosis in March 2010. The recommended restriction is for *treatment of severe primary axillary hyperhidrosis in a patient 12 years or older who has failed or is intolerant to topical aluminium chloride hexahydrate after one to two months of treatment.* The deferred listing is therefore specific to patients who have severe disease without alternative treatment options. In the absence of the recommended listing, these patients do not have access to subsidised treatment.

The deferral of PBS listings following recommendation by the PBAC limits access of Australian patients to new medicines and does not sit well with the intent of the Memorandum of Understanding (MOU) between the Government and Medicines Australia signed in May 2010.

Based on the PBAC's positive recommendation, which was supported by acceptance of clinical need, clinically significant efficacy data and cost-effectiveness, BOTOX® should be made available on the PBS for patients with severe primary axillary hyperhidrosis.

(A) The deferral of listing of medicines on the PBS that have been recommended by the Pharmaceutical Benefits Advisory Committee

Background on hyperhidrosis

Primary focal hyperhidrosis is a condition characterised by abnormally increased perspiration in a localised area of the body, most commonly the palms and soles of the feet (palmoplantar hyperhidrosis; 60–80% of cases) or the underarm (axillary hyperhidrosis; 30–50% of cases). The condition is idiopathic (of no known cause) but genetic factors and dysfunction of the central sympathic nervous system may be involved. Primary focal hyperhidrosis typically commences during adolescence.

Focal hyperhidrosis can be both a distressing and a genuinely disabling condition in both private and professional life (Nauman 2001). In addition to constant wetness and staining of clothing, hyperhidrosis can lead to dehydration and maceration of the skin, which may result in secondary skin infections. Effective treatment for focal hyperhidrosis has been shown to significantly improve social functioning and mental health (Sayeed et al. 1998).

Current treatment options

Medical treatments, specifically topical applications are considered first line treatment for primary axillary hyperhidrosis. Patients are first instructed on the appropriate use of over-the-counter antiperspirants. If unsuccessful, prescription aluminium chloride hexahydrate antiperspirant can be trialled. As these can cause skin irritation, the concentration of the formulation needs to be optimised and the patient may need to also use hydrocortisone cream.

There are currently no other medical treatments for patients who fail to respond to topical applications. Oral anticholinergic drugs cause side effects such as dry mouth and blurred vision and are not TGA indicated for hyperhidrosis. Iontophoresis, a procedure in which the affected areas are soaked in liquid and an electric current is passed through this liquid for up to 30 minutes, is effective for palmar and plantar hyperhidrosis but not axillary treatment as there is anatomical difficulty obtaining the required immersion. Accordingly, iontophoresis and oral anticholinergics are not recommended in treatment guidelines for axillary hyperhidrosis (Hornberger et al. 2004; Solish et al. 2007).

Surgical treatment options (sympathectomy, subcutaneous curettage, liposuction or limited excision) are only considered if all other treatment options, including BOTOX®, have failed. However they are

rarely used because they are invasive, have varied effectiveness and can have associated risks of serious and irreversible complications.

BOTOX® (botulinum toxin type A)

Botulinum toxin type A has been used for over 30 years as targeted treatment for a variety of neurological conditions. It was first used in clinical trials commencing in 1980, and the BOTOX® (onabotulinumtoxinA) preparation received US Food and Drug Administration (FDA) approval in 1989 and Therapeutic Goods Administration (TGA) approval in 1993.

BOTOX® is currently listed on the PBS for the following indications:

- Treatment of blepharospasm associated with dystonia, including benign blepharospasm and VIIth nerve disorders (hemifacial spasm) in patients 12 years and older.
- Treatment of dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients 2 years of age or older and adults treated as children.
- Treatment of spasmodic torticollis, either as monotherapy or as adjunctive therapy to current standard care.
- Treatment of upper limb spasticity in patients following a stroke
- Treatment of upper limb spasticity in children and adults (treated as children) with cerebral palsy

BOTOX® was approved by the TGA for the treatment of severe primary axillary hyperhidrosis in 2001. Treatment for severe primary axillary hyperhidrosis is administered as 50 U at 10–15 injections per side.

Registration of BOTOX® for severe primary axillary hyperhidrosis was supported by two large Phase III randomised controlled trials (RCTs) which demonstrated significant efficacy gains in the extent of which the condition interferes with daily activities, the volume of sweat production and other outcomes. A total of 642 patients were randomised to double-blinded treatment with BOTOX® or placebo injections in Study 016 (Lowe et al. 2007) and Study 505 (Naumann and Lowe, 2001; with long term follow-up reported by Naumann et al. 2003).

The primary outcome in Study 016, the Hyperhidrosis Disease Severity Scale (HDSS), is a patient-rated scale that describes the impact of the condition on a patient's quality of life. The four categories are: 1 = never noticeable/never interferes with daily activities; 2 = tolerable/sometimes interferes; 3 = barely

tolerable/frequently interferes; 4 = intolerable/always interferes. Patients enrolled in the trial had a score of 3 or 4 indicating severe disease which frequently or always interferes with their daily activities. A responder was defined as a patient who obtained a 2-point improvement 4 weeks after treatment. In Study 505, a responder was defined as a patient obtaining a 50% or greater improvement from baseline in the volume of sweat production (gravimetric assessment), also at 4 weeks after treatment.

In Study 016, the proportions of patients with a HDSS response was 75.0% in the 50 U BOTOX® group, compared with 25.0% in the placebo group. Furthermore, a HDSS score of 1 (meaning that the condition is no longer noticeable or interferes with daily activities) was obtained by 60.6% of patients in the 50 U BOTOX® group versus 6.5% in the placebo group. In Study 505, the response rate was 93.8% in the 50 U BOTOX® group, compared with 35.9% in the placebo group. At 16 weeks after treatment, the response rate was 81.8% in the 50 U BOTOX® group, compared with 20.5% in the placebo group. A review of these and other studies evaluating the efficacy and safety of BOTOX® for primary axillary hyperhidrosis was published by Bhidayasiri and Truong (2008).

Developments leading to PBAC submission

Hyperhidrosis sufferers petitioned the House of Representatives on 1 September 2008 requesting that BOTOX® be listed on the PBS for severe primary hyperhidrosis of the axillae. Dr John Primrose and Mr David Learmonth of the Department of Health and Ageing testified before the House of Representatives Standing Committee on Petitions on this matter on 3 December 2008. Dr Primrose stated:

"We are talking about severe axillae hyperhidrosis. It is quite a serious medical condition so it would meet the criteria of clinical need that the PBAC would address for any future application. We are talking about people who have very excessive sweating and drenching, so the social issues are the stigma attached with permanently wet clothing and of course the odour. But in terms of medical complications, these can be quite serious because people get a skin rash in the armpits and skin becomes macerated, as you can imagine, with constantly wet skin and can get abscess formation and the infection becomes eventually resistant to antibiotics."[1]

[1] Proof Committee Hansard, House of Representatives Standing Committee on Petitions, Wednesday 3rd December 2008

The Minister for Health and Ageing stated in her response to this matter tabled before the Committee on 24 November 2008, that she was *"sympathetic to the circumstances faced by people with hyperhidrosis"* and further advised:

"signatories to the petition may wish to contact the manufacturer of this product, Allergan Australia Pty Ltd, to establish its intentions in respect of seeking an extension of the current PBS listings of BOTOX to include the treatment of individuals with severe primary hyperhidrosis of the armpits." [2]

PBAC submissions

Allergan subsequently provided two submissions to the PBAC for BOTOX® for severe primary hyperhidrosis of the axillae and received a positive recommendation for listing in March 2010. When deliberating in November 2009, the PBAC noted that *"no other second line treatments for severe hyperhidrosis of the axillae were available on the PBS"* and *"there was a significant impact on the quality of life of patients with hyperhidrosis and that there was a clinical need for botulinum toxin."* [3]

The recommended wording of the restriction from the PBAC Meeting Minutes is as follows.
Treatment of severe primary axillary hyperhidrosis in a patient 12 years or older who has failed or is intolerant to topical aluminium chloride hexahydrate after one to two months of treatment.
Maximum number of treatments per year is 3, with no less than 4 months to elapse between treatments[4].

It is important to note that the listing recommended by the PBAC is for patients with severe disease who are refractory to other medical treatment options.

Allergan was informed via a telephone call from the Department of Health and Ageing on the afternoon of 24 February 2011 that a PBS listing for BOTOX® for severe primary hyperhidrosis of the axillae had been deferred indefinitely until fiscal circumstances permit it.

[2] House of Representatives Official Hansard, No 17 2008, Monday 24 November 2008, pp 11124-11125

[3] PBAC Public Summary Document, Botulinum Toxin Type A, November 2009 available at http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-Botulinum-nov09

[4] PBAC Public Summary Document, Botulinum Toxin Type A, March 2010 available at http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-Botulinum-mar10

(B) Any consequences for patients of such deferrals

As recognised by the PBAC's recommendation, as well as by Australian and US guidelines, BOTOX® is a unique second-line therapy for patients failing prescription topical aluminium chloride antiperspirants. Patients enrolled in the key clinical trials discussed above had a HDSS score of 3 or 4 indicating that their disease frequently or always interferes with their daily activities. This is the same severity of disease experienced by Australian patients who would be eligible for the recommended listing.

As noted above, focal hyperhidrosis can be both a distressing and a genuinely disabling condition in both private and professional life (Nauman 2001). In addition to constant wetness and staining of clothing, hyperhidrosis can lead to dehydration and maceration of the skin, which may result in secondary skin infections. The sweating can also cause difficulty in grasping objects and writing, making some occupations impossible. Socially, sufferers may become withdrawn. Effective treatment for focal hyperhidrosis has been shown to significantly improve social functioning and mental health (Sayeed et al. 1998).

The deferral of BOTOX® for severe primary axillary hyperhidrosis has prevented access to affordable treatment via the PBS for patients suffering from this disease.

(C) Any consequences for the pharmaceutical sector of such deferrals

The process of listing medicines on the PBS is a complex and lengthy one, which, until the advent of the Government's new approach around deferring listings, has seen access provided to the PBS through a rigorous, evidence-based assessment. This process involves considerable investment by sponsor companies in the development of the required clinical and health economic evidence base as well as the significant cost recovery fees which alone are approximately $120,000 at lodgement of a major submission.

The uncertainty created by the deferrals decision places Australian affiliates of multinational pharmaceutical companies at a considerable disadvantage when competing for funds to invest in PBS related activities and justify the considerable expenditure devoted to PBAC submissions.

(D) Any impacts on the future availability of medicines in the Australian market due to such deferrals

If the deferrals policy continues, the dynamics discussed above will likely lead to situations where PBAC submissions by sponsor companies will be delayed due to the uncertainty around the PBS listing process. In turn, this will impact upon the availability of medicines for Australian patients.

(E) The criteria and advice used to determine the medicines to be deferred

As previously noted, Allergan has been advised by the Department of Health and Ageing and the Minister for Health and Ageing, that the deferral of PBAC recommendations has occurred for fiscal considerations. We have also been advised that the Government will review this decision when fiscal circumstances permit.

Allergan is not aware of any official criteria utilised to determine the medicines deferred from PBS listing. The explanations provided most consistently by the Government for the medicines chosen for deferral have centred around the availability of alternative medicines on the PBS for the particular disease as well as the seriousness of the disease itself. In other words, if there is no alternative PBS listed treatment and the Government judges the disease to be serious (by what criteria this judgement is made are unclear) a medicine which involves a net cost to the PBS might not be expected to be deferred. However, if either of these criteria are not met, a medicine might be deferred from PBS listing.

In the case of BOTOX® for severe primary hyperhidrosis of the axillae, the Minister has acknowledged that there is no alternative treatment available on the PBS[5]. However, the Minister has publicly stated that this severe disease is actually for many people a mild condition[6]. This overlooks both the TGA approved indication and the PBAC's recommended listing for BOTOX® which are for severe disease. Thus even according to considerations around alternatives and severity of disease, BOTOX® should not have been deferred from PBS listing.

[5] Roxon defends deferral of PBS medicines. Sarah Malik. AAP. March 9, 2011

[6] 2GB Sydney with Alan Jones, Transcript Radio Interview – Alan Jones interviewing the Minister for Health and Ageing Nicola Roxon, 15 June 2011, at page 6.

The example of BOTOX® for severe primary hyperhidrosis illustrates the dangers of overlooking an objective, independent expert Committee's recommendations on the basis of criteria which lack an objective clinical and health economic perspective.

(F) The financial impact on the Commonwealth Budget of deferring medicines

Allergan has provided robust estimates to the Department of Health and Ageing for the financial implications of a PBS listing for BOTOX® for severe primary hyperhidrosis of the axillae. These included undertaking a survey of dermatologists to estimate the likely number who would become BOTOX® injectors in the event of a PBS listing, providing a risk sharing agreement with the Commonwealth in order to manage any risk through a rebating mechanism for expenditure on BOTOX® for hyperhidrosis above agreed threshold amounts and the additional protection of the existing constraints around supply of PBS BOTOX® to accredited specialists only, through the Botulinum Toxin Program as administered by Medicare Australia authority arrangements. The estimated annual net cost to the Government for a listing for BOTOX® for hyperhidrosis agreed with the Department of Health and Ageing was just over $1 million in 2011, $3.5 million in 2012, increasing to approximately $7 million in 2015.

(G) The consultation process prior to a deferral

Allergan was not consulted prior to the Government's decision to defer the PBS listing of BOTOX® for severe primary hyperhidrosis of the axillae. Allergan was informed via a telephone call from the Department of Health and Ageing notifying of the indefinite deferral of BOTOX® for fiscal considerations on the afternoon of 24 February 2011. The Minister's statement on this matter occurred the next day in her press release of 25 February "Patients to Benefit from New Medicines on the PBS" [7].

(H) Compliance with the intent of the Memorandum of Understanding signed with Medicines Australia in May 2010

The Government's deferral of PBAC recommended medicines from PBS listing does not sit well with the intent of the Memorandum of Understanding (MOU) signed with Medicines Australia in May 2010. The intent of the MOU with respect to medicines estimated to cost the PBS above $10 million per annum

7 The Hon Nicola Roxon MP, Minister for Health and Ageing. Patients benefit from new medicines listed on the PBS and NIP. Media Release, 25 February 2011.

and therefore subject to Cabinet review under the arrangements in place at that time, was that this review be completed within 6 months, not that deferrals be announced within 6 months. Under its new "deferrals policy" the Government has effectively imposed a Cabinet review on any medicine with any level of net cost to the PBS and has invoked arbitrary criteria by which to defer indefinitely the PBS listing.

Conclusions

The recommended listing of BOTOX® for primary axillary hyperhidrosis on the PBS is for patients with severe disease who have failed other medical treatment options. The severity of the disease is such that it frequently or always interferes with patients' daily activities. The continued deferral of the PBS listing would mean that these patients do not have access to subsidised treatment.

In general, the uncertainty created by the deferrals disadvantages Australian companies and Australian patients in terms of access to new medicines.

In the case of BOTOX® for severe primary hyperhidrosis of the axillae, the apparent criteria for deferrals have not even been appropriately applied: the recommended PBS listing is for patients with severe disease who are refractory to other medical treatment options.

Allergan therefore requests that the Senate Committee recommends the Government makes BOTOX® available on the PBS for patients with severe, refractory primary axillary hyperhidrosis. In addition, and in the interests of good health policy and evidence-based decision making, Allergan recommends that the Government make available the other deferred PBAC-recommended medicines and does not defer future PBAC recommendations based on fiscal considerations.

Reference list (available upon request)

Bhidayasiri R, Truong DD. 2008. Evidence for effectiveness of botulinum toxin for hyperhidrosis. J Neural Transm 115: 641–645.

Hornberger J, Grimes K, Naumann M, Glaser DA, Lowe NJ, Naver H, Ahn S, Stolman LP, the Multi-Specialty Working Group on the Recognition, Diagnosis, and Treatment of Primary Focal Hyperhidrosis. 2004. Recognition, diagnosis, and treatment of primary focal hyperhidrosis. Journal of the American Academy of Dermatology 51(2):274–286.

Lowe NJ, Glaser DA, Eadie N, et al. 2007. Botulinum toxin type A in the treatment of primary axillary hyperhidrosis: A 52-week multicenter double-blind, randomized, placebo-controlled study of efficacy and safety. J Am Acad Dermatol 56(4):604–611.

Naumann M, Hamm H, Kinkelin I, Reiners K. 1999. Botulinum toxin type A in the treatment of focal, axillary and palmar hyperhidrosis and other hyperhidrotic conditions. European Journal of Neurology 6(SUPPL. 4): S111–S115.

Naumann M. 2001. Evidence-based medicine: Botulinum toxin in focal hyperhidrosis. Journal of Neurology 248(SUPPL. 1):I31–I33.

Naumann M, Lowe NJ. 2001. Botulinum toxin type A in treatment of bilateral primary axillary hyperhidrosis: randomised, parallel group, double blind, placebo controlled trial. BMJ 323:596–599

Naumann M, Lowe NJ, 2001, Kumar CR, et al. 2003. Botulinum toxin type A is a safe and effective treatment for axillary hyperhidrosis over 16 months: a prospective study. Arch Dermatol. 139:731–736.

Sayeed RA, Nyamekye I, Ghauri ASK, Poskitt KR. 1998. Quality of life after transthoracic endoscopic sympathectomy for upper limb hyperhidrosis. European Journal of Surgery, Supplement 164(580):39–42.

Solish N, Bertucci V, Dansereau A, et al. 2007. A comprehensive approach to the recognition, diagnosis, and severity-based treatment of focal hyperhidrosis: recommendations of the Canadian Hyperhidrosis Advisory Committee. Dermatologic Surgery 33(8):908–923.

Strutton DR, Kowalski JW, Glaser DA, Stang PE. 2004. US prevalence of hyperhidrosis and impact on individuals with axillary hyperhidrosis: results from a national survey. Journal of the American Academy of Dermatology 51:241–8.