NICE National Institute for Health and Care Excellence

NICE guidance

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

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

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), only if:

- at least 3 preventive medicines have not worked, or are not tolerated or are unsuitable because of safety concerns, and
- the condition is appropriately managed for medication overuse.

1.2 Treatment with botulinum toxin type A that is recommended according to section 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 2 treatment cycles) or
- has changed to episodic migraine (defined as fewer than 15 headache days per month) for 3 consecutive months.

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

2 The technology

2.1 Botulinum toxin type A (Botox, Allergan) is a purified neurotoxin complex, which is derived from the bacterium Clostridium botulinum. It has neuromuscular transmitter blocking effects. It 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 to 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 (see the summary of product characteristics).

2.2 The summary of product characteristics lists the following common adverse reactions that may be associated with botulinum toxin type A treatment: headache, migraine, facial paresis, eyelid ptosis, pruritus, rash, neck pain, myalgia, musculoskeletal pain, musculoskeletal stiffness, muscle spasms, muscle tightness, muscular weakness, and injection site pain. It states that 'in general, adverse reactions occur within the first few days following injection and while generally transient, may have a duration of several months or, in rare cases, longer'. 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; BNF edition 63). 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 by the manufacturer to be £349.40. Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee considered evidence submitted by the manufacturer of botulinum toxin type A and a review of this submission by the Evidence Review Group (ERG).

3.1 The decision problem defined in the scope asked whether botulinum toxin type A is clinically and cost effective in adults whose chronic migraine has failed to respond to at least 3 prior pharmacological prophylaxis therapies and whose medication overuse has been appropriately managed, compared with standard management without botulinum toxin type A excluding invasive procedures. The manufacturer addressed this decision problem in its submission by carrying out a sensitivity analysis.

Clinical effectiveness

3.2 To establish the efficacy of botulinum toxin type A, the manufacturer performed a systematic review to identify randomised controlled trials comparing botulinum toxin type A with placebo. The manufacturer identified 7 relevant trials, of which 4 were against an active comparator and were excluded from consideration. Of the 3 remaining trials, 2 were large phase 3 trials and were the focus of the manufacturer's submission. The third was a small trial (n=60) that was excluded from further discussion because of concerns regarding its quality and relevance to the decision problem.

3.3 Evidence from the 2 randomised controlled trials, PREEMPT 1 and PREEMPT 2 (phase 3 trials evaluating migraine preventive therapy), was presented, as well as the pooled results from these trials. The trials were identically designed with a 56-week treatment period. 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. The first phase of the trial was a 24-week double-blind phase, in which patients received a series of 31 to 39 intramuscular injections of botulinum toxin type A or placebo (saline), at day 0 and week 12. In the second phase of the trial, from week 24 to

56, patients entered into a 32-week, open-label phase in which all patients continuing in the trials received botulinum toxin type A at weeks 24, 36 and 48.

3.4 The PREEMPT trials enrolled people aged 18 to 65 years who had chronic migraine. All patients had to have had at least 15 headache days in the 28 days before week 0, and at least 50% of headache days had to be migraine or probable migraine days. Most people in the trials received at least 1 prior preventive treatment (approximately 64%), and approximately 35% of the patients had received 3 or more prior preventive treatments. Most people in the trials overused acute pain medication (more than 64%). The PREEMPT trials recruited people from North America and Europe, including from the UK. Patients were excluded if they used headache preventive medications within 4 weeks of the start of baseline, or if their headache was attributed to other disorders such as medication overuse. However, chronic migraine patients with protocol-defined overuse of acute medications were included and this was a stratification factor at randomisation.

3.5 The characteristics of the patients in the trials were similar, with no statistically significant differences between baseline characteristics in the PREEMPT 2 trial. In PREEMPT 1, most differences between groups were statistically non-significant, except for mean headache episodes and mean migraine episodes, which were lower in the botulinum toxin type A group compared with the placebo group, and the number of cumulative headache hours, which were higher in the botulinum toxin type A group compared with the placebo group.

3.6 All efficacy analyses from the 2 trials used the intention-to-treat population, which included all randomised patients. The reduction in frequency of headache days (the primary endpoint) was statistically significant in both trials. In PREEMPT 1, there was a reduction of 7.8 headache days from 20.0 (per 28 days) at baseline for patients treated with botulinum toxin type A, compared with a reduction of 6.4 headache days from 19.8 at baseline 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 headache days from a baseline of 19.7 days for those in the placebo arm ($p<0.001$). The difference between the 2 arms of the trials for the frequency of headache episodes was not statistically 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, and moderate to severe headache days. There was no difference in the intake of acute pain medication between the arms in both studies, although there was statistically significant lower triptan use in the botulinum toxin type A arm. The pooled results of the 2 trials 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 headache days from 19.9 days at baseline, compared with a reduction of 6.6 headache days from 19.8 days in the pooled placebo group ($p<0.001$).

3.7 The PREEMPT trials measured health-related quality of life, using the headache impact test 6 (HIT-6) and the migraine-specific quality-of-life questionnaire (MSQ). The HIT-6 was developed for use in people with general headache whereas the MSQ was developed specifically for people with chronic migraine. At 24 weeks, there were statistically significant improvements from baseline in quality of life as measured by the HIT-6 and the MSQ for people in the botulinum toxin type A arm compared with those in the placebo arm in both trials.

3.8 The most frequently reported adverse reactions occurring 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 1 to occur at a rate of 5% or more in the pooled botulinum toxin type A arm compared with the pooled placebo arm.

3.9 A subgroup analysis was conducted for people who had previously received 3 or more headache preventive medications, for the outcome of frequency of headache days (per 28 days), using the pooled data from the PREEMPT trials (231 people in the botulinum toxin type A arm and 248 in the placebo arm). The pooled botulinum toxin type A group had a statistically significant reduction of 7.4 headache days from 20.0 days at baseline, compared with a reduction of 4.7 headache days from 20.2 days at baseline in the pooled placebo group ($p<0.001$). Treatment efficacy for frequency of headache days was similar for the subgroup of people who had previously received 3 or more preventive treatments, those who had previously received 2 preventive treatments, and those who had

previously received 1 or more preventive treatments.

Cost effectiveness

Original submission

3.10 The manufacturer carried out a systematic review for economic evaluations of botulinum toxin type A for people with chronic migraine, but no relevant published studies were identified.

3.11 The manufacturer developed a Markov model using the pooled data from the 2 PREEMPT trials, comparing botulinum toxin type A with placebo. Only approximately 35% of the population met the criteria set out in the NICE scope (people whose condition has failed to respond to 3 or more prior pharmacological prophylaxis therapies). Because of the similarity in efficacy, (see section 3.9) the manufacturer used the population whose condition had failed to respond to 1 or more pharmacological therapies, which was approximately 64% of the trial population, in order to increase the statistical power.

3.12 Six health states were defined in the model according to the number of headache days per month: 0 to 3 (health state 1), 4 to 9 (health state 2), 10 to 14 (health state 3), 15 to 19 (health state 4), 20 to 23 (health state 5) and 24 or more (health state 6). Patients could enter the model in any of the 3 chronic migraine states (health states 4,5 or 6); chronic migraine was defined as 15 headache days or more per 28 days. The cycle length was 12 weeks, which is the same as the frequency of administration of botulinum toxin type A in the trials. The model used the transition probabilities observed in the clinical trials, which include the transitions between the 6 health states as well as an additional transition to discontinuation of therapy. For the placebo arm, the second cycle transition probability was repeatedly applied after week 24. For the botulinum toxin type A arm, the same transitional probability matrix was applied for the third, fourth and fifth cycles; this figure was calculated by averaging these 3 cycles. For people continuing on treatment in cycles 6 to 9, the same average figure was used. The time horizon used in the model was 2 years, in line with the manufacturer's 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.

3.13 As well as using the discontinuation data from the clinical trials in the model, 2 treatment (dis)continuation rules were applied. A negative stopping rule was applied at week 24 for people whose condition responded insufficiently to botulinum toxin type A. Insufficient response was defined as people having an improvement of less than 2 health states (a reduction of between 5 and 10 headache days per 28 days depending on both the number of headache days and the corresponding health state at the start of treatment) after 2 successive cycles of treatment. After discontinuation, they moved between health states using the transition probabilities for placebo treatment, but did not incur treatment costs. A positive stopping rule was applied at week 48 for people whose condition had changed to episodic migraine (fewer than 15 headache days per 28 days). The model assumed that after 1 year, people whose condition had changed to episodic migraine stopped treatment with botulinum toxin type A and remained stable in the episodic migraine health states thereafter.

3.14 Two mapping equations were derived to map the MSQ data (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 utilities for people in the chronic migraine health states, and the other was used for predicting utilities in the episodic health states. Utility was different for each health state in this model and also between treatments within the same health state, the latter being justified on the grounds that treatment with botulinum toxin type A was shown to affect a broad range of relevant outcomes such as 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 by health state and calculating the mean utility per treatment 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. Adverse events affecting health-related quality of life were captured in the model by applying discontinuation rates. There were assumed to be no additional costs relating to adverse events.

3.15 The manufacturer assumed that chronic migraine in the relevant patient population would be managed in a specialist setting, with associated consultant-related costs. Administration time was assumed to be 30 minutes, at a cost of

£73.00. Cost of treatment was calculated based on one 200-unit vial of botulinum toxin type A at £276.40, with no vial sharing, leading to a total cost of £349.40 per 12-week cycle. For people in the placebo arm (standard care), the cost was assumed to be £36.50 per 12 weeks, which is based on a 15-minute appointment with a consultant every 24 weeks to optimise acute therapy. Costs for GP visits, accident and emergency attendance, hospitalisation and the cost of triptan were modelled for each health state but only 3 different costs were used: for health state 1, states 2 to 3 and states 4 to 6. These costs came from a poster by Bloudek et al. (2011) of Scottish resource use according to the International Burden of Migraine Study (IBMS). Costs and quality-adjusted life years (QALYs) were discounted at a rate of 3.5% per year.

3.16 For people whose condition failed to respond to at least 3 prior preventive medications, the total cost and QALYs for placebo were £1,895 and 1.20 respectively, compared with a total cost of £2,438 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 £6,083 per QALY gained for botulinum toxin type A compared with placebo. There was a 69.1% probability of botulinum toxin type A being cost effective if the maximum acceptable ICER was £20,000 per QALY gained. The manufacturer did not report a central estimate of the ICER calculated by probabilistic modelling. For the wider population, which included people whose condition had not responded to 1 or more prior preventive medications, the costs and QALYs were similar, with an ICER of £5,828 per QALY gained for botulinum toxin type A compared with placebo.

3.17 The manufacturer presented a variety of sensitivity analyses, and for most of the cases the ICER for botulinum toxin type A compared with placebo stayed under £10,000 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.

3.18 The manufacturer identified an error in its analyses, in which the original ICERs were based on utilities derived from all people in the trials. It submitted revised ICERs using utilities from people whose condition failed to respond to at least 3 prior preventive medications. After correcting for the error, the ICER for botulinum toxin type A compared with placebo increased from £6,083 to £6,434 per QALY gained.

ERG critique of original submission

3.19 The ERG noted that the trials were generally of good quality. The ERG pointed out that in the PREEMPT 1 trial, at baseline patients in the botulinum toxin type A group had a statistically significantly lower frequency of migraine episodes (11.5 compared with 12.7, p=0.006) and frequency of headache episodes (12.3 compared with 13.4, p=0.023), but had statistically significantly more cumulative hours of headache on headache days (295.7 compared with 274.9, p=0.022) than 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 because of new guidelines for the conduct of clinical trials in chronic migraine. This was considered reasonable by the ERG.

3.20 The ERG found botulinum toxin type A to be effective regardless of the number of previous preventive medications taken. As the number of previous preventive medications rose, so did the relative effectiveness of botulinum toxin type A compared with placebo (reductions of 2.3 and 2.7 headache days per month for the 1 prior preventive medication and 3 or more prior preventive medications subgroups respectively). In addition, the ERG observed that the placebo effect decreased as the number of previous preventive medications increased.

3.21 The ERG stated that a noticeable feature of the trial data was the size of the improvement on placebo, which lasted for at least 24 weeks and was only modestly less than on active treatment. 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 to that of the second placebo injection. The ERG therefore queried whether a negative stopping rule could be applied after the first injection.

3.22 The ERG's main concern about the design of the PREEMPT trials 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 changes in muscle tone such as reduced wrinkling of the forehead. The ERG further explained that because unblinding is an important factor in controlled trials of preventive 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 active or placebo was administered during the trial. This was not done in the PREEMPT trials.

3.23 The ERG considered the manufacturer's model to be reasonable for the decision problem. The ERG noted that the model and trial data sets for headache days per month at week 24 corresponded poorly and that this overestimated the net impact of botulinum toxin type A by 53%. Yet this overestimate had no direct impact on cost effectiveness because it was the distribution between health states that determined the costs and QALYs within the model. The ERG observed that within the validation data, the model and trial were reported by the manufacturer as having no patients in health states 5 and 6 at week 24 in the botulinum toxin type A arm. The ERG noted that this could be because of the negative stopping rule being applied in both sets of data, with these patients falling into the discontinuation category, but could not verify this. Uncertainty remained around this point and also the distribution between health states among those patients modelled as discontinuing because of the negative stopping rule, but who were followed up within the trial. The ERG noted that there were no clinical data to support the use of the 2 stopping rules. The ERG queried whether the negative stopping rule at 24 weeks in the model would apply in practice, and whether the requirement for an improvement could be based on either 1 or 2 health states. It found that an improvement of only 1 health state within 2 cycles increased the ICER for the 3 or more prior preventive medications subgroup from £6,083 per QALY gained to £8,354 per QALY gained. The ERG doubted that the positive stopping rule at week 48 was likely to be implemented. It queried how long people who had stopped treatment would remain stable before needing re-treatment, noting 2-year follow-up data from a published abstract by Rothrock et al. (2011), which estimated the duration of response to treatment with botulinum toxin type A based on a 50% reduction in the number of headache days per month. Of a total sample of 100 people whose chronic migraine responded to treatment with botulinum toxin type A, 68% maintained a good response to treatment with continued injections at a frequency of 3.2 months. A further 24% were able to stop treatment and maintain a good response for at least 6 months; and 8% relapsed back to chronic migraine. The ERG found that removing the positive stopping rule roughly doubled the ICER for the 3 or more prior preventive medications subgroup for botulinum toxin type A arm compared with placebo, from £6,083 per QALY to £12,542 per QALY gained.

3.24 The ERG noted that there were wide disparities between the model inputs for resource use used in the economic model, which were based on the poster by Bloudek et al., and those reported in a published paper by Blumenfeld et al. (2011). The ERG noted that the 2 sources had reported results from the same international study; however, Bloudek et al. appeared to include costs based on Scottish implementation, with no information on the number and ages of the patients, GP visits, hospital outpatient and accident and emergency attendances, hospital admissions or medication use. The ERG noted that because the higher costs for health states 4 to 6 were driven by hospital admission costs and were the same in each of the health states 4 to 6, details of the Bloudek et al. poster were important because it could be that the manufacturer's estimate of resource use was too high. It was for this reason that the ERG preferred the resource use detailed in Blumenfeld et al. which contained more detailed data. The ERG had concerns about the applicability of international data on hospital admission rates for chronic migraine to clinical practice in England and Wales, but recognised that Blumenfeld et al. contained the most detailed data available.

3.25 The ERG observed that utility values were calculated using MSQ estimations at 24 weeks, when the full effect of botulinum toxin type A had occurred. The ERG noted that the manufacturer's model generally assigned higher utility values for the botulinum toxin type A arm than the placebo arm for each health state and that this feature of the model accounted for about half of the anticipated QALY gain for botulinum toxin type A. It noted that for this to be valid, there would have to be a difference in other features such as: the number of headaches experienced during a headache day, the duration of these headaches, or the proportion of headaches that were migraines. The ERG noted that this was plausible, although it was unsure whether the substantial difference in utilities in each health state was justified given the small absolute differences in secondary endpoints in the PREEMPT trials. The ERG commented that the number of headache days per month was not included in the estimate of utilities, which instead relied on IBMS MSQ data. The manufacturer had outlined a regression analysis from the EQ-5D in the IBMS and found that the EQ-5D and the number of headache days per month were statistically significantly negatively correlated. The ERG used these data and showed very little difference in utilities between botulinum toxin type A and placebo in a given health state. The ERG queried whether the IBMS MSQ data could be used to estimate utilities given that the IBMS included a different population to that described in the decision problem. It

noted that a more appropriate estimation of utilities would encompass both MSQ and HIT-6 data. The ERG also explained that there is non-monotonicity (an anomaly in which the utility values are not consistently increasing or decreasing) in the utility values in the botulinum toxin type A arm in which people in health state 5 (20 to 23 headache days per month) have a lower utility than those in health state 6 (24 to 28 headache days per month). The ERG commented that this may highlight some uncertainty between the mapping of MSQ data to utilities and correspondence with the model structure as defined by the number of headache days per month.

3.26 The ERG noted that the model included the cost of administering botulinum toxin type A and of placebo, based on 30 and 15 minutes of neurologist time respectively. The ERG stated that review of a patient and administration of botulinum toxin type A may take between 30 minutes and 1 hour, depending on the experience of the person injecting and the possibility of complications during administration. As a result, the ERG commented that the cost of administering botulinum toxin type A based on 30 minutes of neurologist time may be too optimistic. It also noted that the appropriate cost of follow-up outpatient consultations should be the standard NHS neurological outpatient follow-up reference cost of £140. The ERG noted that administration of botulinum toxin type A was reported to be offset by cost saving because of reductions in GP visits, inpatient admissions and accident and emergency attendance, but it considered the amount of the cost saving to be overestimated.

3.27 The ERG explained that the model submitted by the manufacturer was non-linear, with a central probabilistic estimate of cost effectiveness more than double that of the deterministic estimate, based on ERG exploratory analyses. It stated that some elements of the probabilistic modelling seemed 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 3 or more prior preventive medications subgroup increased from the manufacturer's deterministic ICER of £6,083 per QALY gained to the probabilistic ICER of £11,447 per QALY gained if the ERG's revisions were applied. If the ERG's revisions were not applied the probabilistic ICER was estimated at £14,004 per QALY gained.

3.28 The ERG conducted a number of different exploratory sensitivity analyses. In

these analyses, the ERG used the manufacturer's model with a number of modifications. The modifications included:

- A neurologist outpatient face-to-face follow-up cost of £140 for botulinum toxin type A administration and placebo follow-up (instead of £73 administration cost of botulinum toxin type A administration and £36.50 follow-up placebo cost, based on 30 and 15 minutes of neurologist time respectively).
- Placebo routine care costs incorporated for patients stopping therapy in the botulinum toxin type A arm (instead of no ongoing routine care costs).
- Resource use estimates from Blumenfeld et al., who included all UK participants from the IBMS (instead of from Bloudek et al. who appeared to use costs based on Scottish implementation).
- Transition probability matrices from the 3 or more prior preventive medications patient subgroup (instead of from the 1 prior preventive medication population).
- An average accident and emergency cost of £77.33 (instead of £90.94).

3.29 The ERG reported that applying all the above modifications (using the manufacturer's utility values based on 1 prior preventive treatment) resulted in an increase in the ICERs for botulinum toxin type A compared with placebo to give a deterministic ICER of £10,257 per QALY gained and a probabilistic ICER of £16,165 per QALY gained. The ERG reported that using these assumptions there was a 67% probability of botulinum toxin type A being cost effective if the maximum acceptable ICER was £20,000 per QALY gained, and an 87% probability of botulinum toxin type A being cost effective if the maximum acceptable ICER was £30,000 per QALY gained.

3.30 The ERG also explored the impact on the deterministic ICER of varying the negative and positive stopping rules and applying the same utility values for each arm. In these analyses, all the modifications outlined in section 3.28 were applied and the utilities from the 3 or more prior preventive medications subgroup were used. The ERG also used 2-year follow-up data from the published abstract by Rothrock et al. (2011; see section 3.23).

3.31 Applying the same utilities from the 3 or more prior preventive medications patient subgroup to both arms (based on the updated utility data from the manufacturer) resulted in lower QALYs for botulinum toxin type A with no change in costs, compared with the base case. When the manufacturer's base case with positive and negative stopping rules and different utilities were used, the deterministic ICER for botulinum toxin type A compared with placebo was £11,267 per QALY gained, compared with £20,324 per QALY gained when the same utilities were applied to both arms for each health state. When the positive stopping rule was excluded (compared with using the positive stopping rule for people who move from chronic to episodic migraine) the ICER for botulinum toxin type A compared with placebo increased from £11,267 to £19,483 per QALY gained when different utilities were used in the botulinum toxin type A and placebo arms. When a positive stopping rule was applied to 24% of people who had moved from a health state of chronic migraine to episodic migraine (based on the study by Rothrock et al.) the ICER for botulinum toxin type A compared with placebo increased from £11,267 to £17,438 per QALY gained when different utilities were used. The ERG also applied various negative stopping rules: no negative stopping rule, an improvement of at least 1 health state within the first cycle; improvement of at least 1 health state within 2 cycles; and the manufacturer's base case of an improvement of 2 health states in 2 cycles. When no negative stopping rule was applied and different utilities were used in the botulinum toxin type A and placebo arm, the ICER for botulinum toxin type A compared with placebo was £13,986 per QALY gained. When different negative stopping rules were applied, the ICER for botulinum toxin type A compared with placebo ranged from £9,618 to £13,167 per QALY gained. The scenario that had the most impact on the model results for botulinum toxin type A compared with placebo was when no positive and negative stopping rules were applied. This led to an ICER of £24,387 per QALY gained if different utilities for the 3 or more prior preventive medications patient subgroup were applied to both arms, or £46,290 per QALY gained if the same utilities for the 3 or more prior preventive medications patient subgroup were applied to both arms. The ERG also remarked that applying separate estimates for the transition probabilities for cycles 3, 4 and 5 to be more in line with patient data would further increase the ICERs by 5% to 10%.

Additional submission after consultation

3.32 The manufacturer provided additional analyses after consultation in response to NICE's request for a revised economic model based on the Committee's preferred assumptions, and some clarification of a number of issues relating to the calculation of utilities in the model, the large difference between the deterministic and probabilistic ICER, and resource use. The manufacturer presented:

- a revised economic model (which incorporated the Committee's preferred assumptions when the same and different utilities were assumed within each health state for the botulinum toxin type A and placebo arms)
- scenario analyses which explored the impact of varying the negative stopping rule and the use of UK resources
- some clarification of the way that utilities had been calculated and the likely causes of the difference in the probabilistic and deterministic ICERs.

  In addition, the manufacturer provided analyses varying the time horizon and placebo effectiveness, and also the results of an Australian survey of 10 people who received treatment with botulinum toxin type A for their chronic migraine.

3.33 The revised manufacturer's model presented the cumulative deterministic results for each of the Committee's preferred assumptions on the manufacturer's original deterministic ICER of £6,083 per QALY gained when different or the same utility values were applied for each arm:

- Applying routine care costs in the placebo arm to people stopping treatment because of inadequate response with botulinum toxin type A resulted in an ICER of £7,170 per QALY gained when different utility values were applied, and £13,110 per QALY gained when the same utility values were applied.
- When the 24% positive stopping rule was applied, the ICER increased from £7,170 to £12,355 per QALY gained when different utilities were applied, and from £13,110 to £22,572 per QALY gained when the same utilities were applied.
- Including resource use estimates specified in Blumenfeld et al. increased the

ICER further from £12,355 to £13,776 per QALY gained when different utilities were applied, and from £22,572 to £25,168 per QALY gained when the same utilities were applied.

- A neurologist follow-up cost of £140 for botulinum toxin type A and placebo administration and follow-up decreased the ICER from £13,776 to £11,997 per QALY gained when different utilities were applied, and from £25,168 to £21,917 per QALY gained when the same utilities were applied.
- An average accident and emergency cost of £77.33 increased the ICER from £11,997 to £12,047 per QALY gained when different utilities were applied, and from £21,917 to £22,008 per QALY gained when the same utilities were applied.
- Calculating utility values from data from the 3 or more prior preventive medications subgroup of the PREEMPT trials increased the ICERs to £16,243 per QALY gained when different utilities were applied, and to £23,624 per QALY gained when the same utilities were applied. When the utility values in health states 5 and 6 were pooled to remove non-monotonicity in the utility values, it led to a utility of 0.480 for health states 5 and 6 in the botulinum toxin type A arm, and 0.507 for health states 5 and 6 in the placebo arm. Pooling the utility values for health states 5 and 6 decreased the ICER to £14,876 per QALY gained when different utilities were applied and increased it to £23,975 per QALY gained when the same utilities were applied. When transition probability matrices from the 3 or more prior preventive medications subgroup were applied, the ICER increased to £15,270 per QALY gained when different utilities were applied and to £24,540 per QALY gained when the same utilities were applied.

3.34 The manufacturer's revised cumulative results were based on a negative stopping rule of a 2-health state reduction in 2 cycles of treatment, as assumed in their original model. The manufacturer conducted one-way deterministic sensitivity analyses to assess the impact of different negative stopping rules on the ICER (from no negative stopping rule to a stopping rule of less than 50% reduction in headache days per month increasing in 5% or 10% increments from 0%). The ICER varied between £14,198 and £17,174 per QALY gained when different utilities were applied, and from £23,849 and £30,755 per QALY gained when the same utilities were applied. The ICER when no stopping rule was assumed was £19,508 per

QALY gained when applying different utilities, and £35,637 per QALY gained when applying the same utilities. The manufacturer considered a negative stopping rule of a 30% response rate based on the reduction in the number of headache days per 28 days after 2 cycles of treatment to represent its new base case, based on evidence that it is used in clinical practice in the UK for the treatment of chronic migraine. When using the revised base-case assumptions and inputs (see section 3.33) and a 30% negative stopping rule, the revised base-case deterministic ICER was £14,999 per QALY gained when different utilities were applied, and £24,939 per QALY gained when the same utilities were applied.

3.35 The manufacturer explored the causes of the large difference between the deterministic and probabilistic results observed in the manufacturer's original submission and the ERG's original additional analyses. The manufacturer identified 1 reason for the difference to be the method used to sample the transition probabilities for the probabilistic sensitivity analysis. In their original submission, these were calculated using a Dirichlet based sampling. When the manufacturer recalculated the probabilistic values using a beta tree sampling method, the central probabilistic estimate and the deterministic estimate were broadly in line with 1 another. The manufacturer also identified an error in its application of a continuity correction. When using the revised base-case assumptions and inputs, a 30% negative stopping rule, beta tree sampling, and correcting for the continuity correction error, the probabilistic ICER was £14,959 per QALY gained (compared with a deterministic ICER of £14,999 per QALY gained) when different utilities were applied, and £25,242 per QALY gained (compared with a deterministic ICER of £24,939 per QALY gained), when the same utilities were applied.

3.36 In response to NICE's request after the first Committee meeting, the manufacturer provided additional clarification about the differences in resource use between Bloudek et al. and Blumenfeld et al. The manufacturer highlighted that the primary reason for the differences was the inclusion of data on Brazilian patients in Bloudek et al. The manufacturer also provided one-way deterministic sensitivity analysis using data from the UK subset of the IBMS. When using the revised base-case assumptions, inputs including a 30% negative stopping rule, and resource use data from the UK subset of the IBMS, the deterministic ICER reduced from £14,999 to £12,624 per QALY gained when different utilities were

applied, and from £24,939 to £20,989 per QALY gained when the same utilities were applied. The manufacturer stated that the reduction in the ICER was caused mainly by the higher-than-average number of hospitalisations in the UK patients in the IBMS.

3.37 The manufacturer carried out additional sensitivity analyses that varied the time horizon and the effectiveness of placebo, assuming no retreatment. The cost effectiveness of botulinum toxin type A was sensitive to the time horizon, with the deterministic ICER ranging from £14,999 to £8,825 per QALY gained when the time horizon ranged from 2 to 20 years, and when different utilities were applied. When the same utilities were applied, the deterministic ICER ranged from £24,939 to £11,700 per QALY gained when the time horizon ranged from 2 to 20 years. The manufacturer also performed a sensitivity analysis in which it was assumed that people in the placebo arm remained in their original health state throughout the trial. This was done because the placebo effect observed in the trials would not be expected to exist in clinical practice in people with chronic migraine who have tried 3 or more prior preventive headache medications. When no effectiveness in the placebo arm was assumed, the ICER reduced from £14,999 to £5,677 per QALY gained when different utilities were applied, and from £24,939 to £6,008 per QALY gained when the same utilities were applied to each arm.

3.38 In response to NICE's request for clarification on utilities, the manufacturer provided further details of the mapping algorithms used in its economic model, which were applied to the week 24 data of the PREEMPT trials in the 3 prior preventive medications group. The manufacturer also supplied mean values of the coefficients and of the parameter values of the week 24 data. The manufacturer stated that the rationale for applying different utility values to treatment arms comes from the results of the PREEMPT trials, which showed significant clinical and health-related quality-of-life benefits beyond the reduction in the number of headache days per 28 days.

3.39 The manufacturer provided results of an Australian survey of 10 people with chronic migraine who had received botulinum toxin type A for up to 5 years. The survey indicated that treatment with botulinum toxin type A provides 3 main types of clinical benefit: reduced frequency of migraine and headache days; reduced severity of migraine; and reduced length or duration of migraine

symptoms. Participants also identified additional benefits to treatment, such as reduced reliance on other treatment, less sick leave, fewer accident and emergency and GP visits, as well as overall improvements in personal, social and mental well-being.

ERG critique of the additional submission

3.40 The ERG reviewed the manufacturer's consultation comments and revised economic model. The ERG noted that it might be more appropriate to assume a placebo administration cost of £70 based on 30 minutes of neurologist time compared with a cost of £140 based on 60 minutes of neurologist time, given that the latter cost and time would involve the administration of botulinum toxin type A as well as a consultation. The ERG also justified a lower cost for neurologist time for placebo administration, in view of the fact that patients whose chronic migraine has failed 3 prior prophylaxis therapies have regular follow-up in some but not all neurology clinics. The ERG's analyses showed that when a placebo administration cost of £70 was applied to the manufacturer's revised base case (including a 30% negative stopping rule) the deterministic ICER increased from £14,999 to £19,244 per QALY gained when different utilities were applied. No ICER was calculated for applying the same utilities to each arm.

3.41 The ERG noted that the utility mapping functions were constructed to pick up elements of the condition that are not captured by the frequency of headache days per 28 days (such as severity or intensity of headaches). Therefore, given that health states are defined in terms of the number of headache days per 28 days, it was not surprising that there were non-monotonic utility values. The ERG explained that there are alternative methods for calculating utilities to those chosen by the manufacturer, such as restricting the individual MSQ dimensions to being monotonic or at least non-decreasing, which could reduce or avoid the non-monotonicity observed in the original utility values. It noted that the manufacturer's utility mapping functions have different non-MSQ parameter values between health states for botulinum toxin type A and placebo. The ERG stated that the manufacturer had not provided a rationale as to why these parameter values should be different. When the ERG equalised the non-MSQ parameter values in the mapping functions, less non-monotonicity was observed and the ICER was £18,895 per QALY gained when different utilities were applied

to each health state. The ERG stated that when the individual MSQ dimensions were restricted to being monotonic or at least non-decreasing, the ICER ranged from £17,278 to £18,256 per QALY gained.

3.42 The ERG reviewed the manufacturer's scenario analysis in which people in the placebo arm remained in their original health state throughout the model. The ERG argued that the benefits of botulinum toxin type A include a large placebo effect, therefore it would be wrong to retain the placebo effect when receiving botulinum toxin type A but not when receiving the placebo. The ERG also reviewed the scenario analysis that varied the time horizon. It noted that no clinical trial data existed beyond 12 months, as observed in the PREEMPT trial, but a 2-year time horizon is plausible. It also reviewed the manufacturer's Australian survey of people (n=10) who received botulinum toxin type A for their chronic migraine. The ERG expressed concern that the study included a very small number of participants who were paid to take part, and who received botulinum toxin type A for up to 5 years, which indicates that a positive stopping rule was not applied. It noted that the survey participants reported a good response to treatment with a dose of 100 to 150 units of botulinum toxin type A.

3.43 The ERG reviewed the manufacturer's comments about resource use. The ERG expressed continuing concern that it is unclear how to interpret some of the resource use data from Blumenfeld et al. and Bloudek et al. When reviewing the resource use data for people from the UK with chronic migraine in the IBMS presented by the manufacturer, the ERG noted that the subset included a small number of people (n=57), and a significant number of outlying results (for patients whose resource use contributed to most of the total resource use observed). The ERG stated that the manufacturer should have explored the impact of excluding outlying results from its analyses, and that given the small number of people from the UK with chronic migraine in the IBMS, they considered the Blumenfeld et al. resource use data to be most applicable to the UK.

3.44 The ERG identified an update of the published abstract by Rothrock et al. (see section 3.23). The update, published by Hanlon et al. (2011), closely matched the results published by Rothrock et al., with 25% (compared with 24% in Rothrock et al.) of people able to stop treatment and maintain a good response for at least 6 months after stopping treatment. It noted that 24% to 25% was the most appropriate figure on which to base a positive stopping rule.

3.45 Full details of all the evidence are in the manufacturer's submission and the ERG report.

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of botulinum toxin type A, having considered evidence on the nature of chronic migraine and the value placed on the benefits of botulinum toxin type A by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.2 The Committee considered the impact of chronic migraine on the everyday life of people with the condition. It heard from the patient experts that chronic migraine is accompanied by severe pain, which impacts greatly on people's quality of life, affecting their ability to work and participate in social activities. The patient experts also noted that people with chronic migraine often experience anxiety and depression related to their condition. The Committee considered chronic migraine to be a debilitating condition which significantly affects health-related quality of life.

4.3 The Committee considered current clinical practice for the treatment of chronic migraine. The Committee heard from the clinical specialists that it is important for people first presenting with chronic migraine to try a range of oral preventive treatment options before considering treatment with botulinum toxin type A. The clinical specialists stated that there is no 1 measure of response to treatment and that response is multifaceted. The Committee heard from the clinical specialists that a good response to treatment is typically considered to be a 30% to 50% reduction in the frequency of headache days or headache episodes. The Committee also noted that when a person's response to treatment is assessed, clinicians also take account of any improvement in the person's quality of life, and that improvements may not always be accompanied by substantial reductions in the number of headache days. It heard from clinical specialists that people considered for treatment with botulinum toxin type A are assessed for medication overuse before treatment starts, and that this is monitored during treatment. The Committee also heard from the patient experts that many people with chronic migraine would consider any degree of response to treatment to be valuable and that further treatment options were important.

4.4 The Committee considered the administration of botulinum toxin type A and

monitoring of the potential benefit associated with treatment. It heard from clinical specialists that an initial consultation typically lasts between 45 minutes and 1 hour and includes administration of botulinum toxin type A, which can take between 15 and 30 minutes depending on the experience of the person administering the injection. After treatment patients are asked to keep a headache diary. The clinical specialists stated that the re-treatment interval with botulinum toxin type A varies in practice. Some clinical practices have routine follow-up about every 3 months. This will be either a telephone consultation with a consultant or headache specialist nurse, or a 30-minute clinic appointment with the consultant during which repeat injections may be administered. In other clinical practices there is no routine follow-up and patients must request an appointment to be considered for further treatment with botulinum toxin type A. The Committee concluded that the re-treatment interval with botulinum toxin type A is variable in practice, being 3 months in some patients, but at much longer intervals in others.

4.5 The Committee considered the evidence on the clinical effectiveness of botulinum toxin type A for the prevention of headaches in adults with chronic migraine from the PREEMPT trials, which compared botulinum toxin type A with placebo. The Committee noted that the pooled results for the intention-to-treat population indicated a statistically significant reduction in frequency of headache days per month, migraine days per month and cumulative headache hours with botulinum toxin type A compared with placebo, but considered the absolute numerical benefit of botulinum toxin type A over placebo to be modest. It also noted the statistically significant reduction in the frequency of headache episodes, migraine episodes and frequency of acute headache medication days with botulinum toxin type A compared with placebo, but that the absolute numerical differences between the treatments were small. The Committee observed that there was no statistically significant difference in how often acute pain medication was taken. Further, the Committee noted the large placebo effect seen in the trials. It was also aware that the incremental effect of botulinum toxin type A compared with placebo may have been increased by people in the active treatment arm realising that they were receiving botulinum toxin type A because of its side effects. The Committee noted that the duration of follow-up in the PREEMPT trials was short (1 year) and the study design, which meant that all patients received the active drug from week 24, could not exclude natural improvements in people's condition over time. The Committee heard from the

clinical specialists that at baseline, patients in the clinical trials had fewer headache days per month (a mean of 19) than people with chronic migraine in secondary care in the UK (a mean of 25 to 26 headache days per month). The clinical specialists said that this might explain why the benefit observed in the trials was less than what they would expect to see in clinical practice. The Committee discussed the duration of the therapeutic effect of botulinum toxin type A and heard from the clinical specialists and patient experts that when a person's condition responds to botulinum toxin type A, the re-treatment interval varies, and that many patients need treatment for longer than 2 years. The Committee was aware of the difficulties of conducting clinical trials in people with chronic migraine, particularly with regard to the known significant placebo effect observed in such studies. It noted that the placebo comparator in the trial would not be given in clinical practice in the manner used in the trial. Although the absolute magnitude of benefit with botulinum toxin type A was modest, evidence from clinical specialists and patient experts suggested that the effect was clinically meaningful in people whose chronic migraine had failed to respond to 3 prior preventive treatments and whose condition responds (with at least a 30% reduction in the number of headache days per 28 days) to botulinum toxin type A treatment. The Committee therefore concluded that botulinum toxin type A was clinically effective in people with chronic migraine whose condition had not responded to 3 prior preventive treatments.

4.6 The Committee considered the clinical trial evidence in light of the views of the patient experts and clinical specialists. The Committee noted the improvements in quality of life for patients whose condition responded to botulinum toxin type A. The Committee then considered the use of botulinum toxin type A in clinical practice in the UK. The Committee heard from clinical specialists that if a person's chronic migraine was responding to botulinum toxin type A, the treatment would be continued until the number of headache days was reduced to fewer than 15 headache days per month (episodic migraine). The clinical specialists estimated that people would have at least 2 treatment cycles. They said that after this approximately 50% of people would continue on treatment, and of those 30% would need 5 cycles of treatment before their condition was reclassified as episodic migraine. The remaining patients would continue to receive treatment for longer than 2 years. Alternatively, if chronic migraine does not respond adequately to botulinum toxin type A after at least 2 cycles of treatment, and there is little benefit to the patient, treatment is discontinued and

patients would receive standard care. The Committee noted that the clinical trial evidence on the effectiveness of botulinum toxin type A was for 1 year. The Committee was aware of the abstract by Rothrock et al. (2011) and the update by Hanlon et al. (2011), which estimated duration of response to treatment with botulinum toxin type A, with response to treatment defined as a 50% reduction in the number of headache days per month. The Committee noted that only 24% of the patients who responded to treatment were able to stop treatment and maintain a good response for at least 6 months. The Committee concluded that because there are no long-term clinical trial data, the estimates of Rothrock et al. and Hanlon et al. are likely to be the best current estimates of the duration of benefit for people who respond to botulinum toxin type A in clinical practice in the UK.

4.7 The Committee discussed the adverse reactions of treatment with botulinum toxin type A for chronic migraine. It noted the adverse reactions reported in the trials with botulinum toxin type A (see section 3.8). It heard from the patient experts that there is often pain around an injection site lasting a few days after treatment with botulinum toxin type A. However, people would be willing to tolerate the adverse reactions with botulinum toxin type A treatment to reduce the frequency or severity of their chronic migraine. The Committee concluded that botulinum toxin type A is generally well tolerated; a conclusion supported by the patient experts and clinical specialists.

4.8 The Committee considered the cost effectiveness of botulinum toxin type A compared with standard care, based on the manufacturer's economic model and the critique by the ERG, in the context of the decision problem. The Committee was aware that the scope specified that the population should include adults with chronic migraine whose condition has failed to respond to at least 3 prior pharmacological prophylaxis therapies, and whose medication overuse has been appropriately managed. The Committee was aware that the manufacturer had focused on this population in a sensitivity analysis and that its main submission compared botulinum toxin type A with placebo in people whose condition has failed to respond to at least 1 prior preventive medication. The Committee noted comments from the clinical specialists that people first presenting with chronic migraine will be prescribed a range of oral preventive medication options before treatment with botulinum toxin type A is considered. The Committee concluded that the main decision problem proposed by the manufacturer, comparing

botulinum toxin type A with placebo in people whose condition has failed to respond to at least 1 prior preventive medication, did not reflect clinical practice. It concluded that it was only relevant for the Committee and the NHS to consider the clinical and cost effectiveness of botulinum toxin type A in people whose chronic migraine has failed to respond to at least 3 prior preventive medications and that the trial data from this subgroup should be used to calculate the transition probability matrices used in the economic model.

4.9 The Committee discussed the revised economic model submitted by the manufacturer as part of the response to consultation. The Committee noted that the revised model included their preferred assumptions and inputs. It was aware that the revised model included a negative stopping rule of a 2-health state reduction in 2 cycles of treatment. The Committee noted that the manufacturer's cumulative analyses on the impact of each of the Committee's preferred assumptions resulted in a revised deterministic ICER for botulinum toxin type A compared with placebo of £15,300 per QALY gained when different utilities are applied to each arm, and £24,500 per QALY gained when the same utilities are applied to each arm. The Committee noted that the revised probabilistic ICERs for botulinum toxin type A compared with placebo were similar to the deterministic ICERs. The Committee concluded that the large differences between the deterministic and probabilistic ICER in the original model were no longer apparent in the revised economic model.

4.10 The Committee considered the costs and resource use in the revised economic model. The Committee was satisfied that its request for the placebo follow-up cost to be the same as the administration cost of botulinum toxin type A had been resolved because the revised economic model had included a standard NHS neurological outpatient follow-up reference cost of £140 for the placebo follow-up cost. It noted that the routine care costs used in the placebo arm were applied to people who discontinue botulinum toxin type A because of lack of efficacy in the model, and an average accident and emergency cost of £77.33 was used by the manufacturer, as requested in the Committee's preliminary recommendations. The Committee considered the additional clarification on resource use supplied by the manufacturer. It noted the ERG's concern that the resource use data for people from the UK with chronic migraine in the IBMS presented by the manufacturer included a small number of people (n=57), and a significant number of outlying results (for patients whose resource use

contributed to most of the total resource use observed). The Committee concluded the Blumenfeld et al. resource use data to be most appropriate given the small number of people from the UK with chronic migraine in the IBMS.

4.11 The Committee noted that its preliminary recommendations requested any revised economic model to incorporate a range of negative stopping rules based on the reduction in the number of headache days per 28 days after 2 cycles of treatment for people with chronic migraine. The Committee noted from comments received during consultation that there was agreement between the manufacturer and the clinical community that a 50% response rate is considered to be too high, and that a 30% response rate recommended by the British Association for the Study of Headache is used in clinical practice. The Committee noted that the manufacturer's revised base-case deterministic ICER (based on a negative stopping rule of less than 30% reduction in headache days per month) for botulinum toxin type A compared with placebo was £15,000 per QALY gained when applying different utilities, and £24,900 per QALY gained when applying the same utilities. The Committee concluded that a 30% response rate (that is, a 30% reduction in the number of headache days per month after 2 cycles of treatment) was the most clinically relevant and reasonable negative stopping rule on which to base its decision.

4.12 The Committee discussed the appropriate positive stopping rule. It noted the consultation comments that a positive stopping rule, in which patients stop treatment if their migraine has changed to episodic migraine and remained stable in episodic migraine for at least 3 months, is the most clinically appropriate. The Committee also noted that the marketing authorisation for botulinum toxin type A does not include use in people with episodic migraine. It therefore concluded that a positive stopping rule in which patients stop treatment if their condition has changed to episodic migraine (that is, fewer than 15 headache days per month) for 3 consecutive months is the most clinically relevant. However, the Committee recognised that according to the only published longer term follow-up of patients who responded to treatment with botulinum toxin type A, only 24% to 25% were able to stop treatment with botulinum toxin type A and maintain a good response for at least 6 months (Rothrock et al. and Hanlon et al.) The Committee concluded that these publications provided the most plausible estimate for the likely implementation of the positive stopping rule in clinical practice in England and Wales, with 24% to 25% being the most appropriate figure on which to base a

positive stopping rule in the economic model.

4.13 The Committee considered the use of the same or different utilities within each health state in the botulinum toxin type A and placebo arms. The Committee noted comments from consultees and commentators that treatment with botulinum toxin type A is associated with a range of clinical and non-clinical benefits, which are not included in the reduction in the number of headache days per month. It considered data on botulinum toxin type A on improving secondary outcomes, including the number of headache episodes, the number of migraine or probable migraine days, the number of moderate or severe headache days, and the number of acute medication days from the pooled PREEMPT trial data and evidence given by the patient experts in writing and at the Committee meeting. The Committee was also aware of an online survey of 60 people with chronic migraine recently conducted by Migraine Action, which also provided supportive data. However, the Committee was aware of the absence of robust data supporting the size of the difference in utility values in each arm. The Committee concluded that although using different utility values within each health state in the botulinum toxin type A and the placebo arm was plausible and better than applying the same utility values within each health state to calculate the most appropriate ICER for considering cost effectiveness, there was still considerable uncertainty around the degree to which differential utilities existed within each health state.

4.14 The Committee was aware that its preliminary recommendations stated that any revised economic model should explore removing the non-monotonicity in the original model, that is, for the botulinum toxin type A arm, the utility in health state 5 (20 to 23 headache days per month) is lower than the utility in health state 6 (24 to 28 headache days per month). It heard from the manufacturer that the non-monotonicity in the utility values in the original model was caused by the small number of people in the 3 or more prior preventive treatment group. The Committee further noted the ERG's explanation that the non-monotonicity was not surprising given that health states were defined in terms of the number of headache days per 28 days, while the MSQ utility mapping functions were constructed so as to pick up other elements of the condition (such as severity or intensity of headaches). The Committee considered that this explanation was plausible and that removing the non-monotonicity had little impact on the ICERs. It concluded that there was no need to remove the non-monotonicity in the

updated economic model.

4.15 The Committee considered the explanation from the manufacturer on the way that utilities had been calculated, noting the way in which utilities had been mapped from the MSQ. The Committee noted the ERG's concern that the non-MSQ parameter values were different in the botulinum toxin type A and placebo utility mapping functions. It agreed that the manufacturer had not provided a clear rationale as to why these parameter values should be different. The Committee noted that when the ERG equalised the non-MSQ parameter values, less non-monotonicity was observed, and the deterministic ICER was £18,900 per QALY gained when applying different utility values to each arm. The Committee concluded that this was the most plausible ICER because it incorporated the Committee's preferred inputs and assumptions including a 30% negative stopping rule, applied different utilities to treatment arms (within the Committee's reservations stated in section 4.13), and equalised the non-MSQ parameter values in the utility mapping functions.

4.16 The Committee discussed whether botulinum toxin type A was an appropriate use of NHS resources for the prevention of headaches in adults with chronic migraine. It noted that botulinum toxin type A is the only technology with a UK marketing authorisation for the prevention of headaches in adults with chronic migraine, and that the method of administration of botulinum toxin type A is novel compared with other preventative treatments used in the management of chronic migraine. The Committee accepted the plausibility of using different utility values in the botulinum toxin type A and placebo arms (within the reservations expressed in section 4.13), and considered that the utility values in the economic model encompass the major health-related quality-of-life benefits associated with treatment with botulinum toxin type A, including duration and intensity of migraine, reduction in symptoms, need for rescue treatment, and lower dose of acute medication. It therefore considered that all of the significant or substantial health benefits of botulinum toxin type A treatment had been included in the model. The Committee concluded that because the most plausible ICER presented was less than £20,000 per QALY gained, botulinum toxin type A could be considered an appropriate use of NHS resources for the prevention of headaches in adults with chronic migraine that has not responded to at least 3 prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse.

4.17 The Committee discussed whether NICE's duties under the equalities legislation required it to alter or add to its preliminary recommendations in any way. The Committee was aware that during scoping, consultees and commentators suggested that there is inequity in access to diagnosis and treatment of migraine for people whose first language is not English. It also noted that comments suggested that there is unequal access to treatment for chronic migraine for people with mental health issues and that greater recognition of chronic migraine as a significant clinical problem will help eliminate discrimination in the workplace. It heard from the patient expert and from consultation comments that chronic migraine is more prevalent in women than men. The Committee was aware that consultation comments also suggested that there is inequity in access to treatment with botulinum toxin type A for people on low income. The Committee did not consider access to treatment for people whose first language is not English to be relevant because the recommendations do not specify a particular English language-based test for the diagnosis of chronic migraine. Further, because the recommendations do not differentiate between any groups of people, the Committee concluded that its recommendations did not limit access to the technology for any specific group compared with other groups.

5 Implementation

5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has chronic migraine and the healthcare professional responsible for their care thinks that botulinum toxin type A is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Peter Clark (Chair)
Consultant Medical Oncologist, Clatterbridge Centre for Oncology

Professor Jonathan Michaels (Vice Chair)
Professor of Clinical Decision Science, University of Sheffield

Professor Kathryn Abel
Director of Centre for Women's Mental Health, University of Manchester

Professor Darren Ashcroft
Professor of Pharmacoepidemiology, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

Dr Matthew Bradley
Therapy Area Leader, Global Health Outcomes, GlaxoSmithKline

Dr Ian Campbell
Honorary Consultant Physician, Llandough Hospital

Dr Ian Davidson
Lecturer in Rehabilitation, University of Manchester

Professor Simon Dixon
Professor in Health Economics, University of Sheffield

Dr Martin Duerden
Assistant Medical Director, Betsi Cadwaladr University Health Board

Gillian Ells
Prescribing Advisor, NHS Sussex Downs and Weald

Dr Jon Fear
Consultant in Public Health Medicine, Head of Healthcare Effectiveness NHS Leeds

Paula Ghaneh
Senior Lecturer and Honorary Consultant, University of Liverpool

Dr Susan Griffin
Research Fellow, Centre for Health Economics, University of York

Professor Carol Haigh
Professor in Nursing, Manchester Metropolitan University

Professor John Hutton
Professor of Health Economics, University of York

Professor Peter Jones
Emeritus Professor of Statistics, Keele University

Dr Steven Julious
Senior Lecturer in Medical Statistics, University of Sheffield

Dr Vincent Kirkbride
Consultant Neonatologist, Regional Neonatal Intensive Care Unit, Sheffield

Rachel Lewis
Advanced Nurse Practitioner, Manchester Business School

Professor Paul Little
Professor of Primary Care Research, University of Southampton

Professor Femi Oyebode
Professor of Psychiatry and Consultant Psychiatrist, The National Centre for Mental Health

Professor Katherine Payne
Professor of Health Economics, University of Manchester

Dr John Radford
Director of Public Health, Rotherham Primary Care Trust

Dr Phillip Rutledge
GP and Consultant in Medicines Management, NHS Lothian

Dr Peter Selby
Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Dr Brian Shine
Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford

Dr Murray D Smith
Associate Professor in Social Research in Medicines and Health, University of Nottingham

Paddy Storrie
Lay Member

Dr Lok Yap
Consultant in Acute Medicine and Clinical Pharmacology, Whittington Hospitals NHS Trust

Guideline representatives

The following individual, representing the Guideline Development Group responsible for developing NICE's guideline related to this topic, was invited to attend the meeting to observe and to contribute as an adviser to the Committee.

- Serena Carville, Project Manager and Senior Research Fellow developing the NICE guideline for the diagnosis and management of headaches

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Scott Goulden
Technical Lead

Eleanor Donegan
Technical Adviser

Kate Moore
Project Manager

7 Sources of evidence considered by the Committee

The Evidence Review Group (ERG) report for this appraisal was prepared by Warwick Evidence:

- Royle P, Cummins E, Walker C et al, Evidence review group report: Botulinum toxin type A for the prophylaxis of headaches in adults with chronic migraine, December 2011

The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Manufacturers or sponsors were also invited to make written submissions. Professional or specialist, patient or carer groups, and other consultees, had the opportunity to give their expert views. Manufacturers or sponsors, professional or specialist, patient or carer groups, and other consultees, also have the opportunity to appeal against the final appraisal determination.

Manufacturers or sponsors:

- Allergan

Professional or specialist, and patient or carer groups:

- Migraine Action
- Migraine Trust
- Association of British Neurologists
- British Association for Study of Headache
- British Pain Society
- Institute of Neurology
- Migraine in Primary Care Advisors
- Primary Care Neurology Society

- Royal College of Anaesthetists
- Royal College of Nursing
- Royal College of Physicians
- United Kingdom Clinical Pharmacy Association

Other consultees:

- Department of Health
- Welsh Government

Commentator organisations (did not provide written evidence and without the right of appeal):

- British National Formulary
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety – Northern Ireland
- Healthcare Improvement Scotland
- Medicines and Healthcare Products Regulatory Agency
- National Hospital for Neurology and Neurosurgery
- Warwick Evidence
- National Institute for Health Research Health Technology Assessment Centre
- National Clinical Guidelines Centre

The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer or sponsor consultees and commentators. They gave their expert personal view on botulinum toxin type A by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Fayyaz Ahmed, Consultant Neurologist, nominated by British Association for the Study of Headache – clinical specialist

- Dr Paul Shanahan, Consultant Neurologist, nominated by the National Hospital for Neurology and Neurosurgery – clinical specialist
- Elaine Ransome, nominated by the Migraine Trust – patient expert
- Wendy Thomas, Chief Executive of Migraine Trust, nominated by the Migraine Trust – patient expert

Representatives from the following manufacturer or sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Allergan

8 Update information

June 2025: We have made minor editorial changes to the wording in section 1.1 to align with the NICE guideline on headaches in over 12s: diagnosis and management. This does not affect the meaning or intent of the guidance.

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