NICE National Institute for Health and Care Excellence

NICE guidance

Omalizumab for previously treated chronic spontaneous urticaria

Technology appraisal guidance
Published: 8 June 2015

www.nice.org.uk/guidance/ta339

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1 Recommendations

1.1 Omalizumab is recommended as an option as add-on therapy for treating severe chronic spontaneous urticaria in adults and young people aged 12 years and over only if:

- the severity of the condition is assessed objectively, for example, using a weekly urticaria activity score of 28 or more
- the person's condition has not responded to standard treatment with H_1-antihistamines and leukotriene receptor antagonists
- omalizumab is stopped at or before the fourth dose if the condition has not responded
- omalizumab is stopped at the end of a course of treatment (6 doses) if the condition has responded, to establish whether the condition has gone into spontaneous remission, and is restarted only if the condition relapses
- omalizumab is administered under the management of a secondary care specialist in dermatology, immunology or allergy
- the company provides omalizumab with the discount agreed in the patient access scheme.

1.2 People whose treatment with omalizumab is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

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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. 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; BNF online October 2014). A single dose of 300 mg costs £512.30 and the cost for a 24-week course of treatment is £3,073.80 (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.

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3 The company's submission

The Appraisal Committee considered evidence submitted by Novartis, and a review of this submission by the Evidence Review Group (ERG).

Clinical effectiveness

3.1 The company presented evidence on a narrower population than covered by the marketing authorisation based on feedback from UK clinicians on the 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 (which have been used at 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 is responding inadequately to whichever combination of therapies they are currently having.

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 3 studies (GLACIAL, ASTERIA I and ASTERIA II), 2 phase 2 studies (MYSTIQUE and X-CUISITE) and 1 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 the ASTERIA I and ASTERIA II trials as an appendix to its submission. The companydid 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 3 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;

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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 to 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 LTRAs, 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 women, 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. In the trials, a 'minimum important difference' was defined as a decrease of at least 5 points in the weekly itch severity score.

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 to 6) and the UAS7 is the sum of the daily UAS over 7 days (ranging from 0 to 42). A higher UAS indicates more urticaria activity. Baseline UAS7 was calculated using data from the 7 days before the first treatment date.

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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. In the trials, a 'minimum important difference' was defined as a decrease of at least 11 points in the UAS7.

3.7 At baseline, 54.4% (137 out of 252) of those in the omalizumab group and 49.4% (41 out of 83) of those in the placebo group had angioedema. Patients were tested for the presence of anti-omalizumab antibodies and all but 1 patient tested negative at baseline.

3.8 The duration of the trial was 24 weeks, during which patients had omalizumab, with a follow-on 16-week 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 'minimum 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 minimum 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 in 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.

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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 score from baseline to 12 and 24 weeks of treatment. The results of the subgroup analysis 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 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group trials. The primary end point of these trials was the change in weekly itch severity score from baseline to week 12. 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

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including corticosteroids, and showing that re-treatment 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-week follow-up. At 24 weeks, the incidence of adverse events was similar in the omalizumab and placebo groups (65.1% compared with 63.9% respectively). During the treatment plus follow-up period of 40 weeks, the company saw comparable rates in:

- 1 or more adverse events (83.7% with omalizumab compared with 78.3% for placebo)
- 1 or more adverse events suspected to be caused by the drug (11.1% with omalizumab compared with 13.3% for placebo)
- 1 or more serious adverse events (7.1% with omalizumab compared with 6.0% for placebo) and
- adverse events leading to withdrawal (1.2% in both groups).

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In both groups, the most frequent treatment-related adverse events were infections and infestations (36.9% with omalizumab compared with 30.1% for placebo), gastrointestinal disorders (15.9% compared with 14.5%), and skin and subcutaneous disorders (16.7% compared with 14.5%). Headache (8.7% compared with 3.6%) and upper respiratory tract infections (7.1% compared with 2.4%) were more common in the omalizumab group, whereas sinus congestion (1.2% compared with 4.8%), migraine (1.6% compared with 3.6%) and idiopathic urticaria (2.8% compared with 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% compared with 38.0% respectively), gastrointestinal disorders (11.4% compared with 15.2%) and skin and subcutaneous disorders (17.7% compared with 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

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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 for 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 in the treatment and placebo groups had 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 minimum 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 with the other patients not in the subgroup, as opposed to comparing the subgroup with all patients in the trial.

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 the weekly itch severity score and the 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

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-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 incidences of adverse events and serious adverse events were similar in the omalizumab 300 mg groups and the 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 having combined 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, and the corresponding scores, were:

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

In addition, the model included health states for relapse and death. All

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modelled patients were in either the moderate or severe urticaria health state at baseline and were treated either with omalizumab 300 mg plus 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 get 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 the 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 weeks 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 go into 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 original model, before consultation 'relapse' was defined as moderate or

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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. According to Metz et al., in most patients the disease relapsed 4 to 8 weeks after stopping omalizumab and the longest observed period without reappearance of symptoms after omalizumab treatment was 16 months. The company also did 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 had a relapse 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 re-treated 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 re-treated had a response when first treated with omalizumab. In a scenario, the company assumed instead that some patients would not have a response when re-treated with omalizumab, and that the proportion with no response when re-treated 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

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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 re-treatment, the company assumed the same probabilities for stopping for first and subsequent courses of omalizumab. After stopping omalizumab, patients remained on the background medications. Patients who stopped omalizumab because of adverse events, disease progression, physician decision or patient choice were not re-treated with omalizumab in the model. The probabilities of them moving between health

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states were based on the placebo arm of the GLACIAL trial.

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 for 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. For each of the 5 health states in the model, it used a mixed-effect regression model to estimate the following utility values (rounded mean UAS7 in brackets): severe urticaria 0.712 (34.1); moderate urticaria 0.782 (21.9); mild urticaria 0.845 (11.4); well-controlled urticaria 0.859 (3.1); and urticaria-free 0.897 (0.0). 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], LTRAs [£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 to 2013 (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,

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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 the 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 NICE's technology appraisal guidance on 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). This resulted in an incremental cost-effectiveness ratio (ICER) of £19,632 per QALY gained.

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

3.42 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.

3.43 The ERG noted that the company did not provide details on how it assured quality in the patient-level data analysis. The ERG 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 affect the results.

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3.44 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 study reported different 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 et al. paper, overestimating remission up to around 24 months and underestimating 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 the disease. The clinical advice received by the ERG suggested a spontaneous remission of around 50% to 70% within 2 years and 70% to 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 to 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.

3.45 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.

3.46 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.

3.47 The ERG could not independently verify drop-out rates used by the company in

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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, whereas 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.

3.48 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.

Company's additional post-consultation evidence

Revised base case

3.49 In response to consultation, the company revised its model and provided revised results from base-case analyses. The new assumptions included:

- A different definition of relapse for patients with severe urticaria at baseline, now defined as having a UAS7 of 16 or less instead of 6 or less, as in the original base case. The company did not change the definition of response in the patients with moderate urticaria at baseline, which remained a drop to a UAS7 of 6 or less. In practice, the new response criteria mean that patients' scores must drop at least 2 health states for their disease to be considered to have responded.
- A new early stopping rule for the patients whose disease did not respond to omalizumab. Instead of 16 weeks (after 4 doses), as in the original base case, the company assumed that patients whose disease does not respond stop treatment at 8 weeks (after 2 doses).

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- Corrected data for spontaneous remission from Kaplan–Meier curves from the Nebiolo et al. (2009) paper.
- Revised estimates of relapse rates from the follow-up period of the GLACIAL trial accounting for some patients spontaneously remitting.
- Linear extrapolation of relapse rates from the follow-up period of the GLACIAL trial.

3.50 The company's revised deterministic base-case result showed that, with the patient access scheme, omalizumab was associated with a total incremental cost of £7,222 with an additional gain of 0.263 QALYs, which resulted in an ICER of £27,469 per QALY gained.

3.51 The company's revised probabilistic base-case results, based on running the model with 1,000 iterations, showed that the average incremental cost was £7,191 and the average incremental QALY gain was 0.26, which resulted in an ICER of £27,707 (95% CI 27,548 to 27,886) per QALY gained. The probabilistic analysis indicated that there is a 0.2% and 80.7% probability of omalizumab being cost effective, at the maximum acceptable ICERs of £20,000 and £30,000 per QALY gained respectively.

Revised sensitivity analyses

3.52 The company presented deterministic sensitivity analyses varying various parameters of the model one at a time. To vary the modelled clinical effectiveness of omalizumab, the company presented 4 analyses that varied the proportion of patients in the urticaria-free and well-controlled urticaria health states separately, for each arm. For each analysis, the company calculated the percentage variation between the proportion of patients in the specific 'responder' health state (urticaria-free or well-controlled urticaria) at 24 weeks and the upper and lower limits of its 95% confidence interval. The company applied the same percentage variation at 4, 8, 12, 16, 20 and 24 weeks simultaneously in that health state and distributed the remaining proportions across the mild, moderate and severe health states, keeping the proportion in the other 'responder' state (urticaria-free or well-controlled urticaria) unchanged.

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Varying the proportion of patients in the urticaria-free health state in the omalizumab arm had the most impact (compared with other health state or treatment combinations) and the ICER, with its upper and lower variation, ranged from £26,726 to £28,336 per QALY gained.

3.53 The company also provided deterministic sensitivity analyses by varying other parameters. The results showed that the revised base-case ICER was most sensitive to change in the cumulative relapse rate in people free of urticaria, the acquisition cost of omalizumab, the cost of the severe urticaria health state, and the discount rates for outcomes and costs.

Incremental analyses for various stopping rules

3.54 The company also provided a fully incremental analysis assessing the impact on cost effectiveness of different stopping rules for people whose disease does not respond after the first, second, third and fourth dose, and assuming no early stopping (that is, all patients had omalizumab for 6 doses irrespective of response). The company also provided data on the cumulative response seen in the GLACIAL trial (expressed as a proportion of all treated patients) by dose (see section 3.59). The results showed that more patients benefited from the first dose than from subsequent doses of omalizumab (0.225 QALYs gained for the first dose) and the incremental QALY benefits with subsequent doses were marginal and ranged between 0.038 (for the second dose) to -0.001 (for the sixth dose). The fourth dose dominated (more effective and less costly than) the sixth dose. The corresponding fully incremental ICERs ranged from £26,824 per QALY gained (for the first dose) to £32,493 per QALY gained (for the third dose).

Scenario with waning effect on re-treatment

3.55 The company responded to the Committee's request for a scenario analysis including waning of treatment effect during repeated courses of omalizumab by presenting scenarios in which fixed proportions of prior 'responders' did not respond on re-treatment (varying from 1% to 10%). In these analyses, both incremental costs and QALYs reduced with increasing proportions of prior 'responders' not responding on re-treatment. The proportionate reduction in

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QALYs was slightly greater than the proportionate reduction in costs, leading to a small increase in the ICER from £27,469 per QALY gained in the revised base case to £28,748 per QALY gained in the scenario in which 10% of prior 'responders' did not respond on re-treatment.

Subgroup analysis

3.56 As requested by the Committee, the company also provided separate results for patients with moderate and severe urticaria at baseline as opposed to patients with moderate and severe urticaria combined. The ICERs were £29,951 and £26,278 per QALY gained respectively.

Comparison of the GLACIAL results with model results

3.57 In response to a request by the Committee for the company to provide a clear and quantified explanation for the difference in benefits seen in the GLACIAL trial and those estimated by the model, the company compared the trial results and the model predictions in terms of the proportion of patients with a UAS7 of 0 and a UAS7 of 6 or less at 40 weeks, corresponding to the end of the GLACIAL trial. To generate model outcomes comparable to the trial results, the company changed the following model settings:

- 24 weeks of treatment for all patients (no early stop for 'non-responders')
- imputing missing data using the baseline observation carried forward method (as done in the clinical trial analysis)
- assuming no re-treatment with omalizumab
- assuming no death occurred.

3.58 For patients receiving omalizumab, the proportion of patients with a UAS7 of 0 and a UAS7 of 6 or less predicted by the revised model (12.3% and 19.5% respectively) was similar to that seen in the GLACIAL trial (12.3% and 19.8% respectively). However, for patients in the comparator arm, the model and trial results differed. The proportion of patients with a UAS7 of 0 and a UAS7 of 6 or

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less among patients having only background medication in the GLACIAL trial was 13.3% and 20.5% at 40 weeks. The corresponding values predicted by the model were 1.8% and 8.0%.

'Responders' after each dose in the GLACIAL trial

3.59 The company presented further analyses of the GLACIAL trial, exploring the response in patients with each subsequent dose of omalizumab. The company presented analyses separately for patients with moderate and severe urticaria at baseline. For moderate urticaria, the cumulative response after each of 6 doses was: 53.4%, 71.2%, 78.1%, 82.2%, 82.2% and 83.6%. For severe urticaria, using the revised definition of response (UAS7 of 16 or less), the cumulative responses were: 47.5%, 57.0%, 62.6%, 68.7%, 71.5%, and 72.6%.

Courses of omalizumab needed for patients whose disease responded

3.60 The company also provided the number of courses (of 6 doses each) which a patient re-treated with omalizumab would need over the entire time horizon of the model, assuming the patient's condition had previously responded to treatment. The revised model predicted that 'responders' would need 6.61 courses on average over a time horizon of 10 years. The company also provided the average number of treatment courses after adjusting for patients whose disease may spontaneously remit, who may stop omalizumab because of adverse effects, or who may die. The analysis showed that, on average, a 'responder' who continues to have omalizumab for the entire time horizon would receive 13.69 courses of omalizumab.

Evidence Review Group's comments on the company's additional evidence

3.61 The ERG commented that the revised definition of response may still underestimate the proportion of patients having a clinically significant response.

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For example, to be considered a 'responder', a patient with severe disease and the lowest UAS7 (28) would need to improve by 12 points, whereas a patient with severe disease and the highest UAS7 (42) would need to improve by 26 points. The ERG also noted that, in the company's revised sensitivity analyses, the hazard ratios for remission, health state costs and utility values varied by arbitrary percentage points instead of varying within a clinically meaningful range as requested by the Committee.

3.62 The ERG commented that comparing the results from the GLACIAL trial with the model estimates (see section 3.58) indicated that the model did not perform well in predicting 40-week outcomes. It noted that the clinical trial results suggested little difference in the proportion of patients with a UAS7 of 6 or less between omalizumab and placebo arms, whereas the model predicted a substantial benefit with omalizumab. The ERG noted that the company did not adequately explain the difference between the results from the trial and the model, further noting that it may reflect a serious flaw in the model.

3.63 Full details of all the evidence are in the committee papers.

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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, can make a person feel self-conscious and can cause painful angioedema.

4.2 The Committee discussed the natural history and current management of chronic spontaneous urticaria. It heard from clinical experts that chronic spontaneous urticaria is a naturally remitting disease, that around 50% of 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 duration of the disease does not predict the severity of the disease, but in patients who had the disease for years it was less likely to go into spontaneous remission. The Committee heard that H_1-antihistamines are the standard first-line treatment for chronic spontaneous urticaria, and 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 of H_2-antihistamines in

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patients whose disease is non-responsive to H_1-antihistamines and the use of H_2-antihistamines in clinical practice is decreasing. The Committee noted that a recent clinical guideline jointly issued by the European Academy of Allergy and Clinical Immunology, the Global Allergy and Asthma European Network, the European Dermatology Forum and the World Allergy Organization, referred to in the company's submission, does not recommend H_2-antihistamines for treating chronic severe urticaria. The Committee heard that treating with LTRAs may help some, but not all, patients. The Committee took into account the comment received during consultation that H_2-antihistamines are an out-of-date treatment for chronic spontaneous urticaria. It discussed the company's explanation for positioning omalizumab in a population whose disease had an inadequate response to H_2-antihistamines and noted that the positioning was based on the inclusion criteria of the GLACIAL trial. The Committee also heard from the clinical and patient experts that patients with severe disease may need oral corticosteroids.

4.3 The Committee heard that patients with severe chronic spontaneous urticaria whose disease does not respond to the initial treatments are often offered immunosuppressants such as ciclosporin. The Committee heard that ciclosporin can be effective, but can also cause serious adverse effects. The Committee noted that ciclosporin may cause hypertension, hyperlipidaemia, and hepatic and renal impairment. The Committee also heard from a patient expert that she had gained weight, which she attributed to taking ciclosporin. The Committee further heard from the patient expert that ciclosporin helped relieve her symptoms such as itching and hives, but her overall health had declined because the treatment caused sleepiness, lethargy, and restricted her work and leisure activities. The Committee also heard from the clinical experts that, because of the risks of serious adverse effects, ciclosporin is reserved mainly for patients with severe chronic spontaneous urticaria. The experts estimated that approximately 70% of patients with severe urticaria take ciclosporin. The Committee also heard that patients who take ciclosporin need close monitoring of liver and renal function and therefore need frequent visits to GPs and hospitals.

4.4 The Committee discussed where omalizumab would fit in the treatment pathway of chronic spontaneous urticaria. The Committee heard from the clinical experts that the guideline recommends omalizumab at the same point in the pathway as immunosuppressants, such as ciclosporin. However, because of funding

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restrictions in the NHS, omalizumab is currently usually available only to patients in England whose condition does not respond to ciclosporin. The Committee heard from the clinical experts that they would offer patients omalizumab instead of ciclosporin because omalizumab 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 take omalizumab, their disease improves rapidly within 1 to 2 weeks after the first dose and in many patients their symptoms resolve completely. The Committee heard that patients taking omalizumab 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'; in most patients, the condition relapses within 4 to 6 weeks of stopping omalizumab and patients need treating again. The Committee noted the consultation comment that, because of funding restrictions, clinical experience with omalizumab in England is from a population whose disease has not responded to immunosuppressants and which is more difficult to treat than the population considered in the decision problem.

4.5 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 for use after standard treatment with H_1-antihistamines (up to 4 times the licensed dose), with LTRAs and H_2-antihistamines, whereas the scope and marketing authorisation specified using omalizumab 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 4.4), the Committee concluded that the company had targeted omalizumab at a clinically appropriate population and that omalizumab could be considered as a third- or 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)

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comments 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 Committee concluded that ciclosporin was an appropriate comparator in this appraisal but understood that, because of the lack of robust clinical evidence, no formal comparison could be made.

4.6 The Committee considered the evidence on the clinical effectiveness of omalizumab, noting that the company included evidence from a single phase 3 trial, GLACIAL. It noted that the company included 2 more phase 3 trials, ASTERIA I and ASTERIA II, as supporting evidence. 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. The Committee noted that the patients in the GLACIAL trial had chronic spontaneous urticaria for several years and reflected the patients that clinicians in England would treat with omalizumab. The Committee agreed that the patients in the GLACIAL trial were similar to those who would be offered omalizumab, and concluded that the results from the GLACIAL trial were generalisable to clinical practice in England.

4.7 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 noted that the primary efficacy outcome, weekly itch severity score, and the outcome used in the model to capture clinical effectiveness, urticaria activity score over 7 days (UAS7), do not take into account many other aspects that are important to patients with chronic spontaneous urticaria, such as pain, red skin and angioedema. 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 a clinical expert that the measures, particularly those measuring health-related quality of life, are useful and should be used by clinicians. The Committee also heard that patients are currently often required to complete several of the outcome measures when applying for funding for omalizumab. In general, however, clinicians do not consider these measures

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key in choosing who to treat, or when to continue treating, with omalizumab. The Committee concluded that, although the measures had limitations, the outcomes in the trials were relevant for this appraisal.

4.8 The Committee discussed the results of the clinical trials. It noted that omalizumab was associated with statistically better outcomes compared with placebo in most of the clinical and quality-of-life outcome measures. The Committee noted that, in the GLACIAL trial, the mean weekly itch severity score rapidly decreased after the first dose of omalizumab and stayed lower with omalizumab than with placebo throughout the 24-week treatment period. The Committee noted that patients in the placebo arm had lower weekly itch severity scores 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 randomised to placebo. The Committee also noted that, in the GLACIAL trial, the weekly itch severity score for patients randomised to omalizumab increased after stopping treatment at 24 weeks and reached the same level as for patients on 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 done by the ERG, thereby including a wider population, and noted there was little difference between these results and those using analyses from the GLACIAL trial only. The Committee concluded that omalizumab improves symptoms in chronic spontaneous urticaria.

4.9 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 omalizumab ('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 heard from the clinical experts that they would stop treatment after a course of 6 doses to see if a patient's disease had gone into spontaneous remission. The Committee noted that, for patients whose disease does not respond to omalizumab, the company

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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. The clinicians noted that, nonetheless, patients are usually offered 4 doses. The Committee noted the new evidence submitted by the company in response to consultation, which suggested that a large proportion of patients have a response after the first dose and the proportion of 'responders' continues to increase with each subsequent dose up to 4 doses, and that few additional patients had a response after 4 doses (see section 3.59). The Committee concluded that most patients who are going to have a response will do so by the fourth dose, and that it is appropriate that clinicians consider stopping omalizumab at or before the fourth dose if there is no response.

4.10 The Committee considered the safety data for 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 administering omalizumab, the advice in the summary of product characteristics is that treatment for anaphylactic reactions should always be available during omalizumab treatment. The Committee understood from the clinical experts that anaphylaxis is very rare and the risk decreases with each dose, but that precautionary measures are needed, and that generally omalizumab is given at centres with resuscitation facilities.

Cost effectiveness

4.11 The Committee considered the company's economic model, the assumptions on which the company based its choice of model parameters, the revised analyses presented in response to consultation on the draft guidance, 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 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 noted that relatively small changes in symptoms could lead to a change in health state and, conversely, patients can remain in the same health state despite relatively large changes in symptoms. The Committee noted that the model compared omalizumab only with no further pharmacological treatment,

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and not with other relevant comparators such as ciclosporin. Noting that such comparisons were not possible, the Committee accepted the company's choice of comparator, but noted uncertainty around some of the assumptions used in the model.

4.12 The Committee was concerned about how the company had defined treatment response in the original model in which the company had defined response as achieving an absolute level of UAS7 of 6 or less and the definition did not take into account the baseline (pre-treatment) UAS7. The Committee noted that the revised model maintained the original definition of response for patients with moderate disease at baseline, whereas, for patients with severe urticaria at baseline, the company applied the revised definition of a UAS7 of 16 or less. The Committee noted the ERG's comment that the revised definition may still not identify all patients who have a clinically significant response. The ERG would have preferred the definition of response to reflect an absolute decrease of 10 points or more on the UAS7 scale, in line with clinical opinion. The Committee understood that, given the structure of the model, it was not possible to implement response as an absolute decrement in UAS7. The Committee accepted that the revised definition of response is closer to how clinicians would consider a response than the original definition, but was aware that it may not capture all 'responders'.

4.13 The Committee discussed the probability of a patient's disease relapsing as estimated in the model by first focusing on the cumulative relapse rate seen in the GLACIAL trial. The Committee understood that the company calculated the relapse rate separately for patients in the mild urticaria, well-controlled urticaria and urticaria-free health states using the proportion of patients in each state and the relapse rates seen in the GLACIAL trial up to the end of the observational follow-up period (40 weeks). The Committee noted that the revised cumulative proportion of patients whose disease relapses at 40 weeks in the GLACIAL trial (16 weeks after the end of treatment), after accounting for patients whose disease goes into spontaneous remission, ranged from around 49% (for well-controlled urticaria) to around 62% (for urticaria-free and mild urticaria). Based on the clinical experts' opinion, the Committee had expected the cumulative relapse rate at 16 weeks to be close to 100%. The Committee noted the consultation comment that the difference may reflect that, compared with the trial patients, patients in England who have had omalizumab to date reflect a

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population whose disease is refractory and has not responded to immunosuppressants (see section 4.4). The Committee concluded that, in the NHS, patients who would have omalizumab before having immunosuppressants may have a longer relapse-free period and the probabilities for relapse estimated in the revised model for the immediate post-treatment period are therefore plausible.

4.14 In addition to discussing relapse in the immediate post-treatment period, the Committee discussed the company's original and revised approaches to extrapolating the probability of relapse over the 10-year time horizon. The Committee noted that, in the original analyses, when extrapolating relapse data after the 16-week post-intervention observational follow-up period in the GLACIAL trial, both the company and the ERG assumed that the disease relapses by 64 weeks in all patients who had a response to omalizumab. The Committee noted that this 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 Metz et al. study reported 64 weeks as the longest relapse-free period, and most for patients in the study the relapse-free period was between 4 and 8 weeks. On the Committee's request, the company used a linear function in its revised model to extrapolate relapse that decreased the time to relapse for all 'responders' (see section 3.49). The Committee noted the company's comment received in response to consultation that using a linear extrapolation underestimated the time to relapse when omalizumab is used in a population whose disease has an inadequate response to standard treatment with H_1-antihistamines including high doses, or to LTRAs with or without H_2-antihistamines. The Committee recalled the clinical testimony about quick relapse after stopping omalizumab and also noted that cumulative relapse rates available from the post-treatment period of the GLACIAL trial showed a linear trend. Therefore, the Committee did not accept the company's view that linear extrapolation is a 'worst-case' scenario. The Committee concluded that, because of a lack of robust evidence, long-term relapse rates used in the model were uncertain and linearly extrapolating relapse data from the GLACIAL trial was the most plausible scenario.

4.15 The Committee discussed modelling spontaneous remission. The Committee noted that the company's original approach predicted an improbably high median duration of disease (20.8 years), whereas it heard from the clinical experts that

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spontaneous remission occurs in approximately 90% of patients within 5 years. The Committee noted that the ERG's approach (see section 3.44) predicted a median duration of disease of 6 to 7 years, which was also higher than that expected by clinicians. The Committee was aware that the company, in its original model, used incorrectly reported data from the text of the publication by Nebiolo et al. (2009) whereas the ERG used the data derived from the correctly-reported Kaplan–Meier curves in the same publication. The Committee was satisfied that the company acknowledged its error, and concluded that the company had used the correct data in its revised base case.

4.16 The Committee noted that the company based the utility values in the model on the pooled 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. The Committee heard from the patient expert that severe disease is considerably disabling, affecting her all day long, every day and felt this figure should be much lower. The Committee questioned whether the high value might reflect the wide range of UAS7 values (28 to 42) used by the company to define the severe health state. Following consultation, the Committee noted that the average UAS7 value for patients with severe disease was 34.1, which was close to the midpoint of the range used to define the severe health state. The Committee therefore concluded that this did not explain the apparent high utility value for the severe health state. The Committee then discussed whether the EQ-5D, reflecting pain but perhaps not all other features of urticaria (such as change in appearance, red skin) would capture the true disutility associated with chronic urticaria. It concluded that some aspects of the quality-of-life impact may not be included in the EQ-5D.

4.17 The Committee noted that the company assumed that patients whose disease responded to the first course (6 doses, after which the patient stops regardless of response) of omalizumab and then relapsed could have an unlimited number of further courses of omalizumab. The Committee noted that there was limited evidence on the effectiveness of repeat courses of omalizumab and heard from the clinical experts that, in their experience, re-treating with omalizumab was effective. The Committee noted the comments by the company, received in response to consultation, that published observational studies, the pharmacokinetics of omalizumab and experience with omalizumab in severe persistent asthma supported an assumption that the treatment effect is

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maintained on repeated courses. The Committee concluded that the evidence available to date does not support a waning effect on subsequent repeated courses of omalizumab and therefore it is reasonable to assume a constant effect.

4.18 The Committee discussed the model validation exercise submitted by the company in response to the Committee's request. The Committee noted that, for patients having omalizumab, the model accurately predicted the proportions of patients in the 'responder' health states as per the original definition of response (a UAS7 of 6 or less) at week 40 as seen in the GLACIAL trial. However, it noted that the model underestimated the response in the comparator 'no further pharmacological treatment' arm. The Committee heard from the company that the model incorporated data from the GLACIAL trial only for the first 24 weeks after starting therapy for the first time but, unlike the GLACIAL trial, modelled patients in the base-case analysis could relapse and be re-treated between 24 and 40 weeks after first starting therapy. The Committee was not convinced that re-treatment in the omalizumab arm would result in a lower proportion of 'responders' in the comparator arm. The Committee concluded that there were major concerns about the model in that the modelled data from the trial for the placebo arm seemed to overestimate the effectiveness of omalizumab.

4.19 The Committee noted that, in the company's revised base-case analysis for the combined population with moderate and severe disease, the incremental cost-effectiveness ratio (ICER) was approximately £28,000 per quality-adjusted life year (QALY) gained. The Committee agreed that there was some uncertainty around the results of the model particularly because it underestimated the response in patients in the comparator 'no further pharmacological treatment' arm of the trial (see section 4.18). Because of this, the Committee concluded that the resulting ICERs generated by the company's cost-effectiveness model were likely to underestimate the true ICER. Therefore, the Committee concluded that omalizumab as an add-on therapy for treating chronic spontaneous urticaria in adults and young people aged 12 years and over could not be considered a cost-effective use of NHS resources.

4.20 Having concluded that the company's revised base case underestimated the ICER and that omalizumab was not a cost-effective option for the combined population with moderate or severe urticaria at baseline, the Committee

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discussed whether there are any other factors not reflected in the analyses that could affect the ICERs. The Committee noted that the model did not account for using fewer concomitant medications (such as H_1-antihistamines, LTRAs and H_2-antihistamines) or rescue treatments (such as corticosteroids), and taking these into account would decrease the ICER. The Committee also noted that, because of a cycle length of 4 weeks, the model did not fully capture the rapid relief of symptoms patients experience during the initial weeks after starting omalizumab. The Committee considered that omalizumab may relieve symptoms, such as poor sleep, which is not adequately captured in the quality-of-life measures. The Committee agreed that incorporating these effects would decrease the ICER further. However, the Committee was also aware that there are certain other factors that could increase the estimated ICER, for example, continuing omalizumab beyond 2 doses in patients whose disease was not responding to omalizumab.

4.21 The Committee discussed whether omalizumab was innovative, and whether the economic analysis had captured all changes in health-related quality of life. The Committee acknowledged that most people who receive omalizumab experience a dramatic and rapid improvement. The Committee also acknowledged the 'immunosuppressant-sparing' effect of omalizumab, that is, eliminating or reducing the need for immunosuppressant treatment for severe urticaria. The Committee recognised the limitations of current treatments in terms of their off-label 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, and that many beneficial effects of omalizumab were not fully captured in the estimation of health-related quality of life.

4.22 The Committee discussed the clinical testimony, consultation comments and views of patient experts about unmet need in patients with severe chronic spontaneous urticaria. The Committee noted that, for patients with severe disease at baseline, the revised base-case ICER was lower than that for the combined (moderate and severe) disease and was around £26,000 per QALY gained. However, the Committee noted that the utility value underestimated the severity of disease in the model (see section 4.16), and that a more realistic value for severe disease would likely increase the incremental QALY gain and decrease the ICER to below £26,000 per QALY. The Committee also considered that

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patients with severe disease are presently treated with immunosuppressants, which have many adverse effects on patients' general health. The Committee was aware that, for patients with severe urticaria, the benefit of avoiding the side effects of immunosuppressant treatment was not accounted for in the analyses available and, considering the lifelong nature of these effects, the actual ICER for treating severe disease may decrease even further. Considering all these factors together, the Committee was persuaded that omalizumab could be considered to be a cost-effective use of NHS resources only for patients who have severe urticaria, providing that treatment was not continued beyond a maximum of 4 doses for patients whose disease has not responded to treatment. The Committee also recommended that, for patients whose disease responds, clinicians stop omalizumab after 6 doses to check whether the disease has remitted. The Committee understood that the marketing authorisation for omalizumab specified treatment to be 'initiated by physicians experienced in the diagnosis and treatment of severe chronic spontaneous urticaria', but it agreed that omalizumab should be administered only under the management of a secondary care specialist in dermatology, immunology or allergy. The Committee therefore concluded that omalizumab is recommended as an add-on therapy for treating severe chronic spontaneous urticaria in adults and young people aged 12 years and over only if:

- the severity of the condition is assessed objectively, for example, using a weekly urticaria activity score of 28 or more
- the person's condition has not responded to standard treatment with H_1-antihistamines and LTRAs
- omalizumab is stopped at or before the fourth dose if the condition has not responded
- omalizumab is stopped at the end of a course of treatment (6 doses) if the condition has responded, to establish whether the condition has gone into spontaneous remission, and is restarted only if the condition relapses
- omalizumab is administered under the management of a secondary care specialist in dermatology, immunology or allergy
- the company provides omalizumab with the discount agreed in the patient access scheme.

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4.23 The Committee also highlighted, given the lack of long-term data in this area, the importance of establishing registries to collect data on long-term outcomes in patients who receive omalizumab for chronic spontaneous urticaria.

4.24 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 with physical disabilities or who live far from a treatment centre may therefore have limited access to the technology. The Committee noted that some centres provide transport for patients and, in some situations, community nurses administer omalizumab to patients at home. The Committee concluded that this is an issue of implementation rather than of equality. 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 disease, as is already done for ciclosporin. The Committee concluded that this is a clinical and not an equality issue. The Committee also heard that chronic spontaneous urticaria is more prevalent in women and in the 20 to 40 year age group. However, the Committee concluded that it had not seen any evidence that its recommendation disadvantages women or people between the age of 20 and 40 years.

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5 Implementation

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

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

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, severe chronic spontaneous urticaria and the healthcare professional responsible for their care thinks that omalizumab is the right treatment, it should be available for use, in line with NICE's recommendations.

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6 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

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

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

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

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

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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 and Outcomes Research, Merck Sharp & Dohme

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

Dr Sanjeev Patel
Consultant Physician and Senior Lecturer in Rheumatology, St Helier University Hospital

Dr John Pounsford
Consultant Physician, Frenchay Hospital, Bristol

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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 and 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

Joanna Richardson
Technical Adviser

Jeremy Powell
Project Manager

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7 Sources of evidence considered by the Committee

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

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. Companies were also invited to make written submissions. Professional or specialist and patient or carer groups, and other consultees, had the opportunity to give their expert views. Companies, professional or specialist and patient or carer groups, and other consultees, also have the opportunity to appeal against the final appraisal determination.

Company:

- Novartis

Professional or specialist and patient or 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

Other consultees:

- Department of Health

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- NHS England
- Welsh Government

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

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 were also invited to comment on the appraisal consultation document.

- Dr Clive Grattan, Consultant Dermatologist, Norfolk and 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

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

- Novartis

ISBN: 978-1-4731-1134-9

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