NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Omalizumab for previously treated chronic spontaneous urticaria

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using omalizumab for previously treated chronic spontaneous urticaria in the NHS in England. The Appraisal Committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, and clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see section 9) and the public. This document should be read along with the evidence base (the committee papers).

The Appraisal Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The Appraisal Committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using omalizumab in the NHS in England.

For further details, see the Guides to the technology appraisal process.

The key dates for this appraisal are:

Closing date for comments 10/12/2014

Second Appraisal Committee meeting: 13/01/2015

Details of membership of the Appraisal Committee are given in section 8, and a list of the sources of evidence used in the preparation of this document is given in section 9.

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

1 Appraisal Committee's preliminary recommendations

1.1 The Committee is minded not to recommend omalizumab within its marketing authorisation as an add-on therapy for treating chronic spontaneous urticaria in adults and young people aged 12 years and over.

1.2 The Committee recommends that NICE requests further clarification and analyses from the company for the second Appraisal Committee meeting, including:

- An analysis using the individual patient data from the GLACIAL trial to determine in how many patients whose disease did not respond after the first dose of omalizumab, the disease did then respond after 1 or more subsequent doses.
- The average weekly urticaria activity scores (UAS7) by health state from the pooled analyses from the GLACIAL, ASTERIA I and ASTERIA II trials.
- The average number of courses of omalizumab needed for patients whose disease has responded to treatment for the entire time horizon of the model for the original base case and the subsequent revised base case.
- An update of the base-case analysis:
  - using a different and clinically realistic definition of response
  - employing a stopping rule for people whose disease does not respond after the second dose of omalizumab

  - using a revised estimate of the relapse rates from the GLACIAL trial taking into account that patients may have had spontaneous remission
  - using a linear extrapolation of relapse calculated from the GLACIAL trial
  - using corrected data for spontaneous remission fitted to an appropriate curve.
- Sensitivity analyses:
  - using and varying the effectiveness of omalizumab relative to no further pharmacological therapy
  - varying other parameters to a clinically meaningful degree.
- Scenario analyses both without stopping rules and using alternative stopping rules for people whose disease does not respond after first, third and fourth dose of omalizumab, and a fully incremental cost-effectiveness analysis including all stopping rules.
- A scenario analysis including waning of treatment effect during repeat courses of omalizumab.
- A clear and quantified explanation for the difference in benefits observed in the GLACIAL study and those presented in the model.
- Separate analyses for patients with moderate or severe urticaria at baseline.

2 The technology

2.1 Omalizumab (Xolair, Novartis) is a monoclonal antibody that targets IgE. It has a UK marketing authorisation 'as an add-on therapy for the treatment of chronic spontaneous urticaria in adult and adolescent (12 years and above) patients with an inadequate response to H_1-antihistamines'.

2.2 Omalizumab is available as a 150-mg solution for subcutaneous injection in a pre-filled syringe, and the recommended dose is 300 mg (as 2 injections) once every 4 weeks for up to 24 weeks. In the summary of product characteristics, prescribers are advised to periodically reassess patients for the need for continued treatment. It also notes that clinical trial experience of long-term treatment beyond 6 months in this indication is limited.

2.3 The summary of product characteristics lists sinusitis, headache, arthralgia, upper respiratory tract infections and injection site reactions as common adverse reactions with omalizumab treatment for chronic spontaneous urticaria. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.4 Omalizumab costs £256.15 for a 150-mg prefilled syringe (excluding VAT; 'British national formulary'' [BNF] online October 2014). A single dose of 300 mg costs £512.30 and the cost for a 24-week course of treatment is £3073.80 (excluding VAT).

2.5 The company has agreed a patient access scheme with the Department of Health. This scheme would provide a simple discount to the list price of omalizumab across all indications with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 The company's submission

The Appraisal Committee (section 9) considered evidence submitted by the company making omalizumab, and a review of this submission by the Evidence Review Group (ERG; section 10).

Clinical effectiveness

3.1 The company presented evidence on a narrower population than indicated in the marketing authorisation based on feedback from UK clinicians on the most appropriate population for omalizumab in England. It positioned omalizumab in adults and young people aged 12 years and over with chronic spontaneous urticaria, previously treated with H_1-antihistamines (up to 4 times the licensed dose), leukotriene receptor antagonists (LTRAs) and H_2-antihistamines (also referred to as H_2 receptor antagonists), whose disease had responded inadequately to whichever combination of these therapies that had been used.

3.2 The company carried out a systematic review that identified 6 trials evaluating omalizumab compared with placebo in patients with refractory chronic spontaneous urticaria. These included 3 phase III studies (GLACIAL, ASTERIA I and ASTERIA II), 2 phase II studies (MYSTIQUE and X-CUISITE) and 1 very small (n=10) study by Gober et al (2008). To estimate clinical effectiveness, the company considered only the GLACIAL trial. The company included the methods and results of ASTERIA I and ASTERIA II trials as an appendix to its submission. The company did not include X-CUISITE or the Gober et al. study, noting that the dosage of omalizumab used in these studies was different from the licensed dose (300 mg). The company considered the MYSTIQUE trial 'not important', even though the trial evaluated 300 mg omalizumab, noting that the data from the 3 large phase III trials were sufficient for this appraisal.

The GLACIAL trial

3.3 The primary objective of the GLACIAL trial was to evaluate the safety of the licensed dose of omalizumab (300 mg) over the 24-week treatment period; another objective was efficacy.

GLACIAL was a multicentre, international, randomised, double-blind, placebo-controlled, parallel-group trial. Sixty five centres in 7 countries (including 4 centres in the UK) participated. The trial included patients aged 12–75 years with chronic spontaneous urticaria for more than 6 months, which was refractory to:

- H_1-antihistamines (up to 4 times the approved dose) and either H_2-antihistamines or LRTAs
- or all 3 drugs in combination.

3.4 Patients were randomised in a 3:1 ratio to omalizumab (n=252) or placebo (n=84). The demographics and clinical characteristics of patients at baseline were similar between the omalizumab and placebo groups. The mean age of patients was 43.1 years, 71.9% were female, the mean BMI was 29.8 kg/m^2, 89.0% were white and the median time since diagnosis was 3.6 years (range 6 months to 54.1 years). The mean number of previous medications for chronic spontaneous urticaria was 5.9 (standard deviation [SD] 2.5) in the omalizumab group and 6.4 (SD 2.9) in the placebo group.

3.5 **Outcome measures of itch:** The daily itch severity score is the average score from measuring twice daily (morning and evening) on a scale of 0 (none) to 3 (severe). The weekly itch severity score is the sum of the daily itch severity scores over 7 days and ranges from 0 to 21. A higher itch severity score indicates more severe itching. In the trials, the baseline weekly itch severity score was the sum of the daily itch severity scores over the 7 days before the first treatment. In the GLACIAL trial, the mean values for weekly itch severity score at baseline were 14.0 (SD 3.6) in the omalizumab group and 13.8 (SD 3.6) in the placebo group.

3.6 **Outcome measures of urticarial activity:** The urticaria activity score (UAS) is a composite of scores on a scale of 0 (none) to 3

(intense/severe) for the number of wheals (hives) and the intensity of the itch, measured twice daily (morning and evening). The daily UAS is the average of the morning and evening scores (ranging from 0–6) and the UAS7 is the sum of the daily UAS over 7 days (ranging from 0–42). A higher UAS indicates more urticaria activity. Baseline UAS7 is calculated using data from the 7 days before the first treatment date. The mean values for UAS7 at baseline were 31.2 (SD 6.6) for the omalizumab group and 30.2 (SD 6.7) for the placebo group.

3.7 At baseline, 54.4% (137/252) of those in the omalizumab group and 49.4% (41/83) of those in the placebo group had angioedema. Patients were tested for the presence of anti-omalizumab antibodies and most patients tested negative at baseline.

3.8 The duration of the trial was 24 weeks during which patients received omalizumab, with a follow-on 16 weeks observational period. However, the primary efficacy outcome was the change in the mean weekly itch severity score from baseline to 12 weeks. Secondary outcomes included changes from baseline to week 12 in: the UAS7; the weekly number of hives score; the weekly size of largest hive score; and the proportions of patients whose disease showed a 'minimal important difference' in these outcomes. The results showed that omalizumab improved weekly itch severity score compared with placebo (−8.6, 95% confidence interval [CI] −9.3 to −7.8 for omalizumab compared with −4.0, 95% CI −5.3 to −2.7 for placebo; $p<0.001$). Omalizumab improved all the other reported clinical efficacy outcomes, including change in UAS7 (−19.0, 95% CI −20.6 to −17.4 for omalizumab compared with −8.5, 95% CI −11.1 to −5.9 for placebo; $p<0.001$).

3.9 Omalizumab provided more rapid relief in symptoms than placebo, as measured by the median time to a minimal important difference

in weekly itch severity score (2 weeks compared with 5 weeks, $p<0.001$). The mean change from baseline in weekly itch severity score was lower in patients randomised to omalizumab than patients randomised to placebo from as early as week 1, and remained lower than placebo up to week 24. During the post-treatment follow-up (week 24 to week 40), the mean weekly itch severity score in the omalizumab arm gradually increased to values similar to the placebo group, with no differences between the omalizumab and placebo groups at week 40.

Post-hoc subgroup analysis

3.10 The company submitted a subgroup analysis of the GLACIAL trial, which it defined post-hoc and which investigated the efficacy of omalizumab in patients who took H_1-antihistamines, H_2-antihistamines and LTRAs (instead of just taking 2 drugs: H_1-antihistamines and either H_2-antihistamines or LTRAs). The company analysed individual patient data to estimate the change in UAS7 and Dermatology Life Quality Index scores from baseline to 12 and 24 weeks of treatment. The results of the subgroups are academic in confidence and, although considered by the Committee, cannot be presented here.

ASTERIA I and ASTERIA II trials

3.11 ASTERIA I (n=319) and ASTERIA II (n=322) were international, phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-group trials. The primary endpoint of these trials was change from baseline to week 12 in weekly itch severity score. The trials differed from each other only in the duration of treatment: 24 weeks (6 doses) in ASTERIA I and 12 weeks (3 doses) in ASTERIA II. The trials enrolled patients aged 12 years to 75 years who had chronic spontaneous urticaria for more than 6 months, which was refractory to licensed doses of H_1-antihistamines for at

least 8 consecutive weeks. Patients were randomised to omalizumab 75 mg, 150 mg or 300 mg or to placebo in a 1:1:1:1 ratio. The company considered that the demographics and clinical characteristics of the patients at baseline were well balanced across study groups in both trials.

3.12 The ASTERIA I and ASTERIA II trials showed that omalizumab 300 mg improved most outcomes at week 12 compared with placebo.

Non-randomised studies

3.13 The company identified 1 prospective and 9 retrospective non-randomised studies evaluating omalizumab in patients with chronic spontaneous urticaria. The company's submission summarised the methodology and results of these studies. In the company's view, the non-randomised studies suggested further benefits of omalizumab, such as reducing the need for concomitant medications including corticosteroids, and showing that retreatment with omalizumab is effective. However, because these were observational studies, the results may be biased by confounding.

Evidence for comparators

3.14 For evidence relating to the comparators listed in the scope, the company identified 3 randomised controlled trials (RCTs) and 5 non-randomised studies that included treatment with 1 or more of the comparators. The company identified 2 RCTs and 2 non-randomised studies for ciclosporin; 1 RCT and 1 non-randomised study for methotrexate; and 1 non-randomised study for mycophenolate mofetil. The company did not identify any head-to-head trials of omalizumab with these comparators. The company stated that it did not compare omalizumab with any of the potential comparators indirectly, because the evidence base for the

comparator technologies was characterised by: different outcomes; small sample sizes; differences in treatment duration and disease severity at baseline; and different concomitant therapies used.

Adverse events

3.15 The company presented data from the GLACIAL trial on adverse events during the 24-week treatment period and the subsequent 16 weeks of follow-up. At 24 weeks, the incidence of adverse events was similar in the omalizumab and placebo groups (65.1% versus 63.9% respectively). During the treatment plus follow-up period of 40 weeks, the company saw comparable rates in: 1 or more adverse event (83.7% with omalizumab versus 78.3% with placebo); 1 or more adverse event suspected to be caused by the drug (11.1% with omalizumab versus 13.3% with placebo); 1 or more serious adverse event (7.1% with omalizumab versus 6.0% with placebo); and adverse events leading to withdrawal (1.2% in both groups). In both groups, the most frequent treatment-related adverse events were infections and infestations (36.9% with omalizumab versus 30.1% with placebo), gastrointestinal disorders (15.9% versus 14.5%), and skin and subcutaneous disorders (16.7% versus 14.5%). Headache (8.7% versus 3.6%) and upper respiratory tract infections (7.1% versus 2.4%) were more common in the omalizumab group, whereas sinus congestion (1.2% versus 4.8%), migraine (1.6% versus 3.6%) and idiopathic urticaria (2.8% versus 7.2%) were more common in the placebo group.

3.16 The summary of product characteristics for omalizumab notes that Type 1 local or systemic allergic reactions, including anaphylaxis and anaphylactic shock, may occur with omalizumab, even after a long treatment duration. The company noted that anaphylaxis occurs rarely (in 0.09% of patients) when using omalizumab to treat allergic asthma.

3.17 The most frequent treatment-related adverse events in both the omalizumab and placebo groups of the ASTERIA II trial were infections and infestations (35.4% versus 38.0% respectively), gastrointestinal disorders (11.4% versus 15.2%) and skin and subcutaneous disorders (17.7% versus 8.9%). The company labelled the adverse events data from the ASTERIA I trial as academic in confidence, so these cannot be presented here.

Evidence Review Group's comments on the company's clinical-effectiveness evidence

3.18 The ERG commented that the company identified the relevant studies for this appraisal. The ERG noted that the population of the GLACIAL trial differed from that of the NICE scope (the scope specified people aged 12 years and over with chronic spontaneous urticaria that had an inadequate response to H_1-antihistamines), nor was it in line with the company's decision problem (because only some of the people in the trial were unsuccessfully treated with H_1-antihistamines (up to 4 times the licensed dose), LTRAs and H_2- antihistamines in combination). The ERG did not agree with the company that the ASTERIA I and ASTERIA II trials are not relevant for this appraisal. Specifically, the ERG noted that the ASTERIA trial populations are in line with the scope and the marketing authorisation of omalizumab and, as with the GLACIAL trial, some patients in the ASTERIA trials (although a smaller proportion than in GLACIAL) matched the population specified in the company's decision problem.

3.19 The ERG was unable to assess the quality of the included trials completely because: the company provided few details; published abstracts were not sufficiently detailed; and the ERG received the clinical study reports too late to include them in its critique of the company's submission. The ERG agreed that, taking them at face

value, the trials appeared well conducted and of reasonably good quality.

3.20 The ERG commented that the effectiveness of omalizumab appeared greater in ASTERIA I and ASTERIA II than in the GLACIAL trial. The ERG noted that, in all 3 trials, patients both in the treatment and placebo groups experienced lower weekly itch severity scores, and commented that the company did not address this apparent placebo effect. The ERG noted that the trials did not provide data on reducing or stopping corticosteroids, as specified in the scope. The ERG also noted that the definitions used by the company to define the minimally important difference in itch severity score and UAS7 were based on a small study (n=73) by Mathias et al. (2012), and are not widely accepted. The ERG also noted that the company did not present EQ-5D results from the individual trials despite presenting pooled data from 3 trials to inform the health economic model.

3.21 The ERG commented that the Committee should interpret the results of the subgroup analysis with caution. The ERG would have preferred the company to compare the subgroup to other patients not in the subgroup, as opposed to comparing the results of the subgroup with the results of the whole patient population.

3.22 The ERG performed study-level meta-analyses of the GLACIAL, ASTERIA I and ASTERIA II trials, which the company had not done. This included the differences at week 12 in the mean change from baseline in weekly itch severity score and in UAS7, calculated by pooling the results from GLACIAL, ASTERIA I and ASTERIA II trials, but not including MYSTIQUE. Using a fixed-effect model, the summary effect measure estimated a mean difference of −5.00 (95% CI −5.94 to −4.06) in the weekly itch severity score and of −11.39 (95% CI −13.38 to −9.41) in UAS7. The pooled results for

both outcomes remained unchanged for both the fixed-effect and random-effects models. For the trials evaluating the comparators listed in the scope, the ERG largely agreed with the company that the trials were too different for the results to be compared.

3.23 The ERG agreed that the incidence of adverse events and serious adverse events were similar in the omalizumab 300 mg treated groups and placebo groups in the 3 trials included in the company's submission, but noted that the company did not test the observed differences statistically.

Cost effectiveness

3.24 The company submitted a de novo Markov model. The company assumed that omalizumab improves qualify of life, but does not extend life. The model evaluated the cost utility of omalizumab for patients with an inadequate response despite combining H_1-antihistamines (up to 4 times the licensed dose), with either H_2-antihistamines or LTRAs, or all 3 drugs together, compared with 'no further pharmacological treatment'. The model adopted a 10-year time horizon, with a cycle length of 4 weeks. The model's perspective was that of the NHS and personal social services. All future costs and benefits were discounted at a rate of 3.5%.

3.25 The model comprised 5 discrete health states based on the severity of the symptoms, as measured by 'urticaria activity score over 7 days' (UAS7). These states were:

- severe urticaria (28–42)
- moderate urticaria (16–27)
- mild urticaria (7–15)
- well-controlled urticaria (1–6)
- urticaria-free (0).

In addition, the model included health states for relapse and death. All patients were in either the moderate or severe urticaria health state at baseline and had treatment. These simulated patients had either omalizumab 300 mg in addition to background medications, or only background medications. Patients could move from the baseline states to any of the 5 health states.

3.26 Patients in the omalizumab arm continued to have omalizumab for 4 cycles and were then assessed at 16 weeks to be classified as 'responders' (that is, patients whose disease had responded to treatment defined by health states 'urticaria-free' or 'well-controlled urticaria', or defined by a UAS7 of 6 or less) or 'non-responders' (that is, patients whose disease had not responded to treatment). 'Responders' had a further 8 weeks of omalizumab treatment. During week 16 to 24, 'responders' could only move between 'urticaria-free' and 'well-controlled' urticaria health states. 'Non-responders' (patients in mild, moderate or severe urticaria states) stopped omalizumab after 16 weeks but remained on background medication and could move to any of the 5 states. The company explored a different definition of response in a scenario analysis, considering the mild urticaria health state as a response (UAS7 of less than 15). Patients in the comparator arm had background medication throughout the model. After 24 weeks (6 cycles) 'responders' could relapse, and all modelled patients could experience spontaneous remission or die.

3.27 The company modelled the effect of treatment with omalizumab expressed as the proportion of patients within each of the 5 health states in the omalizumab and comparator arms at a given time. The company used individual patient data from the GLACIAL trial to estimate the proportions, and the model included only patients who had moderate and severe urticaria at the start of the treatment. The model included data up to week 24 for 'responders' (determined at

week 16), and included data only up to week 16 for 'non-responders'. To replace missing data caused by loss to follow-up, the company used the 'last observation carried forward' method in the base-case analysis. In scenario analyses, the company used the 'baseline observation carried forward' method or used the observed data without substituting the missing data. The company provided the distribution of patients between health states at each time point for both omalizumab and comparator arms but, because the company labelled these results academic in confidence, they are not presented here.

3.28 In the model, 'relapse' was defined as moderate or severe urticaria (UAS7 of 16 or more) after a previous response. Patients whose disease had relapsed remained in a 'relapse' health state for 1 cycle and then moved back to the baseline (moderate or severe urticaria) health states. The company assumed that all 'responders' (unless they had gone into spontaneous remission or died) relapsed by 16 cycles (64 weeks) in the base case. The company based this assumption on an observational study by Metz et al. (2014), a review of 51 patients with chronic urticaria treated with omalizumab at a single study centre in Germany, which included 20 patients with chronic spontaneous urticaria. The longest observed period without re-appearance of symptoms after omalizumab treatment was 16 months. The company also conducted a scenario analysis, which assumed that 'responders' could remain relapse-free beyond 16 months.

3.29 Relapse rates in the model were based on data from the GLACIAL trial's 16-week follow-up period, which followed the 24-week treatment period. The company estimated the proportion of patients who experienced relapses after 24 weeks of omalizumab treatment at 28, 32, 36 and 40 weeks using patient-level data stratified by health state (urticaria-free, well-controlled urticaria and mild

urticaria). To estimate the probability of relapse after the treatment and follow-up period (40 weeks), the company used a logarithmic curve fitted to the 4 data points (28, 32, 36 and 40 weeks). The company assumed that all patients relapsed by 64 weeks after the end of treatment (48 weeks beyond the end of the data provided by GLACIAL).

3.30 In the base case, the company assumed that all patients retreated with omalizumab would have a response (and therefore move to the urticaria-free or well-controlled health states) by the end of the 24-week course. The company assumed that all patients being retreated had a response when first treated with omalizumab. In a scenario, the company assumed instead that some patients would not have a response when retreated with omalizumab, and that the proportion with no response when retreated would be the same as the proportion with no response when first treated.

3.31 'Spontaneous remission' meant that all the patient's symptoms resolved. Patients who had a spontaneous remission remained in the urticaria-free health state (UAS7=0) for the remainder of the time horizon. The company applied a probability of spontaneous remission to all patients in both arms. The company stated that a patient could not experience (spontaneous) remission while being treated, but applied a cumulative remission probability (calculated from cycle 1 to the cycle in which treatment ends) at the end of treatment.

3.32 To model spontaneous remission in the base case, the company used data on remission rates from a prospective study of 5 years' duration in patients (n=228) with moderate to severe chronic spontaneous urticaria conducted in Italy (Nebiolo et al. 2009). The company used scenario analyses to explore the effect of using alternative remission rates from other studies (Beltrani et al. 2002,

Toubi et al. 2004 and van der Valk et al. 2002). The company chose a log-logistic distribution to fit the data from Nebiolo et al., as well as for data from Beltrani et al. For the Toubi et al. and van der Valk et al. studies, the company considered the log-normal distribution to be the best fit.

3.33 The company used the term 'drop-out' to refer to patients in the GLACIAL trial who had omalizumab but whose UAS7 data were missing at the end of treatment (week 24). In the company's model, drop-outs did not mean patients were lost to follow-up. To account for these missing observations in the modelled trial data, the company calculated 4-week 'drop-out' rates from the GLACIAL trial data for both arms, stratified according to the baseline health state of the model (moderate or severe urticaria). The company assumed that patients moved to a moderate urticaria health state if drop-out occurred.

3.34 In the GLACIAL trial, patients could stop omalizumab for reasons other than it not improving symptoms; these other reasons included adverse events, disease progression, physician decision or patient choice. The company estimated the risk of stopping omalizumab from the proportion of patients who stopped the study drug (because of the above-mentioned reasons) in the GLACIAL trial. The model allowed for different stopping rates during the first and later treatments; however, because there were no trial data on the probability of stopping associated with omalizumab retreatment, the company assumed the same probabilities for stopping for first and subsequent courses of omalizumab. After stopping omalizumab, patients remained on the background medications. The probabilities of them moving between health states were based on the placebo arm of the GLACIAL study. Patients who stopped omalizumab were not retreated with omalizumab in the model.

3.35 The adverse events included in the company's model were sinusitis, headache, arthralgia, injection site reactions and upper respiratory tract infection. The company stated that no meaningful differences in the rates of adverse events between omalizumab and placebo were reported in the trials.

3.36 The company did not assume in the model that chronic urticaria increases mortality or that omalizumab extends life. The company sourced all-cause mortality data from the UK Office of National Statistics (2011) and calculated the mean mortality by age group and sex, assuming a 50:50 men to women ratio.

3.37 The company calculated pooled EQ-5D scores from the GLACIAL, ASTERIA I and ASTERIA II trials to estimate the utility values in the model. It used a mixed-effect regression model to estimate utility values for each of the 5 health states in the model. The health state utility values were as follows: severe urticaria (0.712); moderate urticaria (0.782); mild urticaria (0.845); well-controlled urticaria (0.859); and urticaria free (0.897). Disutility values for the adverse events were sourced from published literature and were as follows: sinusitis (−0.0022); headache (−0.0297); arthralgia (−0.0402); upper respiratory tract infection (−0.0022); and injection site reaction (−0.0040).

3.38 The company incorporated 3 categories of resource use in the model that included treatment, health state and adverse event costs. The treatment costs for omalizumab included costs for: drug acquisition; administration (£14.21 per administration); and monitoring (£42. 64 for the first 3 administrations and £21.32 for the fourth administration). Treatment costs also included the cost of background medications for both arms (H_1-antihistamines [£0.21 per day], LRTA [£0.36 per day] and H_2-antihistamines [£0.33 per

day]) based on unit costs of the medications from the British national formulary (BNF).

3.39 Health-state costs comprised accident and emergency visits, outpatient attendance and laboratory tests. The costs for emergency and outpatient visits were from NHS reference costs 2012–13 (updated to 2014) and the laboratory tests from the National Institute for Health Research Industry Costing Template (2013). The number of accident and emergency visits, outpatient visits and laboratory tests were estimated from the ASSURE study, an unpublished, company sponsored, retrospective observational study designed to measure the burden of illness of chronic spontaneous urticaria. Costs associated with health states were reported as academic in confidence and therefore are not presented here.

3.40 The costs of treating adverse events were also incorporated in the model. The company took the unit cost of a GP appointment from Personal Social Services Research Unit 2013 (updated to 2014) and the cost of an antibiotic (for sinusitis and upper respiratory tract infections) from the BNF price for a course of ampicillin. The company applied an additional cost of £97.80 for identifying a relapse, which is based on the mean cost of outpatient appointments across several specialities.

3.41 The company's deterministic base-case result showed that with the patient access scheme (implemented for the NICE technology appraisal guidance 278 'Omalizumab for treating severe persistent allergic asthma') omalizumab was associated with a total incremental cost of £7,459 with an additional gain of 0.38 quality-adjusted life years (QALYs), which resulted in an incremental cost-effectiveness ratio (ICER) of £19,632 per QALY gained.

3.42 The company conducted one-way deterministic sensitivity analyses by increasing and decreasing parameters, including the:

- proportion of patients in the urticaria-free and well-controlled urticaria health states (UAS7 of 6 or lower, by 20% (patients in other health states were redistributed to equal 100%)
  - in the omalizumab arm at 16 weeks
  - in the omalizumab arm at 24 weeks
  - in the comparator arm at 16 weeks
  - in the comparator arm at 24 weeks
- cumulative relapse rate at 4, 8, 12 and 16 weeks after treatment by ±20%
  - from the well-controlled urticaria health state
  - from the mild urticaria health state
- spontaneous remission (hazard ratio) by ±1%
- risk of adverse events by ±20%
  - in the omalizumab arm
  - in the comparator arm
- all health state utility values by ±10%
- utility decrement for adverse events by ±15%
- cost of omalizumab treatment by ±20%
  - acquisition cost
  - administration cost
  - monitoring cost
- healthcare costs for health state in the model by ±20%
- cost of adverse events by ±20%
- discount rates (varied between 6% and 0%)
  - for outcomes
  - for costs.

3.43 The company presented the results for only some of these analyses. These indicated that the ICER was most sensitive to the

acquisition cost of omalizumab, the cumulative relapse risk for urticaria-free patients, the health state utilities and the discount rates.

3.44 The company conducted probabilistic sensitivity analysis by running 1000 iterations, and reported the variables and distributions it used. It reported a probability of 49.6% and 100% of omalizumab being cost effective at a maximum acceptable ICER of £20,000 and £30,000 per QLAY gained respectively. The company's submission did not include the disaggregated results for the average costs and QALYs incurred or the probabilistic ICER, however it was possible to extract this from the company's model. In the probabilistic analysis the average incremental cost was £7483 and the average incremental QALY gain was 0.38, which resulted in an ICER of £20,048 per QALY gained.

3.45 The company also conducted several scenario analyses which included:

- alternative imputation methods for patients with missing data (no imputation or baseline observation carried forward)
- alternative stopping rules ('non-responders' at 12 weeks, 'responders' at 12 weeks, 'responders' at 16 weeks and without any stopping rule for 'non-responders')
- alternative data source for spontaneous remission (Beltrani et al. 2002, Toubi et al. 2004, van der Valk et al. 2002)
- varying the treatment horizon (5 years, 15 years, 20 years and lifetime)
- assuming no response to retreatment is possible in previous 'responders'
- assuming that mild urticaria is counted as a response
- assuming relapse-free response beyond 64 weeks

- assuming patients having omalizumab would need only licenced doses of H_1-antihistamines
- excluding monitoring costs for omalizumab including indirect costs due to productivity impact.

Omalizumab dominated no further pharmacological treatment in the scenario which took into account the indirect costs of patients with chronic spontaneous urticaria being less productive in the workplace. The ICERs for the rest of the scenario analyses ranged from £15,665 per QALY gained (assuming that patients on omalizumab would need only licenced doses of H_1-antihistamines) to £24,301(assuming that people whose disease responded to omalizumab on initial treatment may not have a response on retreatment).

Evidence Review Group's comments on the company's cost-effectiveness analyses

3.46 The ERG commented that the structure of the company's economic model was reasonable and consistent with the clinical pathway for urticaria. The ERG commented that the time horizon of 10 years was appropriate given that data from observational studies on the natural history of the disease suggests that in most patients the entire disease lasts less than 10 years. The ERG noted that the model structure did not permit comparison with other comparators such as ciclosporin.

3.47 The ERG commented that having substituted missing data (last observation carried forward), the company's model may have over-estimated the proportion of patients whose disease responded to omalizumab treatment (UAS7 of 6 or lower) compared with the GLACIAL trial. The ERG replicated the last observation carried forward analyses used by the company in its base case and baseline observation carried forward analyses used in its scenario

analyses to validate the model's outputs against the GLACIAL trial outcomes. The ERG found that the over-estimation was more pronounced when using the last observation carried forward method. The ERG noted that the company's choice of a definition for response, (patients having UAS7 of 6 or lower) had no empirical basis.

3.48 The ERG noted that the company did not provide details on how it assured quality in the patient-level data analysis. It noted a minor difference in the proportions of patients with a UAS7 of 0 at week 12 in the omalizumab arm between the data used in the model and the published data. The ERG noted that correcting this would not substantially impact on the results.

3.49 When estimating remission rates, the ERG acknowledged that the company had correctly extracted data from the text of the Nebiolo et al. (2009) study but noted that the paper reported discrepant values between the text and the published Kaplan–Meier curves. The ERG commented that this meant the company's approach to extrapolating the log-logistic function resulted in an extremely poor fit to the Kaplan–Meier curves in the Nebiolo paper, over-estimating remission up to around 24 months and under-estimating remission over longer time periods. The ERG also calculated the median duration of chronic spontaneous urticaria from the company's base-case log-logistic function, noting that 20.8 years was implausibly high. The ERG commented that the company's extrapolated remission rates (22.73% at 1 year, 36.00% at 5 years and 42.65% at 10 years) did not represent the natural history of disease. The clinical advice received by the ERG suggested a spontaneous remission around 50% to 70% within 2 years and 70%-90% within 10 years. The ERG extracted the data from the Kaplan–Meier curves published in Nebiolo et al. and using exponential, Weibull and log-logistic parametric functions for remission, estimated a

median duration of disease as 6–7 years. The ERG conducted exploratory analyses using exponential and log-logistic functions for spontaneous remission and noted that these increase the ICERs to £22,341 and £21,730 per QALY gained, respectively.

3.50 For relapse, the ERG noted that the model could extrapolate the GLACIAL trial data using either a log-normal distribution, as in the base case, or with a linear extrapolation. The ERG noted that using a linear extrapolation increased the company's base case from £19,632 per QALY gained to £23,065 per QALY gained.

3.51 The ERG was concerned with the company's approach to estimating probability of relapse specifically in patients whose disease had initially responded to omalizumab. Therefore, the ERG reconstructed the company's curve-fitting exercise. The ERG considered that an exponential curve fitted the observed trial data better than a log-normal extrapolation, and explored a scenario analysis using alternative probabilities of relapse on cost effectiveness. The ERG reported that using an exponential fit increased the ICER from £19,632 to £22,003 per QALY gained.

3.52 The ERG could not independently verify drop-out and stopping rates used by the company in the model because the company provided only limited information in its submission. The ERG noted that, to model all-cause mortality, the company assumed an equal proportion (50:50) of men and women in the modelled population while in the GLACIAL trial population, there were fewer men than women (30:70). The ERG did not anticipate that this had a substantial impact on the results. The ERG commented that the company collected utility estimates for the health states from a large sample of a directly-relevant population, but noted that the utility decrements the company used for adverse events were

sourced from populations not relevant for this appraisal. The ERG was satisfied with the resource use included in the model.

3.53 The ERG commented that the company did not justify its approach to the deterministic sensitivity analyses of using arbitrary percentage changes in the parameter values instead of confidence intervals or other measures of variation. The ERG also noted that the company did not explore in sensitivity analyses the uncertainty associated with certain important parameters, for example treatment effect and spontaneous remission rates. In the probabilistic sensitivity analysis, the ERG noted some discrepancies between how the company described and actually modelled parametric distributions. In general, the ERG commented that it was unclear whether the company correctly captured the uncertainties in the model.

3.54 The ERG suggested that a more appropriate base case would include remission rates derived from an exponential fit to the Kaplan–Meier curve of Nebiolo et al (2009) and relapse probabilities calculated from survival analyses using the exponential fit to relapse found in the GLACIAL trial. This scenario produces an ICER of £24,989 per QALY gained.

3.55 Full details of all the evidence are in the Committee papers.

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of omalizumab, having considered evidence on the nature of chronic spontaneous urticaria and the value placed on the benefits of omalizumab by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Clinical effectiveness

4.1 The Committee heard from the clinical and patient experts about the nature of the condition. It heard that chronic spontaneous urticaria is characterised by persistent itching which can interfere with activities of daily living and sleep. The Committee heard from patient experts that severe chronic spontaneous urticaria can be unbearable, disabling, affect quality of life, result in patients being unable to work, and disrupt family interactions. The Committee heard how the disease can change the way a person looks and make them feel self-conscious, and that angioedema can cause pain and problems with mobility.

4.2 The Committee discussed the natural history and the current management of chronic spontaneous urticaria, and where omalizumab would fit in the treatment pathway. It heard from clinical experts that chronic spontaneous urticaria is a naturally remitting disease, that around 50% patients have complete resolution of the symptoms within 6 months and that up to 90% of patients have complete resolution within 5 years. The Committee also heard that the severity of the disease did not predict the duration of disease but that in patients who had disease for years spontaneous remission was much less likely. The Committee heard that the first-line treatment for chronic spontaneous urticaria is H_1-antihistamines, which are often used at up to 4 times the dose specified in the marketing authorisation. The Committee heard that although certain H_1-antihistamines are labelled as 'non-sedating', patients often experience sleepiness. The Committee also heard that there is no licensed treatment option for patients whose disease does not respond to H_1-antihistamines but, in practice, clinicians offer patients H_2-antihistamines and leukotriene receptor antagonists (LTRAs). The Committee heard from the clinical experts that there is limited evidence on the effectiveness for

H_2-antihistamines in patients whose disease is non-responsive to H_1-antihistamines and their use in clinical practice is decreasing. The Committee heard that treatment with LTRAs may help some, but not all, patients. The Committee also heard from the clinical experts that guidelines for urticaria recommend omalizumab at the same point in the pathway as immunosuppressants, such as ciclosporin. However, because of funding restrictions in the NHS, omalizumab is currently usually only available to patients in England whose condition does not respond to ciclosporin. The Committee heard that ciclosporin can be effective but can cause serious adverse effects. The Committee also heard from the clinical and patient experts that patients with severe disease may need short courses of oral corticosteroids. The Committee was aware of the adverse effects from frequent use of corticosteroids. The Committee heard from the clinical experts that they would use omalizumab instead of ciclosporin in the treatment pathway, because it is licensed for this condition, has a very good safety profile and patients need less monitoring than with ciclosporin. The Committee heard from the patient and clinical experts that, when patients with severe disease have omalizumab, their disease improves rapidly within 1 to 2 weeks after the first dose and, in many patients, there is complete remission. The Committee heard that patients in remission can often stop taking other drugs such as H_1-antihistamines, H_2-antihistamines, LTRAs and corticosteroids. The Committee heard that omalizumab controls symptoms but is not 'disease-modifying', and that, in most patients, the condition relapses within 4 to 6 weeks of stopping treatment and repeat treatment is needed. One clinical expert suggested that omalizumab may also be used to treat severe disease earlier in the pathway, immediately after treatment with H_1-antihistamines, as specified in the marketing authorisation, but noted that this is not where the company positioned the drug for this appraisal.

4.3 The Committee discussed the company's decision problem, noting that the company had chosen a narrower population than the population specified in its marketing authorisation and the NICE scope: the company positioned omalizumab after treatment with up to 4 times the licensed dose of H_1-antihistamines, LTRAs and H_2-antihistamines, whereas the scope and marketing authorisation specified use after an inadequate response to H_1-antihistamines. Based on what the clinical experts said about when omalizumab would be used in clinical practice in England (see section 4.2), the Committee concluded that the company had targeted omalizumab at a clinically appropriate population and that omalizumab could be considered as a fourth-line option in the pathway, in the same place as immunosuppressants. The Committee noted that the company had not provided analyses using immunosuppressants (such as ciclosporin, mycophenolate mofetil or methotrexate) as comparators for omalizumab, even though they had been listed as comparators in the final scope for this appraisal. The Committee noted that, in its submission, the company had agreed that immunosuppressants (particularly ciclosporin), although used off-label, are appropriate comparators for omalizumab and provided a summary of the evidence on their effectiveness. The Committee noted both the company's and the Evidence Review Group's (ERG's) comments that the evidence from randomised trials on the effectiveness of ciclosporin in chronic spontaneous urticaria was very limited, and did not allow for a robust indirect comparison with omalizumab. The Committee concluded that ciclosporin was an appropriate comparator in this appraisal, but understood that, because of the lack of clinical evidence, no comparison could be made.

4.4 The Committee considered the evidence on the clinical effectiveness of omalizumab, noting that the company included

evidence from a single phase III trial, GLACIAL. It noted that the company included 2 more phase III trials, ASTERIA I and ASTERIA II, as supporting evidence in an appendix. The Committee noted that the GLACIAL trial was primarily a safety trial, although it heard from the company that it was powered for efficacy. The Committee questioned why the main efficacy studies, ASTERIA I and ASTERIA II, were not included by the company in its main analyses. It heard from the company that the ASTERIA trials included patients on licensed doses of H_1-antihistamines and only a small proportion of the trial populations took higher doses of H_1-antihistamines or H_2-antihistamines with or without LTRAs. The Committee heard that, in the GLACIAL trial, 62% of patients were symptomatic despite having high-dose H_1-antihistamines plus H_2-antihistamines and/or LTRAs when they entered the trial. The Committee also noted that the patients in the GLACIAL trial had the disease for several years and therefore reflected the patients that clinicians in England would treat with omalizumab. The Committee agreed that the patients in the GLACIAL trial were representative of those who would have omalizumab, and concluded that the results from the GLACIAL trial were generalisable to clinical practice in England.

4.5 The Committee discussed whether the outcome measures used in the GLACIAL trial were meaningful and considered whether they were used in clinical practice. The Committee heard from the patient expert that she had never been asked to score her disease with the measures used in the clinical trials. The Committee heard from 1 clinical expert that the measures are useful and should be used in clinics, particularly those measuring health-related quality of life. The Committee also heard that patients are currently required to complete several of the outcome measures when clinicians apply for funding for omalizumab. In general, however,

clinicians do not consider these measures key to choosing who to treat, or when to continue treating, with omalizumab. The Committee noted the ERG's concerns with the small study validating the 'minimally important' clinical difference in outcomes, but was aware that the company did not use this definition in its cost-effectiveness model. The Committee concluded that, in general, the outcomes in the trials were relevant for this appraisal.

4.6 The Committee discussed the efficacy results of the clinical trials. It noted that omalizumab was associated with statistically better outcomes compared with placebo in most of the reported clinical and quality-of-life outcome measures. The Committee noted that, in the GLACIAL trial, the primary efficacy outcome (that is, mean change from baseline weekly itch severity score) showed a rapid decrease after the first dose of omalizumab and it stayed lower than placebo throughout the 24-week treatment period. The Committee noted that there was also a statistically significant reduction in this score in the placebo arm compared with the baseline. It heard from the clinical experts that this could be because of increased use of the rescue medication, diphenhydramine, in the patients having placebo. The Committee also noted that, in the GLACIAL trial, the weekly itch severity score started increasing after stopping treatment at 24 weeks and reached the same level as placebo at week 40. The Committee noted that this quick onset and offset of effectiveness was consistent with what it had heard about the clinical experts' experience of using omalizumab in clinical practice. The Committee also noted that omalizumab increased angioedema-free days and improved sleep. The Committee also considered the meta-analysis of the GLACIAL and ASTERIA I and II trials conducted by the ERG, thereby including a wider population, and noted there was little difference in these results compared to those using analysis from

the GLACIAL trial alone. The Committee concluded that omalizumab is an effective treatment for improving symptoms in chronic spontaneous urticaria.

4.7 The Committee discussed how long patients are treated with omalizumab in England, and whether clinicians apply 'stopping rules'. The Committee discussed this separately for patients who benefit from it ('responders') and for those who do not ('non-responders'). It noted that the summary of product characteristics for omalizumab does not specify treatment duration or any stopping rules, but states 'prescribers are advised to periodically reassess the need for continued therapy' and 'clinical trial experience of long-term treatment beyond 6 months in this indication is limited'. The Committee noted that, for patients whose disease does not respond to omalizumab, the company assumed that they would stop treatment at 16 weeks. The Committee heard from the clinical experts that it is usually clear much earlier (after the first 2 doses) whether a patient will have a response to omalizumab and, in clinical practice, the patients who do not have a response after the first dose may be given only 1 more dose. The Committee heard that most people treated with omalizumab will have a response. The Committee heard from 1 clinical expert that, if there is not a full response, they may increase the frequency of the dose to every 2 weeks instead of monthly and also increase the dose, but this reflected 'off-label' use of the drug.

4.8 The Committee considered the safety data of omalizumab. It noted that, in all 3 clinical trials, adverse events in the omalizumab arm and placebo arm were comparable. The Committee noted that, because of a risk of anaphylaxis immediately after administrating omalizumab, the advice in the summary of product characteristics is that medicinal products for the treatment of anaphylactic reactions should always be available for immediate use following

administration of omalizumab. The Committee understood from the clinical experts that anaphylaxis is very rare and, although the risk of anaphylaxis decreases with each dose, appropriate precautionary measures are still needed, and that generally omalizumab is given at secondary or tertiary care centres equipped with resuscitation facilities.

Cost effectiveness

4.9 The Committee considered the company's economic model, the assumptions on which the parameters in the model were based, and the critique and exploratory analyses performed by the ERG. The Committee noted that, to capture the clinical effectiveness of omalizumab, the company did not model effect measures (for example, relative risk) but instead used individual patient data from the GLACIAL trial to estimate the proportions of patients in each health state at any given time. The Committee understood that a change in the proportion of patients in each health state depended on modelled patients moving between health states. However, the Committee was aware that relatively small changes in symptoms could lead to a change in health state and, conversely, that patients could remain in the same health state with a relatively large change in symptoms (see section 4.10). The Committee noted that the model did not compare omalizumab with other comparators (such as ciclosporin). Noting that a robust estimate of the relative effectiveness of omalizumab and ciclosporin was not available, the Committee accepted the company's choice of comparator, but noted uncertainty around many assumptions used in the model.

4.10 The Committee was concerned about how the company defined treatment response in the model. The Committee noted that the company defined response as an as an absolute level of urticaria activity score over 7 days (UAS7) of 6 or less measured after

16 weeks of treatment with omalizumab. The defined response did not take into account the pre-treatment UAS7. Moreover, the Committee noted that, as defined, the response criteria could miss clinically significant responses while incorrectly classify patients as having had a response, for example:

- moving from UAS7 of 42 to a UAS7 of 7 constituted a non-response in the model
- moving from a UAS7 score of 16 to a UAS7 score of 6 constituted a response in the model.

The Committee heard from the clinical experts that using an absolute decrease of 10 or more would be more in line with a view of a clinically significant response. The Committee therefore concluded that the response criterion used in the model was not fit for purpose and, to inform its decision-making, the company needed to use a valid clinical definition of response in the model.

4.11 The Committee understood that only patients with moderate or severe disease were treated with omalizumab. It noted that the company modelled 2 separate cohorts of patients – moderate and severe – based on the severity of urticaria at baseline, and that the company based the model on the GLACIAL trial in which 30% of patients had moderate urticaria and 70% had severe urticaria at the beginning of the trial. The Committee noted the ERG's comment that the company did not vary the proportions of people with moderate or severe disease. The Committee concluded that severe or moderate urticaria should be modelled separately because a difference in cost effectiveness would be expected between the populations.

4.12 The Committee noted that, because data from many patients in the GLACIAL trial were missing, the company used the last observation

carried forward imputation technique to populate the health states in the model. The Committee noted that the company provided scenario analyses using observed data (that is, no imputation) and the baseline observation carried forward method. The Committee understood that baseline observation carried forward is a conservative assumption, but noted that the results were not sensitive to the method of imputation. The Committee concluded the company's method of dealing with patients lost to follow-up was acceptable.

4.13 The Committee discussed the optimal timing for clinicians to assess whether or not patients have had a response to omalizumab. The Committee noted that, in the base case, the company assumed that clinicians identify 'non-responders' at 16 weeks after the fourth dose of omalizumab, and the patients then stop omalizumab treatment. The Committee noted testimony from clinical experts (see section 4.7) suggesting that 'non-responders' can almost always be identified earlier than 16 weeks, and considered it very unlikely that a patient who does not have a response to omalizumab after the first 2 doses would continue treatment with omalizumab until week 16. However, the Committee heard from patient experts that, very infrequently, patients have a response only after 3 to 4 doses of treatment with omalizumab. The Committee noted that the company presented a scenario analysis in which 'non-responders' stopped treatment with omalizumab after 12 weeks, which had little impact on the incremental cost-effectiveness ratio (ICER). The Committee heard that the 16-week stopping rule was based on clinical experience of omalizumab for treating persistent allergic asthma. The Committee agreed that the stopping rule in the model at 16 weeks was not clinically realistic and concluded that, to inform its decision-making, the company needed to provide scenarios in which 'non-responders' were

assumed to stop after 2 doses of omalizumab. In addition, the Committee concluded that it needed the company to clarify from the GLACIAL trial how many additional 'responders' had been identified when assessed according to the protocol after the first dose, including weeks 4, 8, 16, 20 and 24, and to explore the cost effectiveness of different stopping rules incrementally.

4.14 The Committee discussed the probability of relapse in the model first focussing on the cumulative relapse rate in the trial data. The Committee understood that, the company calculated the relapse rate separately for patients in the mild urticaria, well-controlled urticaria and urticaria-free states using the proportion of patients in each state and the relapse rates observed in the GLACIAL study up to the end of the follow-up period (40 weeks). The Committee noted that graphs of cumulative relapse rates used in the model suggested that the cumulative relapse rate at 40 weeks in the GLACIAL study (16 weeks post treatment) ranged from around 45% (for well-controlled urticaria) to around 55% (for urticaria-free and mild urticaria). The Committee noted that this did not reflect the testimony of the clinical experts, who reported that the disease relapses quickly after stopping omalizumab (see section 4.7).The Committee also noted that the trial data on the weekly itch severity score showed that there was little sustained benefit of omalizumab after treatment stops. Based on the clinical experts' experience, the Committee expected the cumulative relapse rate at 16 weeks to be close to 100%. The Committee considered that the difference between the modelled and expected rates of relapse could be explained by the company not having accounted for patients who have (spontaneous) remission when calculating relapse rates from the GLACIAL study. The Committee noted that employing a more realistic relapse rate would be expected to increase the number of repeat courses of omalizumab needed by patients, and would

consequently increase the total modelled cost for patients treated with omalizumab. The Committee concluded that probabilities used to estimate relapse in the model for the immediate post-treatment period overestimated the time to relapse, and that it would be more appropriate to calculate a more realistic relapse rate from the GLACIAL trial by removing the number of patients whose disease goes into spontaneous remission.

4.15 The Committee was also concerned about the company's approach to extrapolating the probability of a patient's disease relapsing after the trial period. The Committee noted both the company's and the ERG's extrapolated data, after the 16-week post-intervention observational follow-up period in the GLACIAL trial (using log and exponential extrapolations respectively). Both the company and the ERG assumed that all patients' disease relapses by 64 weeks. The Committee noted that the assumption was based on an observational study (Metz et al. 2014), which reported the times to relapse for patients who had previously had omalizumab. The Committee noted that the company's model had included an additional extrapolation function, by which it could use a linear function to extrapolate relapse. Based on the testimony by clinicians that the disease relapses quickly after stopping omalizumab, the Committee concluded the company's model underestimated the probability of relapse in its base case and it also agreed that it would be more appropriate for the base-case analysis to use a linear extrapolation of the relapse data from the GLACIAL trial.

4.16 The Committee noted that the company assumed that patients whose disease responded to the first course of omalizumab and then relapsed could have an unlimited number of further courses (6 doses) of omalizumab. The Committee noted that there was limited evidence on the effectiveness of even a single repeat

course of omalizumab, which came from a small retrospective observational study (Metz et al. 2014). The Committee heard from the clinical experts that, in their experience, retreatment with omalizumab was effective, but noted long-term data of patients having repeated courses was lacking. The Committee noted that because of this lack of evidence, the assumption of maintaining the same magnitude of treatment effect with omalizumab during subsequent courses was associated with substantial uncertainty. The Committee concluded that, to inform its decision-making, the company needed to provide scenario analysis in which the effectiveness of repeated doses of omalizumab gradually decreases.

4.17 The Committee discussed the average number of courses of omalizumab that would be needed by patients whose disease responds to omalizumab. It noted that the company's submission did not report the anticipated number of repeat courses of omalizumab. Instead, it reported the average interval between courses of treatments (24.5 weeks in the base-case analysis). Based on that, the Committee inferred that, for a time horizon of 10 years as assumed in the company's base case, the average number of treatment courses would approximate 10, but heard from the company that modelled patients received 3 treatment courses. The Committee concluded that, to inform its decision-making, the company needed to clarify the number of repeat courses predicted by the model for 'responders'.

4.18 The Committee discussed the modelling of spontaneous remission. The Committee noted that the company's approach predicted an improbably high median duration of disease (20.8 years), whereas it heard from the clinical experts that approximately 90% of patients have spontaneous remission within 5 years. The Committee noted that the ERG's approach (see section 3.49) predicted a median

duration of 6−7 years, which was also higher than expected in clinical practice. The Committee noted that the median time from diagnosis to entry into the GLACIAL trial was 3.6 years, and ranged from 6 months to 54.1 years. The Committee understood that patients with difficult-to-treat disease, as included in the model, may have the disease for a longer time. The Committee also noted that the company used incorrectly reported data from the text of the publication by Nebiolo et al. (2009), while the ERG used the data derived from the correctly reported Kaplan–Meier curves in the same publication. The Committee noted that the company acknowledged their error, and concluded that the ERG's approach was more appropriate for modelling spontaneous remission, and that the ERG's estimate could be considered closer to the natural history of disease for the population under consideration.

4.19 The Committee noted that the company based the utility values in the model on the EQ-5D scores collected in the GLACIAL, ASTERIA I and ASTERIA II trials. The Committee noted that the utility value used for the severe health state was 0.712 and discussed whether this was too high, considering the testimonies from the patient experts that severe disease would be considerably disabling. The Committee questioned whether this could be because the company used a wide range of UAS7 (28 to 42) to define the severe health state. It noted that perhaps most patients in the trials had a UAS7 towards the lower end of the range. The company was unable to give the Committee the average UAS7 values for patients whose EQ-5D scores it used to calculate utility values for each health state. The Committee concluded that, to inform its decision–making, the company needed to clarify and justify the utility values used in the model.

4.20 The Committee noted that patients in the model can accrue the maximum utility gain from a single course of omalizumab when

moving from the severe urticaria state (utility value 0.712) at baseline to the urticaria-free state (utility value 0.897) with utility gain of 0.185. The Committee noted, for a 6-month treatment period, this generated a quality-adjusted life year (QALY) gain of 0.0925. The Committee noted that, to get an incremental QALY gain of 0.38, as reported by the company in its base-case results, a modelled patient would have to have more than 4 repeated courses of omalizumab and obtain maximum benefit from it. The Committee was mindful that many patients would gain less benefit, for example, those moving from the moderate urticaria state (utility value 0.782) to the well-controlled urticaria state (utility value 0.859). Therefore, it was mindful that the number of repeat courses of omalizumab would be much higher than 3, as stated by the company (see section 4.17). The Committee understood that, in the company's model, patients could remain in the response health state (urticaria free and well-controlled urticarial) until relapsing (during the 24-week treatment period plus the 64-week relapse-free period), which might explain why the model predicted higher utility gains than expected. However, the Committee agreed that there was some uncertainty around the difference in the observed benefits in the trial and in those predicted by the model. The Committee agreed that, it required a clear and quantified explanation from the company for this difference.

4.21 The Committee noted that, in the company's and the ERG's base-case analyses, the ICERs varied from around £20,000 to £25,000 per QALY gained. The Committee decided that the model had a number of flaws, in particular that the response and relapse rates lacked clinical validity and it also lacked face validity because the modelled QALY gains appeared much larger than what could have been inferred from the change in utility values in the GLACIAL trial. Because of this, the Committee concluded that the results

generated by the company's cost-effectiveness model were uncertain. Therefore, the Committee was minded not to recommend omalizumab as an add-on therapy for treating chronic spontaneous urticaria in adults and young people aged 12 years and over as a cost-effective use of NHS resources. The Committee requested the following further clarifications and analyses from the company to address the issues identified:

- An analysis using the individual patient data from the GLACIAL trial to determine in how many patients whose disease did not respond after the first dose of omalizumab, the disease did then respond after 1 or more subsequent doses.
- The average weekly urticaria activity scores (UAS7) by health state from the pooled analyses from the GLACIAL, ASTERIA I and ASTERIA II trials.
- The average number of courses of omalizumab needed for patients whose disease has responded to treatment for the entire time horizon of the model for the original base case and the subsequent revised base case.
- An update of the base-case analysis:
  - using a different and clinically realistic definition of response
  - employing a stopping rule for people whose disease does not respond after the second dose of omalizumab
  - using a revised estimate of the relapse rates from the GLACIAL trial taking into account that patients may have had spontaneous remission
  - using a linear extrapolation of relapse calculated from the GLACIAL trial
  - using corrected data for spontaneous remission fitted to an appropriate curve.
- Sensitivity analyses:

  - using and varying the effectiveness of omalizumab relative to no further pharmacological therapy
  - varying other parameters to a clinically meaningful degree.
- Scenario analyses both without stopping rules and using alternative stopping rules for people whose disease does not respond after first, third and fourth dose of omalizumab, and a fully incremental cost-effectiveness analysis including all stopping rules.
- A scenario analysis including waning of treatment effect during repeat courses of omalizumab.
- A clear and quantified explanation for the difference in benefits observed in the GLACIAL study and those presented in the model.
- Separate analyses for patients with moderate or severe urticaria at baseline.

4.22 The Committee discussed whether omalizumab was innovative, and whether the economic analysis had captured all changes in health-related quality of life. It recognised the limitations of current treatments in terms of their unlicensed use, adverse effects and requirements for additional monitoring, and agreed that omalizumab, with a better adverse-effect profile and apparent rapid mode of action, could be considered innovative in this disease. The Committee noted that the decrease in use of short courses of oral corticosteroids had not been factored into the modelling and so the model did not capture this additional benefit. The Committee appreciated that, as a consequence, the ICER may decrease. The Committee concluded, however, that these points did not change its current conclusion about the validity of the current cost-effectiveness results.

4.23 The Committee discussed whether any equality issues needed consideration. It heard that, because of the risk of anaphylaxis, omalizumab could only be given under medical supervision. The Committee noted that people who are physically disabled or live far from a treatment centre may therefore have limited access to the technology. The Committee noted that some centres provide transportation for patients and, in some situations; community nurses administer omalizumab to these patients in their homes. The Committee concluded that this is mainly an implementation issue, and did not pose an equality issue. The Committee also heard that the summary of product characteristics advises that omalizumab should be administered with caution in people who have kidney or liver diseases. The Committee noted that this is in line with clinical practice, and was not an equality issue.

Summary of Appraisal Committee's key conclusions

TAXXX	**Appraisal title:**	**Section**
Key conclusion		
The Committee is minded not to recommend omalizumab within its marketing authorisation as an add-on therapy for treating chronic spontaneous urticaria in adults and young people aged 12 years and over. The Committee recommends that NICE requests further clarification and analyses from the company, which should be made available for the second Appraisal Committee meeting.		1.1 1.2
Current practice		

Clinical need of patients, including the availability of alternative treatments	Chronic spontaneous urticaria is characterised by persistent itching, which can interfere with activities of daily living and sleep and, in severe cases, can be unbearable, disabling and considerably affects quality of life. There is no licensed treatment option for patients whose disease does not respond to H_1-antihistamines but, in practice, clinicians offer patients H_2-antihistamines and leukotriene receptor antagonists (LTRAs). Guidelines for urticaria recommend omalizumab at the same point in the pathway as immunosuppressants such as ciclosporin. However, because of funding restrictions in the NHS, omalizumab is currently only available to patients in England whose condition does not respond to ciclosporin.	4.1 4.2 4.2
The technology		

Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee heard from the clinical experts that they would use omalizumab instead of ciclosporin in the treatment pathway because it is licensed for this condition, has a very good safety profile and patients need less monitoring than ciclosporin. The Committee heard that omalizumab controls symptoms but is not 'disease-modifying' and that, in most patients, the condition relapses within 4–6 weeks of stopping treatment and repeat treatment is needed. The Committee recognised the limitations of current treatments in terms of their unlicensed use, adverse effects and need for additional monitoring. It agreed that omalizumab, with a better adverse-effect profile and apparent rapid mode of action, could be considered innovative in this disease. The Committee noted that the decrease in use of short courses of oral corticosteroids had not been factored into the modelling, so the model did not capture this additional benefit.	4.2 4.2 4.22

What is the position of the treatment in the pathway of care for the condition?	The company positioned omalizumab after treatment with up to 4 times the licensed dose of H_1-antihistamines, LTRAs and H_2-antihistamines, whereas the marketing authorisation and therefore the scope specified use after an inadequate response to H_1-antihistamines. The Committee concluded that the population presented by the company in its decision problem was appropriate and that omalizumab could be considered as a fourth-line option in the pathway, in the same place as immunosuppressants.	4.3 4.3
Adverse reactions	The Committee noted that in the clinical trial adverse events in the omalizumab and placebo arms were comparable but that, because of a risk of anaphylaxis, the advice in the summary of product characteristics is to monitor patients. The Committee understood from the clinical experts that anaphylaxis is very rare and although the risk of anaphylaxis decreases with each dose, appropriate precautionary measures as detailed in the summary of product characteristics continue to be needed.	4.8
Evidence for clinical effectiveness		

Availability, nature and quality of evidence	The company included evidence from a single phase III trial, GLACIAL, and included 2 more phase III trials, ASTERIA I and ASTERIA II, as supporting evidence in an appendix.	4.4
Relevance to general clinical practice in the NHS	The Committee agreed that patients in the GLACIAL trial were representative of those who would have omalizumab, and concluded that the results from the GLACIAL trial were generalisable to clinical practice in England.	4.4
Uncertainties generated by the evidence	The Committee noted that the evidence from randomised trials on the effectiveness of ciclosporin in chronic spontaneous urticaria is very limited, and did not allow for a robust indirect comparison with omalizumab. The summary of product characteristics does not specify treatment duration or any stopping rules but states 'prescribers are advised to periodically reassess the need for continued therapy' and 'clinical trial experience of long-term treatment beyond 6 months in this indication is limited'.	4.3 4.7
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	No specific consideration of subgroups.	N/A

Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee noted that omalizumab was associated with statistically better outcomes compared with placebo in most of the reported clinical and quality-of-life outcome measures. The Committee also noted that the weekly itch severity score started increasing after stopping treatment at 24 weeks and reached the same level as placebo at week 40.	4.6
Evidence for cost effectiveness		
Availability and nature of evidence	The company submitted a de novo Markov model. The model evaluated the cost utility of omalizumab for patients with an inadequate response despite combining H_1-antihistamines (up to 4 times the licensed dose), with either H_2 antihistamines or LTRAs, or all 3 drugs together, compared with 'no further pharmacological treatment'.	3.24
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee noted that, for modelled patients whose disease does not respond to omalizumab treatment would stop at 16 weeks (4 doses); however, it heard from the clinical experts that patients whose disease does not respond after the first dose may only be given 1 more dose. The Committee noted that the model did not compare omalizumab with other comparators (such as ciclosporin). The Committee concluded that the response	4.7 4.9

	criteria used in the model was not fit for purpose and, to inform its decision-making, the company needed to use a more valid clinical definition of response in the model.	4.10
	The Committee understood that patients with severe and moderate urticaria are distinguishable populations and should be modelled separately because a difference in cost effectiveness would be expected for between these separate populations.	4.11
	The Committee agreed that the modelled stopping rule at 16 weeks was not clinically realistic.	4.13
	The Committee concluded that relapse probabilities used in the model for immediate post-treatment period overestimated the time to relapse.	4.14
	The Committee agreed that it would be more appropriate for the base-case analysis to use a linear extrapolation of the relapse data from the GLACIAL trial.	4.15
	The Committee noted long-term data of patients having repeated courses was lacking. Because of this lack of evidence, the assumption of maintaining the same magnitude of treatment effect with omalizumab during subsequent courses was associated with substantial uncertainty.	4.16

	The Committee concluded that, to inform its decision-making, the company needed to clarify the number of repeat courses predicted by the model for 'responders'. The Committee noted that the company's approach predicted an improbably high median duration of disease (20.8 years), whereas it heard from the clinical experts that approximately 90% of patients have spontaneous remission within 5 years.	4.17 4.18
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The Committee noted that the utility value used for the severe urticaria health state was 0.712 and bearing in mind the testimonies from the patient experts, considered that severe disease would be considerably disabling. The Committee noted that the decrease in use of short courses of oral corticosteroids had not been factored into the modelling so the model did not capture this additional benefit.	4.19 4.22
Are there specific groups of people for whom the technology is particularly cost	The Committee understood that patients with severe and moderate urticaria are distinguishable populations and should be modelled separately as a difference in cost effectiveness would be expected between	4.11

effective?	these separate populations.	
What are the key drivers of cost effectiveness?	There were no specific Committee considerations on the key drivers of cost effectiveness.	N/A
Most likely cost-effectiveness estimate (given as an ICER)	The Committee concluded the model had a number of fundamental flaws –in particular that the response and relapse rates lacked clinical validity and it also lacked face validity because the modelled QALY gains appeared much larger than what could have been inferred from the change in utility values in the GLACIAL trial. It concluded that the results generated by the company's cost-effectiveness model were very uncertain.	4.21
Additional factors taken into account		
Patient access schemes (PPRS)	The company has agreed a patient access scheme with the Department of Health. This scheme would provide a simple discount to the list price of omalizumab across all indications with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence.	2.5
End-of-life considerations	N/A	
Equalities considerations and social value	The Committee heard that, because omalizumab could only be given under medical supervision, people who are physically disabled or rurally located may not	4.23

judgements	have access to the technology in the same way as the wider population. The Committee noted that some centres provide transportation for patients who need it and, in some situations, community nurses are trained to administer omalizumab to these patients in their homes. The Committee concluded that this is mainly an implementation issue, and did not pose an equality issue that it needed to address. The Committee also heard that the summary of product characteristics advises that omalizumab should be administered with caution in people who have kidney or liver diseases and noted that this is in line with clinical practice and was not an equality issue.	

5 Implementation

5.1 NICE has developed tools [link to www.nice.org.uk/guidance/TAXXX] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

There is no guidance related to this appraisal.

7 Proposed date for review of guidance

7.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Dr Amanda Adler
Chair, Appraisal Committee
November 2014

8 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.

Dr Amanda Adler (Chair)
Consultant Physician, Addenbrooke's Hospital

Professor Ken Stein (Vice Chair)
Professor of Public Health, University of Exeter Medical School

Dr Jeff Aronson
Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Professor John Cairns
Professor of Health Economics Public Health and Policy, London School of Hygiene and Tropical Medicine

Mr Mark Chapman

Health Economics and Market Access Manager, Medtronic UK

Professor Imran Chaudhry

Lead Consultant Psychiatrist and Deputy Associate Medical Director, Lancashire Care NHS Foundation Trust

Dr Lisa Cooper

Echocardiographer, Stockport NHS Foundation Trust

Professor Daniel Hochhauser

Consultant in Medical Oncology, UCL Cancer Institute

Dr Rebecca Kearney

Clinical Lecturer, University of Warwick

Dr Miriam McCarthy

Consultant, Public Health, Public Health Agency, Northern Ireland

Professor Ruairidh Milne

Director of Strategy and Development and Director for Public Health Research at the National Institute for Health Research (NIHR) Evaluation, Trials and Studies Coordinating Centre at the University of Southampton

Dr Peter Norrie

Principal Lecturer in Nursing, DeMontfort University

Mr Christopher O'Regan

Head of Health Technology Assessment & Outcomes Research, Merck Sharp & Dohme

Professor Stephen Palmer

Professor of Health Economics, Centre for Health Economics, University of York

Dr Sanjeev Patel

Consultant Physician & Senior Lecturer in Rheumatology, St Helier University Hospital

Dr John Pounsford

Consultant Physician, Frenchay Hospital, Bristol

Dr Danielle Preedy

Lay Member

Mr Cliff Snelling

Lay Member

Ms Marta Soares

Research Fellow, Centre for Health Economics, University of York

Professor Andrew Stevens

Professor of Public Health, Department of Public Health and Epidemiology, University of Birmingham

Dr Nicky Welton

Senior Lecturer in Biostatistics/Health Technology Assessment, University of Bristol

Dr Nerys Woolacott

Senior Research Fellow, Centre for Health Economics, University of York

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.

Dr Anwar Jilani

Technical Lead(s)

Joanna Richardson
Technical Adviser

Jeremy Powell
Project Manager

9 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by the Southampton Health Technology Assessments Centre (SHTAC):

- Jones J., Cooper K., Picot J. et al., Omalizumab for previously treated chronic spontaneous urticaria, September 2014

B. 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). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company:

- Novartis

II. Professional/specialist and patient/carer groups:

- Allergy UK
- British Association of Dermatologists
- British Society for Allergy and Clinical Immunology
- Royal College of Paediatrics and Child Health
- Royal College of Pathologists
- Royal College of Physicians

III. Other consultees:

- Department of Health
- NHS England
- Welsh Government

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

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on omalizumab by attending the initial Committee discussion and providing written evidence to the Committee. They are invited to comment on the ACD.

- Dr Clive Grattan, Consultant Dermatologist, Norfolk & Norwich University Hospital and St John's Institute of Dermatology, nominated by the British Association of Dermatologists – clinical expert
- Dr Shuiab Nasser, Consultant in Allergy and Asthma, Cambridge University Hospitals NHS Foundation Trust, nominated by British Society for Allergy and Clinical Immunology – clinical expert
- Dr Sinisa Savic, Consultant Clinical Immunologist, Leeds Teaching Hospitals NHS Trust, nominated by Novartis and by the Royal College of Pathologists– clinical expert
- Mrs Maureen Jenkins, Clinical Director, Allergy UK, nominated by Allergy UK – patient expert
- Mrs Deborah Shipman, nominated by Allergy UK - patient expert – patient expert

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

- Novartis