

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Botulinum toxin type A for the prophylaxis of headaches associated with chronic migraine

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Dr Paul Shanahan

Name of your organisation

National Hospital for Neurology and Neurosurgery

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **YES**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **NO**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? **NO**
- other? (please specify)

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Chronic migraine is defined (in the Second Edition of the International Classification of Headache Disorders, ICHD-2) as migraine headache occurring on at least 15 days per month (for at least 3 months) in the absence of medication overuse. A recent systematic review (Natoli et al, Cephalalgia 2010 May; 30(5):599-609) suggests a global prevalence of up to 5.1%, with typical reports suggesting a prevalence of 1.4-2.2%. As such, it represents a significant cause of global disability and constitutes a significant proportion of referrals to general neurology as well as specialist headache clinics.

For chronic migraine, the mainstay of treatment is prophylaxis: In addition to lifestyle measures (trigger avoidance, attention to sleeping patterns etc), and correct usage of acute abortives (with particular attention to the avoidance of medication overuse) most patients will require pharmacotherapy, and a wide range of treatments (with a varying evidence base) are currently used. This includes antidepressants, beta-blockers, anticonvulsants, serotonin modulators, calcium channel blockers and (less commonly) temporary or transitional treatments such as cranial nerve blocks and intravenous dihydroergotamine. While these treatments can all be effective in various patients, not all patients will respond to any given treatment and issues of tolerability and comorbidities may limit treatment options in any given individual. One of the challenges of treating migraine is there is no reliable way to predict medication response in advance.

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The PREEMPT 1 and 2 studies have demonstrated a statistically significant reduction in headache frequency for patients with chronic migraine compared to placebo. The studies show that approximately 50% of treated patients experience a 50% reduction in headache frequency, which is comparable to current treatments.

Since obtaining a license for use in chronic migraine last year, the usage of botox on the NHS has been limited. I feel that, given the nature of the drug, the specificity of the established injection protocol, and the need to monitor response and repeat treatments as required, that this is a treatment best suited for use in specialist headache practice, and preferably after at least 2-3 oral preventative medications have been tried.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Botox treatment for other indications has a long track record, and its safety when used appropriately is well established. In comparison to many oral medications used for chronic migraine its tolerability profile is good, and comparison with placebo does not reveal any significant rate of systemic effects such as sedation, appetite stimulation and mood disturbance, which can be an issue with some of the alternatives. As treatment is given every 12 weeks, there should not be any issues with treatment compliance.

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The PREEMPT studies looked at headache outcomes after 6 months of treatment, and I feel that this would be a reasonable point to assess response and tolerability, and do discontinue treatment in those who have not responded. The evidence to date does not suggest any reliable predictor of response in a given patient or subgroup, so at present patients cannot be stratified a priori. It would seem reasonable to exclude patients with acute medication overuse as it is not possible to make a ICHD-2 compliant diagnosis of chronic migraine until withdrawal has occurred.

Botox is generally well tolerated and the incidence of side-effects (principally head or neck discomfort) in the PREEMPT studies was low. In our clinical experience to date (treatment of approx 100 patients at NHNN) there have not been any adverse experiences beyond those described in the study.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

I am not aware of any registries or co-ordinated audits in this regard. An MHRA-mandated post-licensing study to assess tolerability is currently underway.

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Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

As outlined above, I feel this treatment is best delivered in the setting of a specialist headache service. As such, the requirement would be that the treating specialist (doctor or nurse practitioner) be trained in the technique of injection according to the PREEMPT protocol. This has already occurred in many centres, as Allergan have funded injector training sessions, and extra training requirements should be minimal..

It should be stressed that the appropriate role for botox is as part of the wider assessment and treatment of chronic migraine, and as such it should representn extension of existing services rather than a new service in its own right.