NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

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

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal. Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- Most of the evidence in the trial populations relates to people who have had one preventative treatment. What is the relevance of this evidence for people whose condition has failed to respond to at least three pharmacological treatments?
- There was a large placebo effect in the two PREEMPT trials. What is the relevance of this for people whose condition has failed to respond to at least three pharmacological treatments?

Cost effectiveness

- The duration of treatment and time horizon used for the economic evaluation was 2 years. Does the Committee consider this to be appropriate?
- The administration cost used for the economic evaluation is based upon 30 minutes of consultant time. Does the Committee consider this appropriately reflects the administration of botulinum toxin type A?

- The resource use cost in the economic evaluation was based on results of the International Burden of Migraine Study as reported by Bloudek et al. The ERG noted that there is disparity between the results reported in Blumenfeld et al. and in another paper by Bloudek et al, which is based on a larger subset of patients from the same study. Which paper does the Committee consider is appropriate for resource use cost to be based on?
- The negative stopping rule in the economic evaluation was applied to people whose condition had responded insufficiently (defined as an improvement of less than two health states) to botulinum toxin type A. Does the Committee consider it is appropriate to stop treatment for people who have experienced an improvement in one health state? Is the positive stopping rule considered to be clinically relevant, and what are its practical implications?
- The positive stopping rule in the economic evaluation was applied to people who are responding well to treatment (defined as fewer than 15 headache days per 28 days). What is the Committee's view of stopping treatment for people whose condition is responding to treatment, irrespective of the magnitude of that improvement? Is the positive stopping rule clinically relevant, and what are its practical implications?
- The utilities used in the economic evaluation are different between the botulinum toxin type A and placebo groups for the same health states, because it was assumed that treatment with botulinum toxin type A reduces the intensity and severity of headaches. Does the Committee consider this assumption to be appropriate?
- The economic model is strongly non-linear, with the probabilistic estimate of cost effectiveness being more than double that of the deterministic estimate. Does this Committee consider this to be an issue?

1 Background: Clinical need and practice

1.1 Migraine is primarily a headache disorder. It manifests as recurring attacks that usually last for 4–72 hours, involving

throbbing head pain of moderate to severe intensity. It is often accompanied by nausea, sometimes vomiting, and sensitivity to light, sound and/or other sensory stimuli. Some people have warning symptoms called an aura before the start of a headache. Aura is typically characterised by visual disturbances, including blind spots, tunnel vision and temporary blindness. Chronic migraine is defined by the International Headache Society as the occurrence of headaches on 15 days or more per month for at least 3 months, where the attacks fulfil criteria for pain and associated symptoms of migraine without an aura on at least 8 days per month for at least 3 months, where there is no medication overuse, and where the headaches are not attributable to another causative disorder.

1.2 Prevention (prophylaxis) of headaches is an important in chronic migraine management. The goals are to reduce the frequency, painfulness, and/or duration of migraines, and to increase the effectiveness of medication that is taken at the earliest signs of a migraine headache (known as abortive therapy). It may also help to avoid medication overuse headache (or rebound headache), which is linked to the overuse of pain medications, and is a common problem among people with migraines.

1.3 Preventative interventions include nutritional supplements, lifestyle alterations (for example increased exercise and avoidance of migraine triggers) and pharmacological treatments. Pharmacological preventative treatments are generally considered for people:

- who have at least two attacks a month, or
- whose attacks are increasing in frequency, or
- whose attacks cause significant disability despite abortive treatment, or
- who cannot take abortive treatment for migraine attacks.

These treatments include beta blockers (propranolol, atenolol, metoprolol, nadolol and timolol), valproic acid, sodium valproate, topiramate, antidepressants (amitriptyline, nortriptyline, imipramine, desipramine), pizotifen, gabapentin and cyproheptadine. Despite current preventative treatment, some people continue to experience chronic migraines.

1.4 The manufacturer reports that approximately 141,000 people have a diagnosis of chronic migraine in England and Wales. Of these approximately 49,000 people's condition has failed to respond to at least three prior pharmacological preventative therapies.

2 The technology

2.1 Botulinum toxin type A (Botox, Allergan) is a purified neurotoxin complex which produces seven neurotoxins that are structurally similar but immunologically distinct. It has neuromuscular transmitter blocking effects. Botulinum toxin type A 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 31-39 sites around the head and back of the neck (see figure 1). The recommended re-treatment schedule is every 12 weeks (see the summary of product characteristics).

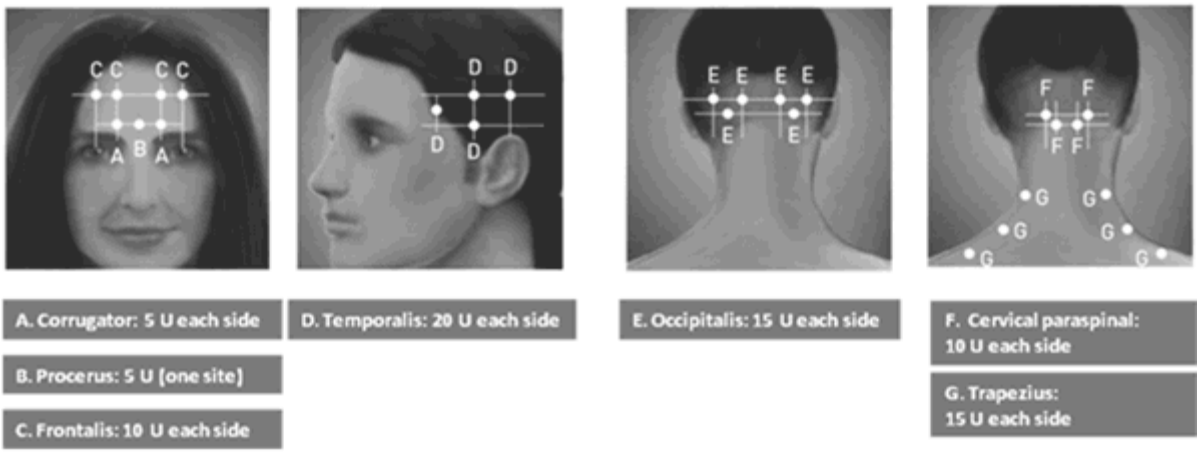

Figure 1. Injection sites for chronic migraine, from the summary of product characteristics

2.2 The summary of product characteristics lists the following adverse reactions for botulinum toxin type A: blepharospasm, cervical dystonia, paediatric cerebral palsy, primary hyperhidrosis of the axillae and focal spasticity of the upper limb associated with stroke. It states that 'in general, adverse reactions occur within the first few days following injection and are transient'. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The net price of a 200-unit vial is £276.40 (excluding VAT; 'British national formulary' [BNF] edition 62). The manufacturer estimates that the administration cost is £73 per treatment, based on a total treatment time of less than 30 minutes. The

total cost for treatment and administration of treatment per 12 week cycle, assuming no vial sharing, is therefore expected to be £349.40. Costs may vary in different settings because of negotiated procurement discounts.

2.4 The manufacturer envisages that botulinum toxin type A will be administered by people experienced and trained in injecting, and that treatment with botulinum toxin type A would be carried out in specialist centres where clinics for managing headache disorders are already in place, and would therefore not need additional infrastructure.

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal is '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.'

	Final scope issued by NICE	**Decision problem addressed in the manufacturer's submission**
Population	Adults with headaches on at least 15 days per month of which at least 8 days are associated with chronic migraine, and • whose condition has failed to respond to at least three prior pharmacological prophylaxis therapies and • medication overuse has been appropriately managed.	
Intervention	Botulinum toxin type A (Botox)	
Comparators	Standard management without botulinum toxin type A excluding invasive procedures	

	Final scope issued by NICE	Decision problem addressed in the manufacturer's submission
Outcomes	The outcome measures to be considered include: • frequency of headache days per month • frequency of migraine days per month • severity of headaches and migraines • number of cumulative hours of headache or migraine on headache or migraine days • reduction in acute pharmacological medication • adverse effects of treatment • health-related quality of life.	The outcome measures considered include: • frequency of headache days per month • severity of headaches • number of cumulative hours of headache or migraine on headache or migraine days • reduction in acute pharmacological medication • adverse effects of treatment • health-related quality of life.

The outcomes addressed by the manufacturer are as defined in the scope, with the exception of severity of migraines and migraine days, which have not been assessed separately because of the lack of relevant data for these outcomes.

	Final scope issued by NICE	Decision problem addressed in the manufacturer's submission
Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY). The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs considered from an NHS and Personal Social Services perspective.	

The ERG points out that the timescale of the modelling is 2 years.

	Final scope issued by NICE	Decision problem addressed in the manufacturer's submission
Other considerations	If evidence allows, people with or without medication overuse should be considered as subgroups.	

3.2 In its submission to NICE, the manufacturer positioned botulinum toxin type A as a preventative treatment targeted towards people with chronic migraine who have previously received three or more oral preventative headache treatments (or are unable to receive such treatments), and who are under the care of a headache specialist in a secondary care centre. It also presented evidence relating to people with chronic migraine who have previously received one or more oral preventative headache treatments.

4 Clinical-effectiveness evidence

4.1 The manufacturer conducted a literature search to identify studies of botulinum toxin type A. It identified seven relevant studies, of which four were against an active comparator and were therefore excluded from consideration. Of the three remaining studies, two were large phase three studies and were the focus of the manufacturer's submission. The third was a small study (n = 60) that was not described.

4.2 Evidence from the two randomised controlled trials, PREEMPT 1 and PREEMPT 2 ('Phase 3 research evaluating migraine prophylaxis therapy'), was presented, as well as the pooled results from these trials. The studies were identically designed with a 56-week-treatment period. The first phase of the trial was a 24-week double-blind phase, in which patients received a series of 31–39 intramuscular injections of botulinum toxin type A or placebo (saline), at day 0 and week 12. In total, 688 people were recruited into the botulinum toxin type A arms of the trials and 696 into the placebo arms. Patients were stratified by their use of acute headache pain medication at baseline.

4.3 From week 24–56, patients entered into a 32-week, open-label phase in which all patients continuing in the studies received botulinum toxin type A at weeks 24, 36 and 48. Patients in both arms were allowed to receive acute rescue medication to manage headache.

4.4 Men and women aged 18–65 years with a history of migraine headache disorder were eligible for enrolment. All patients had to have had at least 15 headache days in the 28 days before week 0. At least 50% of headache days had to be migraine or probable migraine days. PREEMPT 1 recruited people from the USA and from Canada, whereas PREEMPT 2 recruited people from North America and from Europe, including people from the UK.

4.5 Patients were excluded if they used headache preventative medications within 4 weeks of the start of baseline. Investigators excluded patients whose headache they attributed to other disorders such as medication overuse, however, chronic migraine patients with protocol defined excessive use (overuse) of acute medications were included.

4.6 Baseline characteristics of the trials were similar, as shown in table 1. There were no statistically significant differences between baseline characteristics in the treatment groups in PREEMPT 2 ($p < 0.05$). In PREEMPT 1, most differences between groups were statistically non-significant, except for mean headache episodes and mean migraine episodes, which were slightly lower in the botulinum toxin type A treatment group compared with the placebo group; and the number of cumulative headache hours, which was higher in the botulinum toxin type A group than in the placebo group. The majority of

people overused acute pain medication (> 64%) and had tried at least one preventative treatment (> 61%). Approximately 90% of patients (n = 1236) completed the 24-week double-blind phase of the trials and over 70% completed the 32-week open-label phase (n = 1005)

Table 1. Baseline characteristics (week 0) of PREEMPT 1 and PREEMPT 2 (adapted from tables 5.7 and 5.8 of the manufacturer's submission)

	PREEMPT 1			PREEMPT 2		
Characteristics	Botulinum toxin type A (n = 341)	Placebo (n = 338)	p value	Botulinum toxin type A (n = 347)	Placebo (n = 358)	p value
Mean age (years)	41.2	42.1	0.317	41.0	40.9	0.849
Mean time since onset of chronic migraine (years)	20.3	20.6	0.839	18.5	17.6	0.279
Women (%)	89.1	85.8	0.187	86.2	84.6	0.565
White (%)	89.4	91.4	0.381	89.9	89.7	0.913
During baseline (week -4 to week 0)						
Mean headache episodes (SD)	12.3 (5.23)	13.4 (5.71)	0.023	12.0 (5.27)	12.7 (5.29)	0.067
Mean headache days (SD)	20.0 (3.73)	19.8 (3.71)	0.571	19.9 (3.63)	19.7 (3.65)	0.682
Mean migraine days (SD)	19.1(4.04)	19.1(4.05)	0.978	19.2 (3.94)	18.7 (4.05)	0.156
Mean migraine episodes (SD)	11.5 (5.06)	12.7 (5.72)	0.006	11.3 (4.99)	11.7 (5.08)	0.067
Cumulative headache hours occurring on headache days (SD)	295.7 (116.8)	274.9 (110.9)	0.022	296.2 (121.0)	287.2 (118.1)	0.311
Patients who overused acute headache pain medications (%)	66.3	69.8	0.322	63.4	62.6	0.819
≥1 headache prophylaxis medication (%)	59.5	64.2	0.210	64.0	66.2	0.536
SD, standard deviation.						

4.7 All efficacy analyses from the two trials used the intent-to-treat population, which included all randomised patients. Results for most of the trial outcomes were statistically significant. The reduction in frequency of headache days was statistically significant in both trials. In PREEMPT 1, there was a reduction

of 7.8 days from 20.0 (per 28 days) at baseline for patients treated with botulinum toxin type A , compared with a reduction of 6.4 days from 19.8 for those in the placebo arm ($p = 0.006$). In PREEMPT 2, there was a reduction of 9.0 headache days from a baseline of 19.9 in the botulinum toxin type A arm, compared with a reduction of 6.7 days from a baseline of 19.7 days for those in the placebo arm ($p < 0.001$). The difference between the two arms of the trials for the frequency of headache episodes was not significant in the PREEMPT 1 trial, but was statistically significant in the PREEMPT 2 trial. The following were statistically significantly lower in the botulinum toxin type A arm compared with the placebo arm in both trials: total cumulative hours of headache on headache days, the frequency of: migraine days, migraine episodes, and moderate to severe headache days. The pooled results of the two trials are presented in table 2, and were consistent with the results from the individual studies: for the outcome of frequency of headache days (per 28 days), the pooled botulinum toxin type A group had a statistically significant reduction of 8.4 days from 19.9 days at baseline, compared with a reduction of 6.6 from 19.8 days in the pooled placebo group ($p < 0.001$).

Table 2. Pooled trial results from PREEMPT 1 and PREEMPT 2, at week 24 (adapted from tables 5.26, 5.27 and 5.28 of the manufacturer's submission and from table 6 of the ERG report).

	PREEMPT pooled data – change from baseline			
Outcome	Botulinum toxin type A (n = 688)	Placebo (n = 696)	Botulinum toxin type A–placebo difference (95% CI)	p value
Frequency of headache days	−8.4	−6.6	−1.8 (−2.52, −1.13)	< 0.001
Frequency of migraine days	−8.2	−6.2	−2.0 (−2.67, −1.27)	< 0.001
Frequency of moderate/severe headache days	−7.7	−5.8	−1.9 (−2.62, −1.26)	< 0.001
Cumulative total headache hours on headache days	−119.7	−80.5	−39.2 (−48.40, −21.04)	< 0.001
Frequency of headache episodes	−5.2	−4.9	−0.3 (−1.17, −0.17)	0.009
Frequency of migraine episodes	−4.9	−4.5	−0.4 (−1.20, −0.23)	0.004
Frequency of acute headache medication days	−6.1	−5.3	−0.8 (−1.53 to −0.15)	0.016
Frequency of triptan intakes	−3.2	−2.1	−1.1 (−1.74, −0.61)	< 0.001
Frequency of acute headache pain medication intakes (all categories)	−10.1	−9.4	−0.7 (−2.68 to 0.69)	0.247

4.8 Responses to the condition-specific health related quality of life measures, the headache impact test 6 (HIT-6) and the migraine specific quality of life questionnaire (MSQ), were collected during the trials. The HIT-6 was developed for use in people with general headache whereas the MSQ was developed specifically for people with chronic migraine. At baseline, the HIT-6 scores in both arms of each trial were between 65 and 66 (where scores of 78 are associated with the greatest impact

on life and a score of 36 being the least). At 24 weeks, there was a statistically significant improvement in quality of life as measured by the HIT-6 for people in the botulinum toxin type A arm compared with those in the placebo arm: in the PREEMPT 1 trial a reduction of 4.7 points was observed compared with a reduction of 2.7 points respectively ($p < 0.001$), and in PREEMPT 2, a reduction of 4.9 points compared with 2.4 points respectively ($p < 0.001$) was observed. Quality of life as measured by the MSQ was also statistically significantly improved in the botulinum toxin type A arm compared with the placebo arm in both trials ($p < 0.01$). See pages 74, 75 82 and 83 of the manufacturer's submission for further details.

4.9 The most frequently reported adverse events to occur at a higher incidence in the pooled botulinum toxin type A group than in the pooled placebo group were: neck pain, headache, migraine, eyelid ptosis, musculoskeletal stiffness and muscular weakness. Of these, neck pain was the only one to occur at a rate of greater than or equal to 5% in the pooled botulinum toxin type A arm compared with the pooled placebo arm. In addition, the manufacturer noted that over 20 years of safety data on the use of botulinum toxin type A (for a range of conditions) is available. See page 98 onwards of the manufacturer's submission for further information about adverse events.

4.10 A subgroup analysis was conducted on treatment efficacy in people with and without evidence of acute medication overuse. Acute medication overuse was defined as intake during baseline of simple analgesics on 15 or more days, or other medication types or combination of types for 10 or more days, with intake on two or more days per week. Over 60% of

patients had evidence of medication overuse. The results of this analysis were mixed in terms of treatment effectiveness. Reduction in the frequency of headache days for people on botulinum toxin type A compared with placebo was statistically significant in both trials for those who were overusing acute medication. For those who were not overusing acute medication, for frequency of headache days there was no statistically significant difference between treatment groups with a p value of 0.05. The difference in change from baseline for frequency of headache episodes was non-significant for three out of the four populations examined; however in the PREEMPT 2 trial, for people who were overusing acute medication, a statically significant result was obtained. The pooled subgroup analysis of the two trials are presented in table 3, and were consistent with the results from the individual studies.

Table 3. Pooled subgroup analyses for efficacy for people with and without evidence of medication overuse (adapted from table 9 of the ERG report).

	PREEMPT Pooled data			
Efficacy variable (per 28 days)	Botulinum toxin type A	Placebo	Botulinum toxin type A–placebo difference	p value
Overusing (n)	445	459		
Frequency of headache episodes				
Mean baseline	12.8	13.8		
Mean change from baseline	−5.4	−4.9	−0.6	0.028
Frequency of headache days				
Mean baseline	20.1	19.8		
Mean change from baseline	−8.2	−6.2	−2	< 0.001
Not overusing (n)	243	237		
Frequency of headache episodes				
Mean baseline	10.9	11.4		
Mean change from baseline	−5	−4.6	−0.4	0.146
Frequency of headache days				
Mean baseline	19.6	19.7		
Mean change from baseline	−8.8	−7.3	−1.5	0.013
See tables 5.17, 5.18, 5.23 and 5.24 of the manufacturer's submission for results from the two trials reported separately.				

4.11 A further subgroup analysis was conducted for people who had previously received three or more headache preventative medications, for the outcome of frequency of headache days (per 28 days), using the pooled data from the PREEMPT trials. The manufacturer pointed out that the PREEMPT trials were not powered to detect a difference in this subgroup. Approximately 35% of the patients in the trials had received three or more prior preventative treatments. In the botulinum

toxin type A arms of the trials, [redacted] patients met this criteria compared with [redacted] in the placebo arms. A [redacted] in the frequency of headache days of [redacted] days from a baseline of [redacted] was observed for the botulinum toxin type A arm compared with a [redacted] of [redacted] days from a baseline of [redacted] days in the placebo arm [redacted]. Treatment efficacy in terms of frequency of headache days was similar for the subgroup of people who had previously received three or more preventative treatments, those who had previously received two preventative treatments, and those who had previously received one or more preventative treatments. See page 93 of the manufacturer's submission for further details.

ERG comments

4.12 The ERG thought that the trials were generally of good quality. The ERG pointed out that in the PREEMPT 1 trial, patients in the botulinum toxin type A group had at baseline a statistically significantly lower frequency of migraine episodes (11.5 versus 12.7, p = 0.006) and frequency of headache episodes (12.3 versus 13.4, p = 0.023), but had significantly more cumulative hours of headache occurring on headache days (295.7 versus 274.9, p = 0.022) compared with those in the placebo group. The original primary outcome in PREEMPT 1 was to have been frequency of headache episodes, but this was changed to headache days for reasons that seem reasonable to the ERG.

4.13 The ERG found botulinum toxin type A to be effective regardless of the number of previous oral preventative medications taken and that as the number of previous oral preventative medications rose, so did the relative effectiveness of botulinum toxin type A compared with placebo. In addition, the ERG explained that the placebo

effect decreased as the number of previous medications increased.

4.14 The ERG thought that a striking feature of the data was the size of the improvement on placebo, with the placebo effect lasting for at least 24 weeks. In addition the ERG pointed out that the efficacy of botulinum toxin type A was greatest with the first injection and that the second injection had much less effect, with similar efficacy observed to that of the second placebo injection. The ERG therefore queried whether the effect of botulinum toxin type A treatment lasts longer than 12 weeks and whether a negative stopping rule could be applied after the first injection.

4.15 The ERG's main concern was about whether blinding was maintained and if not, what the effect of this was on the results of the trials. The ERG pointed out that in previous botulinum toxin type A trials, 70% of patients receiving botulinum toxin type A correctly guessed what they had received, because of the changes in muscle tone, such as reduced wrinkling of foreheads. The ERG further explained that because unblinding is a significant factor in controlled trials of preventative treatment of chronic migraines, the International Headache Society guidelines recommend that subjects and investigators should be questioned at the end of trials about whether they thought the subject was assigned to the active or placebo group during study. However that this was not done in the PREEMPT trials.

5 Comments from other consultees

5.1 Approximately 25 million days a year are lost from work or education in the UK because of migraine, most of which are

lost by the 10% of people with the most severe symptoms. It is one of the 20 most disabling conditions and has a major impact on people's ability to work and to interact with one another.

5.2 Consultees were very positive about the treatment of migraine with botulinum toxin type A. One commented that after treatment they could '...regain some normality in my life and not have to spend periods of time in bed in the dark, I have been able to go back to work, spend time with friends, go running etc.'. Some people have reported having their lives 'transformed' after having botulinum toxin type A.

5.3 It was pointed out that other medications used to treat chronic migraine have side effects that in some cases were described as 'unbearable', whereas botulinum toxin type A has few, and those that do occur are localised and fade with the metabolism of the treatment. Some consultees remarked that it is an important addition to the treatment strategies available.

5.4 Botulinum toxin type A has advantages in the infrequent dosing schedule, being a long-lasting treatment; repeat administration is only necessary every 12 weeks (some report this being carried out every 6 months, in practice) and so there is adherence to treatment. Botulinum toxin type A was said to be simple to administer, taking 10–15 minutes in 'experienced hands'. In addition it is well tolerated and the taking of tablets is not necessary. The one disadvantage of treatment raised is the number of injections to the head that are necessary, particularly for those who have trypanophobia (fear of needles).

5.5 One consultee suggested that a treatment duration for botulinum toxin type A could be between 12 and 18 months, as is currently the case for a considerable amount of people for

whom oral preventative treatments for chronic migraine are prescribed.

5.6 Botulinum toxin type A is currently available to private funders, or to those who successfully apply for funding through the NHS. It is therefore being used in the UK, although there is reported to be a large variation in its use in the NHS. It is administered by specialists, and consultees considered that this was appropriate.

5.7 Some consultees thought that further training would be needed on giving the injections; others thought that further training would not be necessary as it seems that most specialists have already been trained in the procedure by the manufacturer: over 100 professionals have been trained to date. Training is reported to be straightforward and the potential for harm in the delivery is said to be small.

5.8 One professional group suggested that botulinum toxin type A should be offered to people whose condition has failed to respond to at least two preventative medications, and that no more than three medications should be tried. One consultee commented that it is not ethically appropriate to require failure of more drug families than are licensed, pointing out that beta blockers and topiramate are the only licensed agents.

5.9 One consultee remarked that botulinum toxin type A is either: ineffective over the first few treatments and can be stopped; breaks the cycle (may be needed intermittently in the future); or builds up effect over the first few cycles and is then consistent in its action.

5.10 Comments from professionals who administer botulinum toxin type A were consistent in remarking that if a patient's condition doesn't respond to two rounds of treatment, they would not receive further cycles of treatment. It was suggested that treatment response be assessed after two sets of injections, and for those whose condition does not respond sufficiently, further treatment with botulinum toxin type A would not be offered.

5.11 Medication overuse was highlighted as an issue, and the fact that it is unclear in some cases whether this is the cause or the outcome of chronic migraine. Before considering treatment with botulinum toxin type A, it was suggested that all candidates for treatment have a 4-week analgesic dose reduction, to deal with medication overuse headache.

6 Cost-effectiveness evidence

6.1 No relevant published cost-effectiveness studies were identified by the manufacturer. The manufacturer developed a Markov model using the pooled data from the two PREEMPT trials, comparing botulinum toxin type A with 'off treatment'. Because only approximately 35% of the population met the criteria set out in the NICE scope (patients for whom three or more prior pharmacological therapies had failed), the manufacturer used the population for whom one or more pharmacological therapies had failed, which was approximately 64% of the trial populations.

6.2 The Markov model has six distinct health states, as well as a death state (to capture background mortality), defined by number of headache days per 28 days:

- 24–28 headache days
- 20–23 headache days
- 15–19 headache days
- 10–14 headache days
- 4–9 headache days
- 0–3 headache days.

6.3 Patients can enter the model in any of the chronic migraine states, where chronic migraine is defined as 15 headache days or more per 28 days. The model uses the transition probabilities observed in the clinical trials in its model. The cycle length is 12 weeks, which is the same interval as the administration of botulinum toxin type A in the trials. The time horizon used in the model is 2 years, in line with the expected maximum treatment duration with botulinum toxin type A. For the first of the 2 years, trial data were used if possible, with extrapolation used for the second year, using the last observations from the trial.

6.4 In addition to using the discontinuation data observed in the clinical trials in the model, there were two treatment (dis)continuation rules applied. The negative stopping rule applied to people whose condition responded insufficiently to botulinum toxin type A, which was quantified as people not experiencing an improvement in at least two health states (a reduction of at least 4 headache days per 28 days) following two successive cycles of treatment. After discontinuation, they moved into the off-treatment arm of the model. The positive

stopping rule referred to people whose condition was responding well to treatment. These were those who stopped being in the chronic migraine classification (15 or more headache days per 28 days) and moved to an episodic migraine classification (fewer than 15 headache days per 28 days). In such cases, the clinician may attempt to withdraw treatment. The model assumes that after 1 year, those who have reached an episodic frequency stop treatment with botulinum toxin type A. See pages 132 onwards of the manufacturer's submission for further details.

6.5 Two mapping equations were derived to map the MSQ (as collected during the trials) to EQ-5D utility, so that utilities could be attached to each health state. One equation was used to predict utility scores for people in the chronic migraine health states, and the other was used for predicting utilities in the episodic health states. The ordinary least squares equations had as explanatory variables: [redacted] Utility was assumed to differ for each person in the model and was assumed to be different between treatments, which was justified on the grounds that treatment with botulinum toxin type A was shown to affect the severity and intensity of headaches, as well as the number of headache days. Utility was predicted for each health state using the patient-level data from the trials. This was done by grouping patients as per the health states and calculating the mean utility per group. Utility values used in the model ranged between 0.479 and 0.746 depending on the treatment and on

the number of headaches experienced. See page 151 onwards of the manufacturer's submission for further information.

6.6 Adverse events affecting health-related quality of life were captured in the model through the discontinuation rates applied and through the use of patient-level data in the prediction of utility. No additional costs relating to adverse events were assumed to occur.

6.7 It was assumed that the relevant patient population would be managed in a specialist setting, with costs relating to that of a consultant. Administration time was assumed to be 30 minutes, at a mean cost of £73. Cost of treatment was calculated based on one 200-unit vial of botulinum toxin type A at £276.40, with no potential for vial sharing, leading to a total cost of £349.40 per 12 week cycle. For people on standard care, the cost was assumed to be £36.50 per 12 weeks, which is based on an appointment with a consultant every 24 weeks to optimise acute therapy. Costs for GP visits, accident and emergency visits, hospitalisation and the cost of triptan were modelled for each health state. Costs and QALYs were discounted at a rate of 3.5% per annum.

6.8 In the base case, for people whose condition failed to respond to at least three prior pharmacological preventative therapies, the discounted total cost and QALYs for placebo were £1895 and 1.20 respectively, compared with a total cost of £2438 and 1.29 QALYs for botulinum toxin type A. This gave an incremental cost and incremental QALYs of £543 and 0.09 respectively and an ICER of £6083 per QALY gained for botulinum toxin type A compared with placebo. The probability that botulinum toxin type A was cost effective in the base case

was 69.1% at a threshold of £20,000 per QALY gained. For the wider population that included those whose condition had not responded to one or more prior preventative treatments, the costs and QALYs were similar, with an ICER of £5828 per QALY gained for botulinum toxin type A compared with placebo.

6.9 The manufacturer presented a variety of sensitivity analyses, and for the majority of cases the ICER for botulinum toxin type A compared with placebo stayed under £10,000 per QALY gained. Excluding patients who overused acute medication slightly increased the ICER to £5971 per QALY gained. Excluding the positive and negative stopping rules increased the ICER to £15,294 per QALY gained. Restricting the time horizon to 1 year increased the ICER to £14,098 per QALY gained. Adopting a so called societal view, in which lost work time was incorporated into the analysis based on average earnings of £14.60 per hour, reduced the ICER to £4033 per QALY gained. The manufacturer noted that this did not capture the full societal cost of migraine because other factors such as lost family and personal time, opportunities at work and lost education time had not been included. See page 175 onwards of the manufacturer's submission for further details of the sensitivity analyses.

ERG comments

6.10 The ERG found the manufacturer's model to be reasonable for the decision problem. The ERG thought that the negative stopping rule at 24 weeks in the model was reasonable. The ERG suggested that the requirement for an improvement could be based on either one or two health states, and found that an improvement of only one health state within two cycles

increases the ICER for the three prior pharmacological preventative therapies from £6083 per QALY gained to £8354 per QALY gained.

6.11 The ERG questioned the likelihood in practice of implementing a positive stopping rule for people who have moved from having chronic migraines to episodic migraines at 48 weeks. It also questioned how long people who have stopped treatment would remain stable before needing re-treatment. The ERG found that removing the positive stopping rule roughly doubled the ICER for the three prior pharmacological preventative therapies from £6083 per QALY to £12542 per QALY gained.

6.12 The ERG noted that the construction of the transition probability matrices for cycles 3, 4 and 5 in the botulinum toxin type A arm of the model was unusual in that the data are not specific to the time frames of these cycles, but rather are pooled between them. Alternative approaches may increase the ICER by between 5% and 10%.

6.13 The ERG explained that the model submitted by the manufacturer is non-linear, with the probabilistic estimate of cost effectiveness being more than double that of the deterministic estimate. Some elements of the probabilistic modelling as submitted by the manufacturer seem unwarranted; for example, treating the identity matrix as having an uninformed prior and modelling it probabilistically. The ERG found that removing these elements reduced the degree of non-linearity but did not eliminate it. The ICER for the three prior pharmacological preventative therapies group increased from the manufacturer's deterministic ICER of £6083 per QALY gained to the probabilistic ICER of £11,447 per QALY gained if

the ERG revisions are applied and to the probabilistic ICER of £14,004 per QALY gained estimated if the ERG revisions are not applied.

6.14 The ERG had some concerns about the estimation of utilities. Botulinum toxin type A is anticipated to result in additional quality of life gains over placebo for a given health state. The manufacturer supplied some supporting data for this. But a particular concern for the ERG was that the utility values and botulinum toxin type A increments were estimated from the one or more prior preventative therapies patient population, and then applied to the three prior preventative therapies patient population. The ERG did not consider that the manufacturer demonstrated that similarly large utility increments for a given health state would apply within the three prior preventative therapies patient population. The ERG pointed out that these within-health-state utility increments account for around half of the estimated treatment benefit of botulinum toxin type A compared with placebo.

6.15 The ERG applied the following alternative assumptions to the manufacturer's base case model to get revised estimates of cost effectiveness (see page 120 onwards of the ERG report for more information):

- The neurology outpatient consultant face to face follow-up cost of £140, for botulinum toxin type A administration and placebo follow-up. The ERG explained that the cost of a botulinum toxin type A administration based upon 30 minutes of consultant time may be too optimistic and that it might be more appropriate to instead apply the consultant-led follow-up neurology outpatient cost of £140.
- Placebo routine care costs are incorporated for those stopping therapy in the botulinum toxin type A arm. In the manufacturer's model, those stopping therapy because of lack of efficacy are assumed to incur no ongoing routine care costs, which benefits the botulinum toxin type A arm. See page 111 of the ERG report for further details.
- The resource use estimates specified within Blumenfeld and colleagues (2010), as the ERG believed the costs offsets were overestimated in the manufacturer submission (see page 105 onwards of the ERG report for further details).
- The transition probability matrices from the three prior preventative therapies patient subgroup (for reasons described in section 6.12).
- An average accident and emergency cost of £77 be used rather than the £90.94 in the manufacturer's calculation, as the ERG explains that its calculation is based on a larger subset of patients from the same study.

6.16 In all cases the ERG focused on the population whose condition failed to respond to at least three prior pharmacological preventative therapies, as specified in the scope. Because of its concerns about the use of the positive stopping rule in practice, the ERG conducted sensitivity analyses without the positive stopping rule applied.

Table 4. Costs, QALYs and ICERs for the ERG revisions

	Costs	QALYs	Δ Costs	Δ QALYs	ICER
Deterministic analysis **with** positive stopping rule applied					
Placebo	£1657	1.20			
Botulinum toxin type A	£2573	1.29	£916	0.09	£10,257
Probabilistic analysis **with** positive stopping rule applied					
Placebo	£1457	1.16			
Botox	£2513	1.22	£1,056	0.07	£16,165
Deterministic analysis **without** positive stopping rule					
Placebo	£1657	1.20			
Botulinum toxin type A	£3167	1.29	£1,510	0.09	£17,517
Probabilistic analysis **without** positive stopping rule					
Placebo	£1466	1.16			
Botulinum toxin type A	£3114	1.22	£1,646	0.06	£26,494
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.					

6.17 As shown in table 4, there was a substantial difference between the ICERs of the deterministic analysis (£10,257 per QALY gained), compared with those from the probabilistic analysis (£16,165 per QALY gained). The ERG reported that at a threshold of £20,000 per QALY gained, there is a 67% chance that botulinum toxin type A is cost effective, whereas as at a threshold of £30,000 per QALY gained, there is an 87% chance of it being cost effective.

6.18 Removing the positive stopping rule also had a substantial impact on the ICER, increasing it from £10,257 to £17,517 for the deterministic analysis and from £16,165 to £26,494 for probabilistic analysis. The ERG found that at a threshold of £20,000 per QALY gained, there is a 19% chance that botulinum toxin type A is cost effective, whereas as at a threshold of £30,000 per QALY gained, there is a 60% chance of it being cost effective.

6.19 The ERG concluded that the outputs from its revised assumptions, as described above, correspond well with those of the manufacturer's model.

7 Equalities issues

7.1 No relevant equalities issues were raised during scoping or by the manufacturer.

8 Innovation

8.1 The manufacturer notes that botulinum toxin type A is the first and only treatment licensed for the treatment of headaches in adults with chronic migraine. Some consultees considered that compared with many preventative oral medications, botulinum toxin type A has a favourable tolerability and adverse event profile. Furthermore, as treatment is administered every 12 weeks, there would be no issues with treatment compliance.

9 Authors

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Appendix A: Supporting evidence

Related NICE guidance

Published

- Percutaneous closure of patent foramen ovale for recurrent migraine. NICE interventional procedure guidance (2010). Available from www.nice.org.uk/guidance/IPG370
- Deep brain stimulation for intractable trigeminal autonomic cephalalgias. NICE interventional procedure guidance (2011). Available from www.nice.org.uk/guidance/IPG381

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Diagnosis and management of headaches in young people and adults. NICE clinical guideline. Earliest anticipated date of publication December 2012.