

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## GUIDANCE EXECUTIVE (GE)

### Review of TA260; Botulinum toxin type A for the prophylaxis of headaches associated with chronic migraine

This guidance was issued in June 2012.

The review date for this guidance is June 2015.

#### 1. Recommendation

The guidance should be transferred to the 'static guidance list'. That we consult on this proposal.

#### 2. Original remit(s)

To appraise the clinical and cost effectiveness of botulinum toxin type A within its licensed indication for the prophylaxis of headaches associated with chronic migraine.

#### 3. Current guidance

1.1 Botulinum toxin type A is recommended as an option for the prophylaxis of headaches in adults with chronic migraine (defined as headaches on at least 15 days per month of which at least 8 days are with migraine):

- that has not responded to at least three prior pharmacological prophylaxis therapies and
- whose condition is appropriately managed for medication overuse.

1.2 Treatment with botulinum toxin type A that is recommended according to 1.1 should be stopped in people whose condition:

- is not adequately responding to treatment (defined as less than a 30% reduction in headache days per month after two treatment cycles) or
- has changed to episodic migraine (defined as fewer than 15 headache days per month) for three consecutive months.

1.3 People currently receiving botulinum toxin type A that is not recommended according to 1.1 and 1.2 should have the option to continue treatment until they and their clinician consider it appropriate to stop.

#### **4. Rationale<sup>1</sup>**

No significant new evidence has been identified that would be likely to change the current recommendation in TA260. It is therefore appropriate to transfer this guidance to the 'static guidance list'.

#### **5. Implications for other guidance producing programmes**

There is no proposed or ongoing guidance development that overlaps with this review proposal.

#### **6. New evidence**

The search strategy from the original ERG report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from December 2010 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

#### **7. Summary of evidence and implications for review**

The marketing authorisation for botulinum toxin type A is unchanged from that considered in the original appraisal, that is, 'for 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)<sup>1</sup>'.

The cost has also not changed since the original appraisal, that is, a net price of £276.40 for a 200 unit vial.

The comparator for the appraisal was standard care (placebo arm in the clinical trial); there is therefore nothing to report regarding changes to marketing authorisation or price of comparators. There are no new interventions or comparators that have come to the market since the original guidance.

The majority of papers identified in the literature review were analyses based on the 2 PREEMPT studies, which supported the submission for TA260, and many of these were conference papers. A UK-based real world study on the use of botulinum toxin A in 254 patients with chronic migraine was published by Khalil et al. (2014). This study's outcomes support findings of PREEMPT studies. A UK cost-effectiveness study based on PREEMPT data reported an ICER of £15,028 per QALY gained, somewhat lower than the ICER considered most plausible by the Committee of £18,900 per QALY gained. A meta-analysis published in 2012 by Jackson et al. reported that botulinum toxin A compared with placebo was associated with a small to modest benefit for chronic daily headaches and chronic migraines but was not associated with fewer episodic migraine or chronic tension-type headaches per

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<sup>1</sup> A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

month. This meta-analysis did not cite relevant evidence that was not reported in TA260.

Blumenfeld et al. (2012) report the rationale for study and design of COMPEL, a phase 4, long-term, open-label study that will complement existing data from PREEMPT. According to Clinicaltrials.gov the estimated study completion date is March 2016. In addition to COMPEL, there are several other ongoing or planned long-term observational studies.

In summary, given the fact that the cost of botulinum toxin type A has not changed, that there are no new comparators, and no significant changes in the evidence-base, it is unlikely that the new evidence would lead to a change in the recommendations of the original guidance.

## **8. Implementation**

A submission from Implementation is included in Appendix 3.

No prescribing data was provided given botulinum toxin A has multiple indications, therefore it was not possible to assess uptake. One nephrologist has fed back concerns with the implementation of the guidance.

## **9. Equality issues**

The Committee concluded that its recommendations did not limit access to the technology for any specific group compared with other groups

**GE paper sign off:** Helen Knight, Associate Director, 29/05/2015

### **Contributors to this paper:**

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## Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – ‘Yes/No’
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the [specify STA or MTA] process.	A review of the appraisal will be planned into the NICE’s work programme.	No
The decision to review the guidance should be deferred to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE’s work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE’s work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	<p>The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review.</p> <p>This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.</p>	No

Options	Consequence	Selected – ‘Yes/No’
The guidance should be updated in an on-going clinical guideline.	<p>Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn.</p> <p>Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).</p>	No
The guidance should be transferred to the ‘static guidance list’.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

- i. The technology falls within the scope of a clinical guideline (or public health guidance)
- ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement
- iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment
- iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;
  - Spending on a treatment for the indication which was the subject of the appraisal continues to rise
  - There is evidence of unjustified variation across the country in access to a treatment

- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed
  - The treatment is excluded from the Payment by Results tariff
- v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

## Appendix 2 – supporting information

### Relevant Institute work

#### *Published*

Headaches (2015) NICE pathway.

Transcranial magnetic stimulation for treating and preventing migraine (2014) NICE interventional procedures guidance 477.

Migraine prophylaxis: flunarizine (2014) NICE evidence summary of unlicensed or off-label medicines 33.

Occipital nerve stimulation for intractable chronic migraine (2013) NICE interventional procedures guidance 452.

Deep brain stimulation for intractable trigeminal autonomic cephalalgias (2011) NICE interventional procedures guidance 381.

Percutaneous closure of patent foramen ovale for recurrent migraine (2010) NICE interventional procedures guidance 370.

#### *In progress*

Headaches: diagnosis and management of headaches in young people and adults (update) NICE guideline. Publication expected November 2015.

#### *Referred - Qs and CGs*

Headaches in young people and adults (2013) NICE quality standard 42.

Headaches: Diagnosis and management of headaches in young people and adults (2012) NICE guideline CG150.

## Details of changes to the indications of the technology

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
<p>Botox has a UK marketing authorisation 'for 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 recommended reconstituted dose is 155–195 units, administered intramuscularly as 0.1 ml (5 units) injections to between 31 and 39 sites around the head and back of the neck. The recommended re-treatment schedule is every 12 weeks.</p> <p>The net price of a 200 unit vial is £276.40 (excluding VAT; 'British national formulary' [BNF] edition 63).</p>	<p>The indication is unchanged.</p> <p>Source: SPC (March 2015)</p> <p><b>Cost</b></p> <p>50 unit vial = £77.50            100 unit vial = £138.20            200 unit vial = £276.40</p> <p>Source: BNF (April 2015)</p>

## Registered and unpublished trials

Trial name and registration number	Details
<p>Long-term Efficacy, Safety, and Tolerability Study of BOTOX in Patients With Chronic Migraine</p> <p>NCT01516892</p> <p>COMPEL</p>	<p>Method: Single Group Assignment, Open Label</p> <p>Status: ongoing, not recruiting</p> <p>Enrollment: 713</p> <p>Start date: December 2011</p> <p>Expected completion date: March 2016</p>
<p>Efficacy and Safety Study of BOTOX Compared to Topiramate for the Prevention of Chronic Migraine in Adults</p> <p>NCT02191579</p> <p>Phase 4</p>	<p>Purpose: prophylactic onabotulinumtoxinA compared to topiramate in adults with chronic migraine</p> <p>Method: Randomized, Parallel Assignment, Open Label</p> <p>Status: recruiting</p> <p>Enrollment: 400</p> <p>Start date: July 2014</p> <p>Expected completion date: June 2017</p>

## Relevant services covered by NHS England specialised commissioning

NHS England commissions adult highly specialist pain management services and CCGs commission community and secondary care pain management services.



NHS England (2014) Manual for prescribed specialised services 2013/14 Chapter 3 - adult highly specialist pain management services.

NHS England (2013) NHS standard contract for specialised pain. schedule 2- the services- a. service specifications.

### **Additional information**

Botox is not recommended for use within NHS Scotland for the prophylaxis of headaches in adults with chronic migraine. The submitting company did not present a sufficiently robust clinical and economic analysis to gain acceptance by SMC.

Source: Scottish Medicines Consortium (2013) Botulinum toxin type a (Botox). 692/11

### **References**

Blumenfeld AM, Aurora SK, Laranjo K et al. (2012) Rationale for study and design of compel: An open-label, multicenter study of the long-term efficacy, safety, and tolerability of onabotulinumtoxinA for headache prophylaxis in adults with chronic migraine. *Headache* 52(5): 881.

Jackson JL, Kuriyama A, Hayashino Y (2012) Botulinum toxin A for prophylactic treatment of migraine and tension headaches in adults: A meta-analysis. *JAMA - Journal of the American Medical Association* 307(16): 1736-1745.

Khalil M, Zafar HW, Quarshie V et al. (2014) Prospective analysis of the use of OnabotulinumtoxinA (BOTOX) in the treatment of chronic migraine; real-life data in 254 patients from Hull, U.K. *Journal of Headache & Pain* 15: 54.

## **Appendix 3 – Implementation submission**

### **1. Routine healthcare activity data**

Botulinum toxin type A has multiple indications therefore prescribing data has not been provided.

### **2. Implementation studies from published literature**

Information is taken from the uptake database website

A search of the uptake database has found no relevant information.

### **3. Qualitative input from the field team**

***The implementation field team have recorded the following feedback in relation to this guidance:***

Implementation Consultant: Lesley Edgar created on: 28/02/2014

Feedback from a Trust neurologist as to why they will not be implementing TA 260 Botulinum toxin type A for the prevention of headaches in adults with chronic migraine in the Trust:

1. The trials 'establishing' its use were funded by the pharmaceutical company that manufactures botulinum toxin. The results are therefore liable to bias in favour of the compound. No independent trials have been performed.
2. The rationale behind its mechanism of action is unclear. Botulinum is injected into the scalp, yet the pathophysiology of migraine involves a spreading wave of depolarisation over the surface of the brain, accompanied by a change in the arterial blood flow in the intracranial vessels - none of these areas are affected by extracranial administration of botulinum toxin.
3. Botulinum toxin has previously been shown to be ineffective in episodic migraine. 'Chronic' migraine is frequent episodes of episodic migraine. Thus it is difficult to see how there could be benefit in the same condition.
4. The two trials (PREEMPT 1 and PREEMPT 2) both had large placebo effects.
5. In PREEMPT 1, the primary endpoint was not achieved.
6. The use of other analgesics was not restricted in either trial, and the use was not statistically different between placebo and treatment groups, which would indicate that there was no significant reduction in the level of pain.