botulinum toxin type A, 50 unit, 100 unit and 200 unit powder for solution for injection (Botox®) SMC No. (692/11)

Allergan Ltd.

04 March 2011

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

**ADVICE:** following a full submission

**botulinum toxin type A (Botox®)** is not recommended for use within NHS Scotland.

**Indication under review:** 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).

In pooled analysis of two phase III studies, botulinum toxin type A was superior to placebo for the primary endpoint, headache days. However, there were weaknesses in the clinical data that limit the ability to assess its likely clinical effectiveness in the target treatment population.

Overall the manufacturer did not present a sufficiently robust clinical and economic analysis to gain acceptance by SMC.

The licence holder has indicated their intention to resubmit.

Overleaf is the detailed advice on this product.

**Chairman,**

**Scottish Medicines Consortium**
**Indication**
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).

**Dosing Information**
The recommended reconstituted botulinum toxin type A dose for treating chronic migraine is 155 units to 195 units administered intramuscularly (im) using a 30-gauge, 0.5 inch needle as 0.1 ml (5 units) injections to 31 and up to 39 sites. Injections should be divided across seven specific head/neck muscle areas. The recommended re-treatment schedule is every 12 weeks. Doses recommended for botulinum toxin type A (Botox®) are not interchangeable with other preparations of botulinum toxin.

The injections should be administered by appropriately trained personnel in hospital specialist centres.

**Product availability date**
July 2010

**Summary of evidence on comparative efficacy**
Botulinum toxin type A blocks the release of neurotransmitters associated with the genesis of pain. The presumed mechanism for headache prophylaxis is by blockade of peripheral signals to the central nervous system, which inhibits central sensitisation, as suggested by pre-clinical and clinical pharmacodynamic studies.

The submitting company has requested that the Scottish Medicines Consortium (SMC) considers the use of this product when positioned for use in patients with chronic migraine who have previously failed on or are unsuitable for oral prophylactic medications and who are in the care of a headache specialist in a secondary care centre.

Two identically designed, multi-centre, double-blind, placebo-controlled studies have been conducted in adults with a history of chronic migraine meeting International Classification of Headache Disorders (ICHD-II) (2004) criteria. Following a 28-day baseline screening period there was a 24-week double-blind, parallel-group, placebo-controlled phase with two injection cycles, followed by a 32-week, open-label phase with three injection cycles. During the baseline period, patients were required to have ≥15 headache days with each day consisting of ≥ 4 hours of continuous headache and with ≥ 50% of days being migraine or probable migraine days, and ≥ 4 distinct headache episodes, each lasting ≥ 4 hours. Patients with overuse of acute migraine medication were included. In addition, two-thirds of patients had tried at least one oral prophylactic medicine prior to enrolment.

Eligible patients were randomised equally to botulinum toxin type A or placebo, stratified based on the frequency of acute headache pain medication intake during the 28-day baseline period (yes/no) and overuse of acute headache pain medications (defined as intake during baseline of
simple analgesics on ≥15 days or other medication types or combination of types for ≥ 10 days, with intake ≥2 days/week from the category of overuse). Botulinum toxin type A (155 units) or placebo (sodium chloride 0.9%) was administered intramuscularly in 31 fixed-site, fixed-dose injections across seven specific head/neck muscle areas. An additional 40 units could be administered into the temporalis, occipitalis and/or trapezius muscles at the investigator’s discretion. All efficacy analyses used the intent-to-treat population, which included all randomised patients.

In the first study the primary endpoint was the mean change from baseline in frequency of headache episodes (defined as patient-reported headache with a start and stop time indicating that the pain lasted at least 4 continuous hours recorded in the patient diary) for the 28-day period ending with week 24. In the second study the primary efficacy endpoint was the mean change from baseline in frequency of headache days (defined as a calendar day when the patient reported four or more continuous hours of a headache, in the patient diary) for the 28-day period ending with week 24. Botulinum toxin type A was superior to placebo for the primary endpoint in the second study only. Primary and some secondary endpoints for the two studies are included in the tables below.

**Table 1: study one, efficacy at week 24.**

<table>
<thead>
<tr>
<th>Efficacy variable</th>
<th>Botulinum toxin type A (n=341)</th>
<th>Placebo (n=338)</th>
<th>Difference (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean change</td>
<td></td>
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<tr>
<td><strong>Primary endpoint</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Headache episodes</td>
<td>12.3 -5.2</td>
<td>13.4 -5.3</td>
<td>0.1 (-1.12 to 0.39)</td>
<td>p=0.344</td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache days</td>
<td>20.0 -7.8</td>
<td>19.8 -6.4</td>
<td>-1.4 (-2.40 to -0.40)</td>
<td>p=0.006</td>
</tr>
<tr>
<td>Migraine episodes</td>
<td>11.5 -4.8</td>
<td>12.7 -4.9</td>
<td>0.1 (-1.21 to 0.26)</td>
<td>p= 0.206</td>
</tr>
<tr>
<td>Migraine days</td>
<td>19.1 -7.6</td>
<td>19.1 -6.1</td>
<td>-1.5 (-2.60 to -0.59)</td>
<td>p=0.002</td>
</tr>
</tbody>
</table>

CI=confidence interval
Table 2: study two, efficacy at week 24.

<table>
<thead>
<tr>
<th>Efficacy variable</th>
<th>Botulinum toxin type A (n=347)</th>
<th>Placebo (N=358)</th>
<th>Difference (95% CI) p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Mean change</td>
<td>Baseline Mean change</td>
<td></td>
</tr>
<tr>
<td>Primary endpoint</td>
<td></td>
<td></td>
<td>-2.3 (-3.25 to -1.31) p&lt;0.01</td>
</tr>
<tr>
<td>Headache days</td>
<td>19.9 -9.0</td>
<td>19.7 -6.7</td>
<td></td>
</tr>
<tr>
<td>Secondary endpoints</td>
<td></td>
<td></td>
<td>-0.7 (-1.65 to -0.33) p=0.003</td>
</tr>
<tr>
<td>Headache episodes</td>
<td>12.0 -5.3</td>
<td>12.7 -4.6</td>
<td></td>
</tr>
<tr>
<td>Migraine episodes</td>
<td>NR NR</td>
<td>NR NR</td>
<td></td>
</tr>
<tr>
<td>Migraine days</td>
<td>19.2 -8.7</td>
<td>18.7 -6.3</td>
<td>-2.4 (-3.31 to -1.36) p&lt; 0.001</td>
</tr>
</tbody>
</table>

CI=confidence interval, NR=not reported

There were no significant differences between groups in the frequency of acute headache pain medication consumption in either study, although there were significant differences in favour of botulinum toxin type A for triptan intake.

In the pooled analysis of the studies the primary endpoint, mean change from baseline to week 24 in headache days, was significantly superior for botulinum toxin type A versus placebo-treated patients; -8.4 versus -6.6, difference -1.8; 95% CI -2.52 to -1.13. Also, headache episodes were significantly reduced in the botulinum toxin type A group versus placebo (-5.2 versus -4.9). The number of patients who had a history of headache medication prophylaxis at enrolment was 425 and 454 in the botulinum toxin type A and placebo groups respectively. At baseline in this sub-group the frequency of headache days was 20.1 in both groups and at week 24 the change from baseline was -7.9 for the botulinum toxin type A group and -5.6 for the placebo group (p<0.001). For the whole population there was a statistically significant difference in favour of botulinum toxin type A in terms of the total Headache Impact Test-6 score (mean change from baseline at week 24: -4.8 versus -2.4). Changes in the three domains of the Migraine-Specific Quality of Life Questionnaire (preventive, restrictive and emotional) were also significantly superior for botulinum toxin type A versus placebo.

During the open-label phase in which all patients received treatment with botulinum toxin type A at weeks 24, 36 and 48, the mean change in number of headache days continued to fall for both groups (those who had previously received botulinum toxin type A and those who has previously received placebo). However, the group of patients that had received botulinum toxin type A since the start of the studies continued to improve more during the open-label phase resulting in a significant difference between the two patient groups at one year. Discontinuation rates at the end of the double-blind phase were 11.8% versus 9.6% compared to 25% versus 29% at the end of the open-label phase in patients that were initially assigned to the botulinum toxin type A and placebo groups respectively.

*Other data were also assessed but remain commercially confidential.*
Summary of evidence on comparative safety

There are limited safety data versus active comparators. In the pooled analysis the frequency of adverse events (AE) was 62% for botulinum toxin type A versus 52% for placebo. The frequency of treatment-related AE was 29% and 13% respectively. There were 33 (4.8%) versus 16 (2.3%) serious AE and 26 (3.8%) versus 8 (1.2%) discontinuations related to AE. No deaths were reported. AE with an incidence ≥ 5% were neck pain (6.7% versus 2.2%) and muscular weakness (5.5% versus 0.3%). No unexpected treatment related AE were observed.

The Medicine and Healthcare products Regulatory Agency (MHRA) noted that the safety profile of botulinum toxin type A is well known and the incidence of adverse reactions of concern is low.

Summary of clinical effectiveness issues

The submitting company has requested that SMC considers the use of this product when positioned for use in patients experiencing chronic migraine who have previously failed on or are unsuitable for oral prophylactic medications and who are in the care of a headache specialist in a secondary care centre. The summary of product characteristics (SPC) notes that botulinum toxin type A injections should be administered by appropriately trained personnel in hospital specialist centres. This may have implications for service delivery as well as the patient.

It should be noted that the placebo response in the studies was high. In addition, it is unlikely that blinding could have been maintained as patients receiving botulinum toxin are likely to have been aware of which arm of the study they were in.

There are no comparative data versus other prophylactic treatments for chronic migraine. The submitting company was unable to perform an indirect comparison versus drugs and interventions that are currently tried after failure of first-line oral prophylactics (gabapentin, venlafaxine and greater occipital nerve [GON] block) due to deficiencies with the available comparator evidence. The submitting company has proposed that best supportive care (BSC) (which includes combinations of first-line oral prophylactics, off-label prophylactics, GON blocks and in some cases acute migraine medications only) is the relevant comparator. However, as the placebo arm of the pivotal studies excluded patients who were receiving concurrent treatment with oral prophylactics the comparative efficacy versus BSC is unknown.

For the first study the primary outcome was not met, although at baseline there were significant differences between groups for headache episodes, migraine episodes and cumulative headache hours occurring on headache days. The primary outcome in the second study was changed to frequency of headache days prior to the study’s completion and treatment unmasking. The primary outcome was, however, met in the second study and in a pooled analysis of the two studies. The MHRA was satisfied with the consistency of the results between the various endpoints for both trials.

Both studies allowed patients who had overused acute migraine medication to be recruited and this accounted for approximately two-thirds of patients overall. As the ICHD-II (2006) classification excludes patients who overuse acute medication in a diagnosis of chronic
migraine the study population may therefore not reflect the population of patients who would currently be diagnosed with chronic migraine. Nevertheless randomisation in the studies was stratified for this variable and the MHRA concluded that the trial population was representative of the target population of patients with chronic migraine as currently defined. In addition, analysis of the headache days endpoint in the sub-group of patients who overused acute medication at enrolment (n=904 in the pooled population) resulted in a similar outcome to that of the total population.

There are limited efficacy data in males, who accounted for only 14% of the phase III study population. The SPC notes that the treatment effect appeared smaller in the subgroup of male patients (N=188) than in the whole study population.

Quality of life as measured by three tools was significantly improved for botulinum toxin type A versus placebo treated patients.

*Other data were also assessed but remain commercially confidential.*

**Summary of comparative health economic evidence**

The manufacturer submitted a cost-utility analysis comparing botulinum toxin type A injections given every 12 weeks to best supportive care in patients experiencing chronic migraine who had previously failed on oral prophylactic therapy due to side-effects or lack of efficacy and were in the care of a headache specialist in a secondary care centre. Best supportive care was assumed to encompass use of off-label treatments such as gabapentin, venlafaxine and GON blocks or alternatively patients may not have been given prophylaxis but managed by acute treatments only. A stopping rule was incorporated into the model whereby treatment would be discontinued at 24 weeks due to non-response. Based on expert clinical advice, the manufacturer assumed that if a patient was in the same or a worse health state at 24 weeks, treatment would be discontinued due to non-response. A two year time horizon was used for the analysis.

Effectiveness data for the model was taken from patient-level data from the post hoc pooled analysis of the key studies. The average headache days over a 28 day period was used to categorise patients into various health states in the model, with a total of 7 health states being used. Best supportive care was assumed to be as effective as the sodium chloride 0.9% injections used in the placebo arm of the key studies. Clinical study data were available for up to one year for botulinum toxin type A treated patients and the manufacturer assumed that the transition probability at week 60 of the model would be sustained in the second year of the model. For BSC patients, the transition probabilities at week 24 were used to extrapolate the data over the 2 year duration of the model.

The manufacturer used EQ-5D data from the International Burden of Migraine Study (IBMS) in order to estimate utility values for the various states in the model. Drug acquisition costs for botulinum toxin type A injections plus associated administration costs were incorporated into the analysis. Administration was assumed to be by a neurologist in an outpatient setting. No drug costs were assumed for the comparator arm of the model, despite the assumption that medicines would be used as part of best supportive care, however this is a conservative assumption. Patients in the BSC arm were however assumed to have a consultant neurologist
visit every 12 weeks. Other resource use relating to acute treatment was estimated from the International Burden of Migraine Study.

The base case incremental cost per quality adjusted life year (QALY) was £17,436 based on an incremental cost of £1,394 and a QALY gain of 0.08. This was also presented in terms of £33 per headache avoided.

Sensitivity analysis showed that the results were sensitive to changes in utility values and the time horizon. The one-way analysis showed that the results were most sensitive to the utility values assumed for botulinum toxin type A injections patients compared to BSC patients. If the upper values for the utility scores for BSC patients were used (i.e. meaning that the utility scores for BSC patients were higher than for botulinum toxin type A injections patients in the same health state) then the cost per QALY estimates were between £20k and £23k. A one year time horizon gave an ICER of £24,467. If the dosing interval was increased from 12 to 18 weeks in the second year, which the manufacturer suggested would reflect how clinicians would use the drug in practice, the ICER reduced to £14,028.

Other data were also assessed but remain commercially confidential.*

There were a number of limitations associated with the analysis:

- There was uncertainty in relation to the effectiveness of the comparator, which was assumed to be the same as the placebo response rate in the pooled analysis. The results were sensitive to changes in the effectiveness assumed for BSC, such that if changes were made to the effectiveness assumed in the base case, the QALY gain fell by a quarter and the ICER rose to around £25k.
- The resource use assumptions in the base case may not be appropriate and therefore may have introduced some bias. Two-way sensitivity analysis was provided where the duration of outpatient appointment required to administer the injections was increased to 45 minutes and the number of outpatient visits in the BSC arm was reduced by 30%. This resulted in the ICER increasing to £25,386. The combined effect of increasing the effectiveness assumed for BSC and using more conservative resource use assumptions would be likely to increase the cost per QALY above acceptable limits.
- There was uncertainty regarding the continued efficacy of treatment and the results of the analysis were sensitive to the assumed time horizon. When no additional benefit was assumed after week 24, the cost per QALY increased to £26,445.
- The clinical data were based on a post hoc subgroup analysis.
- A sensitivity analysis using a mapping approach to utility values resulted in a much higher ICER compared to the method used in the base case.
- No training costs were included in relation to the administration of botulinum toxin type A injections, which may not be appropriate given this is a new treatment modality in this setting. However, additional sensitivity analysis was provided to include an allowance for staff time for training and this did not significantly affect the results.

Given these issues, in particular the uncertainty associated with the effectiveness data used in the economic model, the economic case has not been demonstrated.

**Summary of patient and public involvement**

A Patient Interest Group submission was received from the Migraine Trust.
The Scottish Intercollegiate Guideline Network (SIGN) published; Diagnosis and management of headache in adults, a national clinical guideline (no. 107) in November 2008. Propranolol is recommended for first-line use for migraine prophylaxis and timolol, atenolol, nadolol and metoprolol may be used as alternatives to propranolol.

Topiramate, gabapentin, amitriptyline or venlafaxine are alternative treatment options to beta blockers. The guideline states that botulinum toxin A is not recommended for the prophylactic treatment of migraine but the guideline predates the publication of the pivotal studies and the licensing of botulinum toxin A in this indication.

The British Association for Study of Headache (BASH) published Guidelines for All Healthcare Professionals in the Diagnosis and Management of Migraine, Tension-Type, Cluster and Medication-Overuse Headache (3rd edition) in 2010. The following recommendations are based on evidence and expert clinical experience. First-line prophylactic drugs include beta-adrenergic blockers without partial agonism (atenolol, metoprolol, propranolol or bisoprolol) or amitriptyline. Second-line prophylactic drugs include topiramate and sodium valproate. Third-line prophylactic drugs include gabapentin or methysergide. The guidelines note that a preparation of botulinum toxin type A is licensed for prophylaxis in patients with more than 15 headache days per month, of which at least eight days are with migraine. The difference between active and placebo treatments was small in reported clinical trials, although statistically significant.

The European Federation of Neurological Societies (EFNS) published EFNS guideline on the drug treatment of migraine – revised report of an EFNS task force in June 2009. The recommended drugs of first choice for the prophylactic drug treatment of migraine according to the consensus of the Task Force are; metoprolol, propranolol, flunarizine, valproic acid and topiramate. No recommendation is given for botulinum toxin type A.

All guidelines predate the publication of the pivotal botulinum toxin type A phase III studies and the licensing for prophylactic treatment of chronic migraine.

**Additional information: comparators**

Propranolol, topiramate, gabapentin, amitriptyline or venlafaxine are recommended by SIGN for the prophylaxis of chronic migraine and may be considered as comparators. Gabapentin, amitriptyline and venlafaxine are used off-label for the prophylaxis of chronic migraine.
Cost of relevant comparators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost per year (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botulinum toxin type A (Botox®)</td>
<td>155 to 195 units intramuscularly every 12 weeks.</td>
<td>1,198</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>1,200mg to 2,400mg orally per day</td>
<td>60 to 398</td>
</tr>
<tr>
<td>Topiramate</td>
<td>50mg to 200mg orally per day</td>
<td>75 to 152</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>75 to 150mg orally per day</td>
<td>47 to 61</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>25mg to 150mg orally per day</td>
<td>12 to 39</td>
</tr>
<tr>
<td>Propranolol</td>
<td>80mg to 240mg orally per day</td>
<td>24 to 30</td>
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</tbody>
</table>

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 9 December 2010. The cost of botulinum toxin type A is based on 5 treatments. The dose regimens for comparators are taken from the SIGN 107 guideline (and may be higher than SPC recommendations), and are used off-label for gabapentin, amtriptyline and venlafaxine.

Additional information: budget impact

The manufacturer estimated a gross drug budget impact of £106k in year one rising to £1.3m in year five. Adding in administration costs gave figures of £156k and £1.9m in years one and five respectively. These figures assumed a two-year treatment duration and a stopping rule for non-responders after two treatments. The manufacturer has indicated that estimates of the eligible patient population and market share should be regarded as commercial in confidence.

Other data were also assessed but remain commercially confidential.*
References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.


*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/

This assessment is based on data submitted by the applicant company up to and including 11 February 2011.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.