NICE National Institute for Health and Care Excellence

NICE guidance

Omalizumab for treating severe persistent allergic asthma

Technology appraisal guidance
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Your responsibility

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

Contents

This guidance replaces TA133 and TA201.

1 Recommendations

1.1 Omalizumab is recommended as an option for treating severe persistent confirmed allergic IgE-mediated asthma as an add-on to optimised standard therapy in people aged 6 years and older:

- who need continuous or frequent treatment with oral corticosteroids (defined as 4 or more courses in the previous year) **and**
- only if the manufacturer makes omalizumab available with the discount agreed in the patient access scheme.

1.2 Optimised standard therapy is defined as a full trial of and, if tolerated, documented compliance with inhaled high-dose corticosteroids, long-acting $beta_2$ agonists, leukotriene receptor antagonists, theophyllines, oral corticosteroids, and smoking cessation if clinically appropriate.

1.3 People currently receiving omalizumab whose disease does not meet the criteria in section 1.1 should be able to continue treatment until they and their clinician consider it appropriate to stop.

2 Clinical need and practice

2.1 Asthma is a long-term inflammatory disorder of the airways characterised by signs or symptoms including breathlessness, chest tightness, wheezing, sputum production, airflow obstruction, hyper-responsiveness of airways and cough (particularly at night). Symptoms vary in frequency and severity, from intermittent and mild, to frequent and severe. Allergic and non-allergic forms of asthma exist. Allergic asthma results from excess immunoglobulin E (IgE) produced in response to environmental allergens such as house dust mites, pollen and moulds. Non-allergic asthma can be triggered by factors such as anxiety, stress, exercise, cold air, smoke and infection.

2.2 The Quality and Outcomes Framework (2008) estimated that 5.9% of the UK population receives treatment for asthma. Prevalence is highest in children aged 5 to 15 years, and decreases in adulthood until the age range of 55 to 64 years, when it rises again. In 2008 to 2009, there were over 67,000 emergency hospital visits for asthma in the UK, with more than 40% of these for children aged 15 years or under. People with asthma may have an impaired quality of life, with symptoms leading to fatigue, and absence from school or work. Psychological problems, which can include stress, anxiety and depression, are up to 6 times more common than in the general population, and are particularly common in people with severe and difficult-to-control asthma. There are between 1000 and 1200 deaths from asthma each year in the UK, where, in 2008, the rate of premature death from asthma was 1.5 times higher than in the rest of Europe.

2.3 There is no cure for asthma and the aim of treatment is to control symptoms while minimising the adverse reactions to treatment. Current guidelines from the British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN) recommend a stepwise approach to treatment aligned with the pathway of the Global Initiative for Asthma (GINA). Good control, characterised by no symptoms, normal lung function and no exacerbations, is achieved by stepping up or down treatment as necessary. Severe persistent allergic asthma is defined as poor control despite eliminating environmental allergens and correctly optimising standard care.

2.4 Step 1 (for mild intermittent asthma) of the GINA pathway recommends using

inhaled short-acting beta$_2$ agonists occasionally, and step 2 recommends introducing inhaled corticosteroids at 200 to 800 micrograms per day in people aged 12 years and over and at 200 to 400 micrograms per day in children aged 5 to 12 years. Step 3 recommends adding an inhaled long-acting beta$_2$ agonist and, if control remains inadequate, increasing the dosage of inhaled corticosteroids to 800 micrograms per day in adults and adolescents and to 400 micrograms per day in children. If a person's asthma does not respond to an inhaled long-acting beta$_2$ agonist, a leukotriene receptor antagonist (oral), a theophylline (oral) or a slow-release beta$_2$ agonist (oral) may be considered instead. Step 4 recommends increasing the dosage of inhaled corticosteroids to up to 2000 micrograms per day in adults and adolescents and up to 800 micrograms per day in children. As with step 3, adding a leukotriene receptor antagonist, a theophylline or an oral beta$_2$ agonist may also be considered. Before moving to step 5, clinicians should refer people whose asthma is inadequately controlled to specialist care. Step 5 recommends daily corticosteroid tablets at the lowest dose that provides adequate control, alongside high-dose inhaled corticosteroids. Treatments that can minimise the use of corticosteroid tablets may also be considered. The adverse effects of long-term oral corticosteroids are significant and include adrenal suppression, glucose intolerance, decreased bone mineral density, cataracts and glaucoma, and growth failure in children.

3 The technology

3.1 Omalizumab (Xolair, Novartis) is a monoclonal antibody that binds to IgE. It has a UK marketing authorisation as add-on therapy to improve control of asthma in adults and adolescents 12 years and over (hereafter referred to as adults and adolescents) and children aged 6 to 11 years (hereafter referred to as children) with severe persistent allergic asthma who have:

- a positive skin test or in vitro reactivity to a perennial aeroallergen
- reduced lung function (forced expiratory volume at 1 second [FEV_1] less than 80% in adults and adolescents)
- frequent daytime symptoms or night-time awakenings
- multiple documented severe exacerbations despite daily high-dose inhaled corticosteroids plus a long-acting inhaled $beta_2$ agonist.

3.2 The marketing authorisation states that omalizumab treatment 'should only be considered for patients with convincing IgE (immunoglobulin E) mediated asthma'. It also specifies that, 16 weeks after the start of omalizumab, physicians should assess how effective the treatment is, and should continue omalizumab only in patients whose asthma has markedly improved. It also specifies that omalizumab should be initiated and monitored in a specialist centre by a physician experienced in the diagnosis and treatment of severe persistent asthma.

3.3 Omalizumab is given subcutaneously every 2 or 4 weeks. The dosage is determined by the concentration of serum IgE before the start of treatment and body weight. (See the summary of product characteristics.)

3.4 The summary of product characteristics lists injection site pain, swelling, erythema and pruritus, and headaches as the most commonly reported adverse reactions for omalizumab treatment in adults and adolescents. The most commonly reported adverse reactions for omalizumab treatment in children are headaches, pyrexia and upper abdominal pain. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.5 The price of omalizumab is £256.15 for a 150-mg vial and £128.07 for a 75-mg vial (excluding VAT; BNF edition 63). The dosage administered is 75 to 600 mg every 2 or 4 weeks, up to a maximum dosage of 600 mg every 2 weeks. The cost of omalizumab ranges from approximately £1,665 per patient per year (excluding VAT) for a 75 mg dose administered every 4 weeks to approximately £26,640 per patient per year (excluding VAT) for a 600 mg dose (the maximum recommended dose in the summary of product characteristics) administered every 2 weeks. Costs may vary in different settings because of negotiated procurement discounts. The manufacturer of omalizumab has agreed a patient access scheme with the Department of Health, which makes omalizumab available with a discount applied to all invoices. The size 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.

4 Evidence and interpretation

The Appraisal Committee considered evidence from several sources.

4.1 Clinical effectiveness

4.1.1 The Assessment Group focused on 5 specific questions: the efficacy of omalizumab; the long-term efficacy of omalizumab; the corticosteroid-sparing effect of omalizumab; the safety of omalizumab; and the adverse effects of oral corticosteroids.

4.1.2 The Assessment Group identified 11 randomised controlled trials to include in its review on efficacy, which compared omalizumab with placebo or no added treatment. Nine of the randomised controlled trials were relevant only to adults and adolescents, 1 trial was relevant only to children and 1 trial was relevant to both age groups (the trial included people between the ages of 6 and 20 years). Three of the randomised controlled trials had populations that met or closely approximated the criteria in the marketing authorisation for adults and adolescents (INNOVATE [n=419], EXALT [n=404] and a study by Chanez et al. 2010 [n=31]). Two randomised controlled trials had populations that were broader than those specified in the UK marketing authorisation, but contained relevant subgroups resembling the marketing authorisation (IA-04 in adults [n=164] and IA-05 European population subgroup in children [n=235]). The Assessment Group also identified 6 trials as supporting evidence in which an unknown proportion of the population met the criteria in the marketing authorisation (Hanania et al. 2011 [n=850], Bardelas et al. 2012 [n=271], Vignola et al. 2004 [SOLAR, n=405], Hoshino et al. 2012 [n=30] and Ohta et al. 2009 [n=327], and the trial by Busse et al. 2011 [n=419] in children and young adults).

4.1.3 The 10 randomised controlled trials enrolling adults and adolescents lasted from 16 to 52 weeks. Trials in which the entire population met the criteria in the marketing authorisation lasted from 16 weeks (Chanez et al.) to 32 weeks (EXALT); INNOVATE ran for 28 weeks. In children, IA-05 ran for 52 weeks, of which the final 28 weeks was a corticosteroid-sparing phase. The study by Busse et al. included in the review by the Assessment Group as supporting evidence ran

for 60 weeks.

4.1.4 The inclusion criteria and treatment regimen varied even among trials in which the whole population or a defined subgroup met the criteria in the marketing authorisation. For example, EXALT included people on a lower dose of inhaled corticosteroids (800 micrograms or more of beclometasone dipropionate or its equivalent) than did the IA-04 study European population subgroup or INNOVATE (both 1000 micrograms or more of beclometasone dipropionate equivalent). All of the trials in which the whole population or a defined subgroup met marketing authorisation criteria required the use of a long-acting $beta_2$ agonist, but the concomitant treatments used (such as leukotriene antagonists and theophylline) varied between studies. The proportion of people taking oral corticosteroids was comparable (approximately 20%) between EXALT, INNOVATE and the trial by Chanez et al.; oral corticosteroid use was not reported in IA-04. In the European population subgroup in the IA-05 study, all children took 500 micrograms or more of inhaled fluticasone or the equivalent plus a long-acting $beta_2$ agonist. The mean dose of inhaled fluticasone was 743 micrograms and 58% took an additional drug; most of the children received a leukotriene antagonist.

4.1.5 The primary outcomes of the trials selected varied. The primary outcome for INNOVATE was the rate of clinically significant asthma exacerbations. Secondary outcomes included the rate of clinically significant severe exacerbations and the rate of emergency visits for asthma. The IA-05 trial and Hanania et al. had clinically significant exacerbations as a primary outcome; in SOLAR it was 1 of the designated primary outcomes together with disease-related quality of life. In other trials, persistence of response (EXALT), asthma deterioration-related incidents (IA-04), Asthma Control Test score, and other measures of symptoms and lung function were the primary outcomes measured.

4.1.6 The Assessment Group considered that the quality of the included randomised controlled trials was generally high, and that the 5 studies in which the population or a defined subgroup represented the licensed population adequately allocated and concealed randomisation. Eight of the 11 trials included in the review were double blind and placebo controlled and had a low risk of bias. However, the Assessment Group considered that the open-label EXALT and IA-04 trials in adults had a higher risk of bias. The Assessment Group therefore did not pool the data from EXALT and IA-04 with the INNOVATE trial for the base-case analysis,

but did so for EXALT and INNOVATE in the exploratory sensitivity analysis in the economic evaluation.

4.1.7 In addition to the trial data presented, the Assessment Group used data from observational studies to support evidence from the trials and, in particular, observational studies that provided data on longer-term response to omalizumab and on corticosteroid sparing. These included open-label continuation studies, uncontrolled cohort studies (in which all patients took omalizumab) and post-marketing studies.

Clinical effectiveness results

4.1.8 For effectiveness of treatment, 4 of the 10 randomised controlled trials for the adult population (INNOVATE, EXALT, SOLAR and Bardelas et al.) and 1 randomised controlled trial in children (IA-05 European population subgroup) reported the global evaluation of treatment effectiveness (GETE). There was a response to treatment in a higher proportion of people randomised to omalizumab compared with the comparator as assessed by the GETE ratings of good or excellent. Response to treatment with omalizumab was higher in the open-label EXALT trial (70% compared with 28.2% at 16 weeks, relative risk [RR] 2.24, 95% confidence interval [CI] 1.71 to 2.92) than in the double-blind trials (INNOVATE, 56.5% compared with 41.0% at 28 weeks [RR 1.38, 95% CI 1.13 to 1.69]; SOLAR, 59.3% compared with 41.3% at 28 weeks [RR 1.44, 95% CI 1.17 to 1.76]; Bardelas et al., 55.1% compared with 48.1% at 24 weeks [RR 1.15, 95% CI 0.91 to 1.44]). Response rates in adults measured by the GETE were also reported in 4 uncontrolled observational studies and were higher than in the double-blind INNOVATE trial. In the IA-05 European population subgroup of children, 74% of the omalizumab group responded to treatment as assessed by the GETE ratings of good or excellent at 52 weeks compared with 64.5% in the placebo group, but this was not statistically significant (RR 1.15, 95% CI 0.95 to 1.39).

4.1.9 For the outcome of clinically significant exacerbations, all of the 11 randomised controlled trials reported data with the exceptions of Bardelas et al. and Hoshino et al. The Assessment Group observed that clinically significant exacerbations were defined differently between trials, but still considered it appropriate to compare these trials. The Assessment Group found a consistent benefit for

people randomised to omalizumab compared with the comparator group, both in terms of the rate of exacerbations and the proportion of people who experienced no exacerbations during follow-up. For example, the rate of total exacerbations in the INNOVATE trial over 28 weeks was 0.68 for omalizumab compared with 0.91 in the placebo arm (rate ratio 0.738, 95% CI 0.552 to 0.998). In EXALT, the rate of total exacerbations over 32 weeks was 0.55 for omalizumab compared with 0.98 for the comparator (no added treatment; rate ratio 0.570, 95% CI 0.417 to 0.778) and, in the IA-04 European population subgroup, the rates over 52 weeks were 1.26 and 3.06 respectively (rate ratio 0.41, 95% CI 0.288 to 0.583). The trial by Chanez et al. showed no statistically significant difference between the groups at 16 weeks (RR 0.71, 95% CI 0.37 to 1.37). For children, the results from the IA-05 European population subgroup showed a statistically significant benefit in the rate of total exacerbations for omalizumab (0.42 compared with 0.63 in the comparator arm at 24 weeks, rate ratio 0.662, 95% CI 0.441 to 0.995). In both children and adults, observational studies and trials used to support trial evidence showed that people taking omalizumab had reductions in the exacerbation rate from baseline.

4.1.10 Three of the included trials reported separately the incidence of clinically significant severe exacerbations (defined as an exacerbation in which peak expiratory flow or FEV_1 is less than 60% of a patient's personal best) and clinically significant non-severe exacerbations. For adults, the rate of clinically significant severe exacerbations was statistically significantly lower in patients randomised to omalizumab compared with the comparator (INNOVATE, 0.24 compared with 0.48, rate ratio 0.50, 95% CI 0.32 to 0.78; EXALT, 0.24 compared with 0.42, rate ratio 0.56, 95% CI 0.34 to 0.92). For children, the results from the IA-05 European population subgroup favoured omalizumab, but were not statistically significant (0.14 compared with 0.22 at 24 weeks follow-up, rate ratio 0.66, 95% CI 0.30 to 1.42). The Assessment Group commented that this small subgroup lacked power. Evidence from a single non-comparative observational study (Deschildre et al. 2010) showed a reduction in severe exacerbations in children (from 4.4 severe exacerbations per year to 0.51 per year (statistical significance not recorded).

4.1.11 The manufacturer provided rates of exacerbations for the following 5 subgroups defined post hoc in the studies: people who were hospitalised before the onset of the study; people on oral corticosteroids at baseline; people not on oral corticosteroids at baseline; people who had 2 or fewer exacerbations per year at

baseline; and people who had 3 or more exacerbations per year at baseline. The Assessment Group commented that data from the INNOVATE trial show that omalizumab may work better in people on maintenance oral corticosteroid therapy than the overall population. The relative risk of total exacerbations in the population taking maintenance oral corticosteroids was 0.662 (compared with 0.74 in the total population) and the relative risk of clinically significant severe exacerbations was 0.36 (compared with 0.50 in the total population), but with no statistical significance reported.

4.1.12 Four trials (INNOVATE, EXALT, the IA-04 European population subgroup in adults and the IA-05 European population subgroup in children) reported results on the effectiveness of omalizumab for the 'responder' subgroup (that is, patients randomised to omalizumab whose asthma responded compared with patients randomised to placebo or standard care alone) using GETE ratings or Asthma Quality of Life Questionnaire scores (IA-04 European population subgroup). In these analyses, the relative risk for total exacerbations was 0.37 (95% CI 0.27 to 0.52) in INNOVATE, 0.41 (95% CI 0.31 to 0.55) in EXALT, 0.37 (95% CI 0.24 to 0.55) in the IA-04 European population subgroup and 0.38 (95% CI 0.15 to 0.91) in the IA-05 European population subgroup, showing a statistically significant advantage for omalizumab. This pattern in the results was similar for the outcome of clinically significant severe exacerbations.

4.1.13 Six randomised controlled trials (INNOVATE, EXALT, IA-04, Chanez et al., IA-05 and Busse et al.) compared rates of hospitalisation during the studies. The results favoured the omalizumab group but were not statistically significant, apart from in the EXALT study in which randomisation to omalizumab compared with no additional treatment was associated with a rate ratio of 0.33 (95% CI 0.12 to 0.94). Three studies in adults (INNOVATE, EXALT and IA-04) presented data separately for the outcomes of emergency department visits and unscheduled doctor visits. As with rates of hospitalisation, the only study to show a statistically significant benefit with omalizumab for these outcomes was EXALT. There were, however, statistically significant reductions associated with omalizumab in total emergency visits, including hospital admissions, emergency department and unscheduled visits to the doctor (INNOVATE compared with placebo: risk ratio 0.56, 95% CI 0.33 to 0.97; EXALT: risk ratio 0.40, 95% CI 0.24 to 0.65; IA-04 European population subgroup: risk ratio 0.76, 95% CI 0.64 to 0.89). For children, the IA-05 European population subgroup showed no

difference between treatment groups for emergency department visits, unscheduled doctor visits or total emergency visits. The Assessment Group commented that limited data from observational studies showed evidence of fewer hospitalisations and unscheduled healthcare visits compared with baseline; when statistical tests were reported, these showed statistically significant benefits of omalizumab treatment relative to baseline or standard care. However, there were no data available for children from observational studies on visits to the doctor or emergency room, or hospitalisations.

4.1.14 Analyses limited to people receiving omalizumab whose asthma responded compared with people receiving placebo or standard care showed evidence of statistically significant benefit from both INNOVATE and EXALT for hospitalisation and other unscheduled medical care except emergency department visits in INNOVATE. Children in the IA-05 European population subgroup with a response to omalizumab had a statistically significant reduction in hospitalisation rates compared with children in the placebo arm with a response, but no benefits for other unscheduled healthcare measures.

4.1.15 The various studies assessed asthma severity differently and used a wide range of scales and measures to assess response to treatment. In INNOVATE, total asthma symptom score improved more at 28 weeks with omalizumab than with placebo (change from baseline -0.66 with omalizumab compared with -0.40 with placebo, p=0.039). In EXALT, people randomised to open-label omalizumab experienced a greater improvement in total asthma symptom score at 32 weeks than people randomised to standard care without omalizumab using the Asthma Control Questionnaire (change from baseline -0.91 with omalizumab compared with -0.04 without omalizumab, RR 0.87, 95% CI -1.09 to -0.65) and in the IA-04 European population subgroup at 52 weeks using the Wasserfallen symptom score (change from baseline -6.7 with omalizumab compared with 0.5 with no additional treatment, p<0.05). For children, no statistically significant benefit for omalizumab compared with placebo was shown in the IA-05 European population subgroup using the total asthma clinical symptom score and the Wasserfallen symptom score (p>0.05 for both measures at 24 weeks and at 52 weeks). In addition, an observational study in children with severe uncontrolled allergic asthma (Brodlie et al. 2000) found statistically significant increases in the scores of the Asthma Control Test (measuring asthma symptoms) after treatment with omalizumab (p=0.001). Evidence on the impact of individual symptom measures

for children, adolescents and adults was limited and mixed.

4.1.16 There was limited evidence about whether treatment with omalizumab changed the need for rescue treatment, most commonly salbutamol (albuterol) and terbutaline. In the population that met marketing authorisation criteria, INNOVATE, the IA-04 European population subgroup and the trial by Chanez et al. reported data on rescue treatment for adults, and the IA-05 European population subgroup reported data for children. The IA-04 European population subgroup was the only trial in the licensed population to show a statistically significant difference between the treatment groups. This trial found that the mean puffs of salbutamol per day per patient over 14 days was 3.91 in the omalizumab group compared with 5.33 in the group not taking omalizumab (p=0.008). Data from Hanania et al. included by the Assessment Group as supporting data, reported a statistically significant reduction in the use of rescue treatment in people randomised to omalizumab compared with placebo. Observational studies provided limited evidence, with 2 studies reporting reduced use of rescue treatment compared with baseline use, but with no results of statistical tests. In children the IA-05 European population subgroup initially showed a statistically significant benefit but this lost significance after adjustment for multiple testing. There was no additional evidence from supporting randomised controlled trials or observational studies in children.

4.1.17 Randomised controlled trials of the population reflecting the marketing authorisation showed benefits of omalizumab compared with the comparator arm in improving lung capacity as measured by percentage of predicted FEV_1, although these absolute benefits were small. These included INNOVATE at 28 weeks (67.0% with omalizumab compared with 64.2% without omalizumab, p=0.043), EXALT at 32 weeks (68.1% with omalizumab compared with 63.7% with no omalizumab, p=0.007), and the IA-04 European population subgroup at 52 weeks (71% with omalizumab compared with 60% with no additional treatment, p<0.01). Supporting trials did not show a statistically significant benefit, but the Assessment Group commented that these studies were conducted in people with better lung function. Some observational studies provided additional evidence that omalizumab is associated with statistically significant improvements in lung function in adults with uncontrolled severe asthma. In children, there was no randomised controlled trial evidence for FEV_1 for the licensed population. The trial of children and young adults by Busse et al.

included in the Assessment Group's review as supporting evidence and the observational studies in children reported no statistically significant differences between treatment groups.

4.1.18 Six trials in adults (INNOVATE, EXALT and IA-04 European population subgroup in the licensed population, and SOLAR, Hanania et al. and Hoshino et al. among the supporting studies) plus 1 trial in children (the IA-05 European population subgroup) reported some measure of asthma-related quality of life. All trials employed either the Asthma Quality of Life Questionnaire or, in the case of the IA-05 European population subgroup, the paediatric Asthma Quality of Life Questionnaire. EXALT also reported EuroQol 5-D (EQ-5D) scores. In INNOVATE, there was a statistically significant improvement at 28 weeks in the Asthma Quality of Life Questionnaire score (ranging from 1 to 7, with a higher score indicative of a better quality of life) in the intention-to-treat omalizumab group compared with placebo (change from baseline 0.91 with omalizumab compared with 0.46 with placebo, $p<0.001$; 61% of people randomised to omalizumab experienced a 0.5-point or greater increase [0.5 points or more representing a clinically significant difference] compared with 48% with the comparator, $p=0.008$). Statistically significant improvements favouring omalizumab were also found in EXALT at 31 weeks using the Asthma Quality of Life Questionnaire (change from baseline 1.06 [95% CI 0.88 to 1.24] with omalizumab compared with -0.07 [95% CI -0.31 to 0.17] with no omalizumab treatment; 74% of people randomised to omalizumab experienced a 0.5-point or greater increase compared with 26% with the comparator, $p<0.001$) and in the IA-04 European population subgroup at 52 weeks (change from baseline 1.32 with omalizumab compared with 0.17 with no additional treatment, $p<0.001$; 77% of people randomised to omalizumab experienced a 0.5-point or greater increase compared with 42% with the comparator, $p<0.001$). The supporting trials also showed quality-of-life benefits associated with omalizumab. In children, the IA-05 European population subgroup reflecting the licensed indication demonstrated a substantial placebo response and showed no statistically significant evidence of treatment benefit (change from baseline 0.78 with omalizumab compared with 0.70 with the comparator, $p=0.566$; 62% of people randomised to omalizumab experienced a 0.5-point or greater increase compared with 58% with the comparator, $p=0.654$). The Assessment Group stated that the lack of evidence for improvements in symptoms and quality of life in children may reflect the subgroup of the IA-05 European population being underpowered to detect differences.

4.1.19 The Assessment Group commented that 3 (APEX, eXpeRience, and PERSIST) of the 5 observational studies that reported a measure of quality of life showed at least a minimally important increase of 0.5 points in score for the Asthma Quality of Life Questionnaire. In the uncontrolled prospective therapeutic trial by Brodlie et al., there was evidence of statistically significant increases in mini-Asthma Quality of Life Questionnaire scores associated with taking omalizumab in children dependent on oral corticosteroids in the UK. Statistically significant improvements in scores were observed in children aged under 12 years (change from 2.3 [1.7 to 4.2] at baseline to 5.2 [3.5 to 6.9], p=0.019) and in young people aged 12 to 16 years (change from 3.8 [1.0 to 8.4] at baseline to 6.1 [3.2 to 9.9], p=0.0037). The Assessment Group commented that, although the population for this analysis was small (n=24), it represented the only evidence for children with very severe asthma who need oral corticosteroids.

4.1.20 Nine randomised controlled trials reported rates of discontinuing omalizumab or the comparator. The double-blind randomised controlled trials in adults reported discontinuation rates in the omalizumab arm of between 2.4% and 19.4% compared with 7.7% and 22.2% in the placebo arms. In the open-label trials the discontinuation rates were much higher in the comparator than the omalizumab arm (EXALT: 19.1% compared with 8.1%; IA-04: 30.6% compared with 17.4%). In the 1 trial in children (IA-05 European population subgroup), the discontinuation rate was approximately 20% in both arms.

4.1.21 The Assessment Group commented that there was very limited evidence relating to the effectiveness of omalizumab beyond 12 months in either adults and adolescents, or children. Three randomised controlled trials and 4 observational studies reported follow-up data at 52 weeks or longer. Although the PERSIST observational study reported some follow-up data at 120 weeks, these were limited.

4.1.22 Two randomised controlled trials provided data on changes in oral corticosteroid use, 1 in the licensed population (EXALT) and 1 in a population with controlled asthma (trial 011). Trial 011, published by Holgate et al. (2004), was a randomised placebo-controlled trial evaluating the effect of omalizumab on disease control and oral corticosteroid reduction. The Assessment Group commented that it excluded trial 011 from the other sections of its review because only a few patients received a long-acting $beta_2$ agonist, but included it in its analysis of

corticosteroids because data on changes in oral corticosteroid use were scarce. In the EXALT trial, at 32 weeks, people in the omalizumab group were more likely to have stopped or reduced their use of oral corticosteroids (62.7% compared with 30.4% in the control group, RR 2.06, 95% CI 1.08 to 3.94) and to have reduced their dose of oral corticosteroid (mean difference 6.70 mg/day, 95% CI 12.93 to 0.47). In contrast, in trial 011, the proportions reducing or stopping oral corticosteroids at 32 weeks follow-up were similar in both the omalizumab and the placebo groups (74.0% compared with 73.3%, RR 1.01, 95% CI 0.79 to 1.28). The Assessment Group commented that the EXALT study was unblinded and trial 011 did not sufficiently adjust oral corticosteroid doses during the run-in phase. Randomised controlled trial data on oral corticosteroid use in children were not available.

4.1.23 Ten uncontrolled observational studies reported data on oral corticosteroid use after omalizumab treatment. The Assessment Group commented that all except 1 of these studies were uncontrolled, with greater potential for bias, relatively small, and did not provide data beyond 12 months. For adults on maintenance oral corticosteroids, the proportion of patients reducing or stopping oral corticosteroids ranged from 25.9% to 71.2% after omalizumab treatment. The outcomes for children on oral corticosteroid maintenance were reported in uncontrolled studies by Brodlie et al. and Kirk et al. (2011) performed in study populations that may have overlapped. Patients in both studies showed a statistically significant decrease in oral corticosteroid use after 16 weeks of treatment with omalizumab, with the proportion of patients reducing or stopping oral corticosteroids being 13.3% (in the subgroup of children aged 5 to 12 years) and 22.2% (in children aged 6 to 11 years). The median baseline daily oral corticosteroid dose in the Brodlie et al. study was 20 mg (range 5 to 50 mg), which fell to 5 mg (range 0 to 40 mg). All patients in the Kirk et al. study either reduced or stopped oral corticosteroid treatment at follow-up, with a mean daily oral corticosteroid dose reduction of 14 mg. Those patients who did not stop oral corticosteroids had a mean reduction from 20 mg to 5 mg per day. The Assessment Group included a summary of published systematic reviews of the adverse effects of oral corticosteroids, stating that the reliability of the data was unclear. The reviews included the known adverse effects of bone fracture, diabetes mellitus, peptic ulcer, cardiovascular events including myocardial infarction and stroke, cataract and glaucoma, sleep and mood disturbance, and weight gain and, for children, failure to reach expected adult height.

4.1.24 The Assessment Group identified 4 reviews of adverse effects associated with omalizumab; these were published between 2007 and 2011 and had a sample size ranging from 3429 to 57,300 people. Two of the reviews included randomised controlled trials and 1 included both randomised controlled trials and open-label studies. One review included people with severe persistent allergic asthma, the second included people with moderate-to-severe persistent allergic asthma, the third included people who had received omalizumab, but in whom the indication was unclear, and the fourth review assessed the incidence of anaphylaxis from the Adverse Event Reporting System in people with asthma who had received omalizumab.

4.1.25 The key adverse events considered by the Assessment Group were anaphylaxis and arterial thrombotic events. The Assessment Group stated that both occur rarely and have not been conclusively linked to omalizumab. The Assessment Group commented that the evidence that associated omalizumab with cancer is also uncertain. The Assessment Group concluded that, although evidence exists for the short-term safety of omalizumab, there was insufficient evidence on long-term safety to draw any conclusion.

4.2 Cost effectiveness

4.2.1 The Assessment Group identified 6 published studies that evaluated the cost effectiveness of omalizumab for asthma. All studies compared omalizumab with standard care, which differed between studies. For example, Oba and Salzman (2004), Wu et al. (2007) and Campbell et al. (2010) considered inhaled corticosteroid plus additional rescue treatment (as needed) as standard care, whereas Dewilde et al. (2007), Brown et al. (2007) and Dal Negro et al. (2011) considered high-dose inhaled corticosteroids and long-acting beta$_2$ agonists as standard care. All of the cost-effectiveness models in these studies assumed that omalizumab conferred benefits, compared with standard care, by reducing clinically significant exacerbations. The studies varied in methodology and conclusions; 5 of 6 studies used quality-adjusted life years (QALYs) to assess effectiveness for omalizumab compared with standard care, and the resulting incremental cost-effectiveness ratios (ICERs) ranged from approximately £21,700 to £516,500 per QALY gained. Brown et al. concluded that omalizumab was cost effective, Oba and Salzman and Dewilde et al. concluded that omalizumab may

be cost effective for people with severe asthma, Wu et al. concluded that omalizumab was not cost effective unless its acquisition price was reduced substantially, and Campbell et al. and Dal Negro et al. concluded that, although omalizumab improves health-related quality of life, it also increases costs substantially. The Assessment Group commented that the studies had common issues and limitations that precluded reliable conclusions, and included differing populations, differing relative efficacy and adverse effects of omalizumab compared with oral corticosteroids, lacked robust data for asthma-related mortality and health-related quality of life, lacked consensus on treatment duration, and differed as to whether treatment persists over time.

Manufacturer's economic model

4.2.2 The manufacturer submitted an economic evaluation with a model structure identical to that used in NICE's previous technology appraisal guidance on omalizumab for severe persistent allergic asthma, and omalizumab for the treatment of severe persistent allergic asthma in children aged 6 to 11 (both now replaced by this guidance). This compared the costs and health outcomes of omalizumab as an add-on treatment to standard care compared with standard care alone in people with severe persistent allergic asthma uncontrolled despite daily high-dose inhaled corticosteroids plus a long-acting $beta_2$ agonist at BTS/SIGN step 4 or 5. The manufacturer used a Markov model that extrapolates the effects of omalizumab treatment for 10 years and follows a hypothetical cohort over a lifetime time horizon (up to age 100 years). People enter the model on either omalizumab in addition to standard care, or standard care alone in a health state characterising day-to-day symptoms of asthma. At 16 weeks (the end of the first cycle), asthma in people taking omalizumab either does or does not respond to treatment based on the proportion of response in the trials. People whose asthma responds to omalizumab remain on it for the treatment duration, and the model assumes that they experience exacerbations at the rates observed for people whose asthma has responded in the clinical trials. The model assumes that people whose asthma does not respond stop taking omalizumab revert to standard care alone and have rates of exacerbation experienced by patients in trials randomised to standard care. During each subsequent cycle of the model, people either remain in the day-to-day symptom state or can experience an exacerbation. The manufacturer assumed that an asthma-related

death occurs only during a clinically significant severe exacerbation, with each exacerbation being associated with a mortality risk of 0.097% for children under 12 years, 0.319% for those aged 12 to 16 years, 0.383% for those aged 17 to 44 years, and 2.478% for those aged 45 years and over, all of which the manufacturer derived from mortality data for people hospitalised for acute severe asthma from Watson et al. (2007). The model also assumes that people with asthma can die from non-asthma related causes. After a non-fatal exacerbation, a person returns to the day-to-day asthma symptoms health state.

4.2.3 The manufacturer's model includes 2 separate base-case populations: adults plus adolescents aged 12 years and over (average age approximately 40 years), and children aged 6 to 11 years (average age 9 years) and 2 subgroups: people who are hospitalised in the year before entering the model, and a subgroup of people who receive maintenance oral corticosteroids when entering the model. The model evaluates costs from the perspective of the NHS and personal social services, and discounts costs and health outcomes at a rate of 3.5% per annum, in accordance with the NICE reference case.

4.2.4 The manufacturer derived the evidence on the clinical effectiveness of omalizumab as add-on treatment in the model's base case from the results of INNOVATE (adults and adolescents) and IA-05 (children) and, for the model's scenario analysis in adults and adolescents, from EXALT and APEX. The effectiveness of treatment was based on data from trials on whether or not patients' asthma responded to omalizumab and their rates of clinically significant non-severe exacerbation and clinically significant severe exacerbation.

4.2.5 The manufacturer included the costs of acquiring, administering and monitoring omalizumab. Omalizumab dose depends on a patient's baseline serum IgE and weight, and the base-case model assumes an average dose corresponding to the dose distribution in the populations in INNOVATE, EXALT, APEX and IA-05. The manufacturer estimated the costs of administration by assuming that it takes a specialist asthma nurse 10 minutes to administer omalizumab, and that specialist asthma nursing care costs the NHS £47 per hour. The manufacturer included costs to monitor for anaphylaxis and for the 16-week assessment. Standard care costs included 2 routine outpatient appointments per year with a hospital specialist and 2 extra visits for people taking omalizumab. The cost of standard care in the model corresponded to the standard care used in the trials. In

addition, the cost of exacerbations, including GP consultations, outpatient appointments, emergency admissions, rehabilitation appointments, general ward stays and intensive care were calculated from the INNOVATE, EXALT, APEX and IA-05 trials.

4.2.6 The manufacturer estimated health-related quality of life (expressed in QALYs) by quality adjusting the period of time the average patient was alive within the model and applying a corresponding utility score. The 2 key elements determining health-related quality of life were day-to-day symptoms and exacerbations (clinically significant non-severe and severe). For day-to-day symptoms in the base-case analysis, the manufacturer estimated utility values from the Asthma Quality of Life Questionnaire scores collected in INNOVATE and mapped these onto EQ-5D values; the values were 0.669 for people receiving standard care and 0.779 for people taking omalizumab whose asthma responded to omalizumab (resulting in a difference in EQ-5D of 0.110). For the subgroup reflecting patients from INNOVATE who were hospitalised in the year before trial entry, the manufacturer used a utility difference of 0.138 and, for the subgroup from INNOVATE who required maintenance oral corticosteroids, the manufacturer used a utility difference of 0.106. To estimate a person's utility decline associated with a clinically significant non-severe or severe exacerbation, the manufacturer used values from a prospective study conducted in the UK in 4 specialist asthma centres where health-related quality-of-life data were collected (n=112) using the EQ-5D, mini Asthma Quality of Life Questionnaire, and Asthma Symptom Utility measures (Lloyd et al. 2007). The mean utility value assigned to a clinically significant non-severe exacerbation was 0.572, and to a clinically significant severe exacerbation was 0.326, compared with 0.889 for no exacerbations. The manufacturer assumed that children aged 6 to 11 years taking omalizumab did not experience any improvement in health-related quality of life.

Results of manufacturer's economic model

4.2.7 The base-case deterministic ICER for omalizumab as an add-on treatment to standard care compared with standard care alone in adults and adolescents was estimated by the manufacturer to be £32,076 per QALY gained, and the probabilistic ICER to be £33,268 per QALY gained. The deterministic base-case ICER for children was estimated to be £80,747 per QALY gained and the

probabilistic ICER to be £88,998 per QALY gained. The manufacturer estimated that the probability that omalizumab is cost effective at £20,000 and £30,000 per QALY gained for adults and adolescents is 0.005 and 0.267 respectively.

4.2.8 The manufacturer presented cost-effectiveness results for alternative scenarios based on data from the EXALT study, the best study to provide a scenario for open-label use of omalizumab, and APEX, the best observational study to provide a scenario relevant to UK practice. The ICER for omalizumab as an add-on treatment to standard care compared with standard care alone was £61,687 per QALY gained using data from EXALT and £29,773 per QALY gained using data from APEX. The difference in ICER between the INNOVATE base case and the EXALT scenario resulted largely from the lower effect of treatment with omalizumab among people whose asthma responded to omalizumab observed in EXALT compared with INNOVATE, and the difference in improvement in health-related quality of life for day-to-day symptoms estimated in INNOVATE (Asthma Quality of Life Questionnaire mapped to EQ-5D) being greater than that in EXALT (directly observed EQ-5D data). Omalizumab reduced the rate of total exacerbations more in INNOVATE (RR 0.373) than in EXALT (RR 0.410), and the health utility improvement was also greater in INNOVATE than in EXALT.

4.2.9 The manufacturer conducted several deterministic sensitivity analyses on the base-case populations (INNOVATE and IA-05 European population). The manufacturer concluded that the results were sensitive to changes in the time horizon, exacerbation rates, asthma-related mortality, health-related quality-of-life values for day-to-day asthma symptoms, omalizumab drug costs and the discount rate. The parameters that had the most effect on the results in the manufacturer's model were asthma-related mortality and assumptions around health-related quality of life with omalizumab. The ICER for omalizumab as an add-on treatment to standard care compared with standard care alone in adults and adolescents increased from £32,076 to £72,113 per QALY gained when asthma-related mortality risk was set to zero. For children, the effect on the ICER was less pronounced because the asthma-related risk of dying is much lower in children than in adults and adolescents. For children, treatment duration and the age at which a child starts treatment with omalizumab impacts on the cost effectiveness of omalizumab, reflecting the manufacturer's assumption that treatment with omalizumab does not improve health-related quality of life until age 12 years or over. Assuming a treatment duration of 2 years instead of

10 years increased the ICER from £80,747 to £662,893 per QALY gained. Similarly, reducing the age of starting treatment from 9 to 6 years increased the ICER to £130,475 per QALY gained. Assuming a health-related quality-of-life gain with omalizumab in children equal to that seen in adults and adolescents (0.779) reduced the ICER in children to £61,731 per QALY gained.

4.2.10 For the subgroup reflecting people who had been hospitalised in the year before starting therapy with omalizumab, the ICERs for omalizumab as an add-on treatment to standard care compared with standard care alone were £27,928, £35,198 and £30,407 per QALY gained for adults and adolescents (based on data from INNOVATE, EXALT and APEX respectively) and £65,100 per QALY gained for children (based on data from the IA-05 European population). For the subgroup reflecting people who required maintenance oral corticosteroids at the time of starting omalizumab, the ICERs for adults and adolescents were £26,320, £37,604 and £29,685 per QALY gained (based on data from INNOVATE, EXALT and APEX respectively). Data for the maintenance oral corticosteroid subgroup were not available from the IA-05 European population because only 6 patients were on maintenance oral corticosteroids at baseline.

4.2.11 The manufacturer conducted a sensitivity analysis, acknowledging the adverse effects of using maintenance oral corticosteroids, and calculated a potential 'oral corticosteroids-sparing' effect of treatment with omalizumab. The manufacturer conducted these analyses in the subgroup of patients on maintenance oral corticosteroids in EXALT and APEX; the protocol of INNOVATE did not allow investigators to change a patient's ongoing standard care during the study period. In EXALT, 41.9% of people whose asthma responded to omalizumab stopped maintenance oral corticosteroids after 32 weeks, whereas in APEX 45.1% of people whose asthma responded to omalizumab had stopped maintenance oral corticosteroids at follow-up. For people whose asthma responded to omalizumab and who stopped maintenance oral corticosteroids, the manufacturer applied lower costs and higher QALYs in the model, and the ICER for omalizumab as an add-on treatment to standard care compared with standard care alone was reduced from £37,604 to £28,319 per QALY gained (using data from EXALT) and from £29,685 to £25,099 per QALY gained (using data from APEX).

Assessment Group's critique of manufacturer's cost-effectiveness

analysis

4.2.12 The Assessment Group commented that the manufacturer assumed that the effectiveness of treatment with omalizumab (in people whose asthma had responded to omalizumab by a given time point) did not diminish over time. In contrast, in the EXALT study, 8.6% of patients whose asthma had responded to omalizumab at 16 weeks no longer responded to omalizumab at 32 weeks. The Assessment Group commented that the study's open-label design may have influenced the results in favour of omalizumab because knowing the patient's treatment may have affected how the investigator assessed response to omalizumab as well as how the patients reported exacerbations.

4.2.13 The Assessment Group commented that, to estimate the health-related quality-of-life benefit with omalizumab, measuring EQ-5D directly is more appropriate than the manufacturer's method of mapping Asthma Quality of Life Questionnaire scores (from INNOVATE) onto EQ-5D values. In addition, the manufacturer assumed that children under 12 years do not experience any improvement in health-related quality of life with omalizumab until they reach 12 years whereas the Assessment Group considered that the observational study of children by Brodlie suggested that young children also experience an improvement in asthma-related quality of life.

4.2.14 The Assessment Group considered that the manufacturer's subgroup sensitivity analyses in people on maintenance oral corticosteroids were generally reasonable, considering the limited evidence. However, to estimate health utility losses from adverse effects related to oral corticosteroids, the manufacturer used disability-adjusted life-years (DALYs), which it assumed are equivalent to QALYs, an assumption the Assessment Group considered may not have been appropriate.

4.2.15 The Assessment Group commented that the manufacturer had addressed some of the uncertainties previously identified in NICE's previous technology appraisal guidance on omalizumab for severe persistent allergic asthma, and omalizumab for the treatment of severe persistent allergic asthma in children aged 6 to 11 (both now replaced by this guidance), in particular, the relative efficacy, safety and costs of omalizumab compared with maintenance oral corticosteroids, and a subgroup consisting of people who were hospitalised for asthma in the year

before starting omalizumab, but also that several key uncertainties remained. For example, according to the Assessment Group the manufacturer had not adequately addressed the mortality associated with asthma; the relationship between mortality, age and severity of exacerbations; the degree to which omalizumab improves health-related quality of life; and the influence of age on the cost-effectiveness results. The Assessment Group commented that the asthma-related mortality rates applied by the manufacturer in the model may have overestimated the number of asthma deaths because the manufacturer assumed that an individual dies from asthma only when experiencing a clinically significant severe exacerbation (from the health state of 'clinically significant exacerbation'), whether or not hospitalised; however, the manufacturer applied a mortality risk derived only from hospitalised patients. Data from INNOVATE showed that only about 20% of clinically significant severe exacerbations resulted in admission to hospital. In addition, the manufacturer used the mean age at which patients in trials started omalizumab in the model, which made the effect of omalizumab in different age groups difficult to discern. The Assessment Group commented that, because age affects the risk of asthma-related mortality, the manufacturer should have considered the impact of age at the start of treatment, either by presenting ICERs by subgroups based on age or by combining estimates for different ages into a weighted ICER estimate. The Assessment Group commented that there is uncertainty about the association between clinically significant severe exacerbations and death. The Assessment Group considered that, because the manufacturer only included studies that linked severe exacerbations to asthma deaths in its systematic review on asthma-related mortality, it may have excluded studies relevant to the appraisal. The Assessment Group also highlighted that, if the asthma-related mortality rate used by the manufacturer (2.478% in adults aged 45 years and over; derived from Watson et al.) was applied to the INNOVATE study, 2 or 3 asthma deaths would have been expected out of the 100 observed clinically significant severe exacerbations. In addition, if the same ratio of clinically significant exacerbations to clinically significant severe exacerbations in the INNOVATE study was applied to the APEX study, 3 deaths per year from asthma would have been expected among the 261 observed exacerbations. However, because nobody in these trials died from asthma, the Assessment Group commented that the rates for asthma-related mortality used in the manufacturer's submission for adults and adolescents were likely to have overestimated mortality.

Assessment Group's economic model

4.2.16 The Assessment Group developed an economic model from the perspective of the UK NHS to assess the cost effectiveness of omalizumab as an add-on treatment to optimised standard care of severe asthma compared with optimised standard care alone. The outcomes of the model are expressed in costs per QALY and costs in UK pound sterling at a 2009 to 2010 price base. The Assessment Group evaluated both costs and outcomes over a lifetime, assuming an omalizumab treatment duration of 10 years and discounting at an annual rate of 3.5%, in accordance with the NICE reference case.

4.2.17 The evidence of effectiveness of omalizumab compared with not using omalizumab for the base-case population in the Assessment Group's model came from INNOVATE for adults and adolescents, and from the IA-05 European population subgroup for children. In addition, the model included a subgroup defined as people admitted to hospital in the year before starting omalizumab (for adults and adolescents, 38.4% of the total INNOVATE trial population at baseline and, for children, 17% of the IA-05 European population subgroup at baseline), and a subgroup of adults and adolescents who reflect people receiving maintenance oral corticosteroids at the start of treatment with omalizumab (21.7% of the INNOVATE population at trial baseline; for children, data were not available from the IA-05 trial).

4.2.18 The model structure used by the Assessment Group was similar to the manufacturer's but differed in the assumptions for asthma-related mortality and health-related quality of life. In its model, the manufacturer linked asthma-related deaths directly to a clinically significant severe exacerbation, whereas the Assessment Group's model assumed that people in the state of day-to-day asthma symptoms (and not only the state of clinically significant severe exacerbation) have an elevated risk of asthma-related death compared with people without asthma. The Assessment Group systematically reviewed the literature for estimates of asthma-related mortality and considered that the most appropriate data for the base case comes from de Vries et al. (2010), which used data from the General Practice Research Database from patients without chronic obstructive pulmonary disease registered in general practice in England aged 18 years and over who received a prescription for inhaled short-acting or long-acting beta$_2$ agonists. The study followed patients from 1993 and until

death, death from asthma or hospitalisation for asthma, and derived incidence rates stratified by treatment steps (1 to 5) of the BTS. In sensitivity analyses, the Assessment Group used alternative mortality rates from Watson et al., as used in the manufacturer's model. In the base case, the Assessment Group estimated, using the de Vries et al. data, that the probability of death over a 3-month period (the cycle length used in the model) was 0.001 for all ages and acknowledged an absence of data for children. The Assessment Group also estimated, using the Watson et al. data, that the probability of death specifically related to asthma over a 3-month period was 0.0049 for people 45 years and over, 0.0008 for those 17 to 44 years, 0.0006 for those 12 to 16 years, and 0.0001 for children under 12 years.

4.2.19 As in the manufacturer's model, the Assessment Group's model considered health-related quality of life associated with day-to-day symptoms of asthma, the degree to which exacerbations worsen the symptoms, and the degree to which treatment with omalizumab improves them. However, to estimate health-related quality of life for day-to-day symptoms, the Assessment Group used EQ-5D data from EXALT, whereas the manufacturer mapped Asthma Quality of Life Questionnaire scores from INNOVATE onto EQ-5D values. The Assessment Group assumed that children experience the same improvement in health-related quality of life from omalizumab treatment as do adults and adolescents, whereas the manufacturer's model assumed no health-related quality-of-life benefit from treatment with omalizumab in children. In the base-case population, the Assessment Group applied a health utility value for day-to-day asthma symptoms for people receiving standard care of 0.719 (compared with 0.669 in the manufacturer's model) and for people taking omalizumab and whose asthma responded to omalizumab at 32 weeks, a utility value of 0.767 (compared with 0.779 in the manufacturer's model). The improvement in utility attributed to omalizumab was smaller in the Assessment Group's model at 0.048 than in the manufacturer's model, with a difference of 0.110. For patients hospitalised in the year before starting (or not starting) omalizumab, the Assessment Group estimated that the difference in utility attributable to omalizumab was 0.130 (compared with 0.138 in the manufacturer's model) and for patients on maintenance oral corticosteroids at the start (or not) of treatment with omalizumab was a difference in utility of 0.105 (compared with 0.106 in the manufacturer's model). To estimate the decrease in utility caused by clinically significant non-severe and severe exacerbations, the Assessment Group and the

manufacturer used data from a prospective study conducted in 4 UK specialist asthma centres, which collected EQ-5D data (Lloyd et al.). The Assessment Group commented that exacerbations leading to hospitalisation may have been more severe in the Lloyd et al. study than in the INNOVATE study, which could have led to overestimation of the effect of an exacerbation on health-related quality of life. The Assessment Group indicated that the combined impact of these factors is unclear.

4.2.20 The Assessment Group included in its model the costs of omalizumab and its administration, and costs related to monitoring patients. The costs of omalizumab reflected every 2 to 4 week dosing dependent on serum IgE and body weight. The Assessment Group used the unit price of the 75-mg syringe (£128.07) to estimate an average annual cost of omalizumab per patient based on the dose distribution used in the trials (INNOVATE for adults and adolescents and IA-05 European population subgroup for children) obtained from the manufacturer's submission. The Assessment Group assumed 10 minutes of a specialist asthma nurse's time to administer omalizumab, and 15 minutes of nurse's time (both at £47 per hour) to monitor the patient up to the third time a patient received omalizumab. From the fourth administration up to the 16-week assessment, monitoring by the specialist nurse was assumed to take 1 hour. From 16 weeks onwards, no monitoring costs were incurred. The Assessment Group assumed that a patient's 16-week assessment took place during a routine appointment. This differs from the manufacturer's model, which assumed that clinicians assess the patient during an additional follow-up appointment. The Assessment Group calculated the annual average cost of omalizumab for adults and adolescents as £8,056 plus administration costs of £260 in the first year and £146 in subsequent years; for children, the annual average cost of omalizumab was £8,455 plus administration costs of £268 in the first year and £151 in subsequent years. The distribution of the dose of omalizumab for the subgroups (when starting omalizumab when hospitalised in the previous year, or on maintenance corticosteroids) was not available; therefore, the Assessment Group used data from the base-case patient population for the subgroups. The Assessment Group took the costs of exacerbations and standard care from the manufacturer's submission and applied them to both modelled treatment groups.

Results of Assessment Group's economic model

4.2.21 For adults and adolescents, and for children, omalizumab add-on treatment was more costly and more effective than standard care alone. For adults and adolescents, the mean cost of omalizumab add-on treatment was £72,938 compared with £33,218 for standard care without omalizumab; the mean QALYs were 14.13 and 13.66 respectively. This resulted in an ICER for omalizumab as an add-on treatment to standard care compared with standard care alone of £83,822 per QALY gained. For children the mean cost of omalizumab add-on treatment was £92,497 compared with £40,218 for standard care without omalizumab; the mean QALYs were 17.39 and 16.72 respectively. This resulted in an ICER for omalizumab of £78,009 per QALY gained. The Assessment Group estimated that the probability that omalizumab was cost effective at £30,000 per QALY was zero in both populations.

4.2.22 For the modelled subgroup reflecting people who had been hospitalised the year before starting treatment, omalizumab add-on treatment was more costly and more effective than standard care without omalizumab. For adults and adolescents, the mean cost of treatment with omalizumab was £75,826 compared with £36,449 for standard care with mean QALYs of 12.68 and 11.83 respectively. This resulted in an ICER for omalizumab of £46,431 per QALY gained. For children, the mean cost of omalizumab was £83,145 compared with £44,718 for standard care; the mean QALYs were 15.32 and 14.45 respectively. This resulted in an ICER for omalizumab of £44,142 per QALY gained. The Assessment Group estimated that the probability that omalizumab was cost effective at £30,000 per QALY gained was zero in both populations.

4.2.23 For the modelled subgroup reflecting people who took maintenance oral corticosteroids, omalizumab add-on treatment was more costly but also more effective than standard care alone. For adults and adolescents, the mean cost of omalizumab add-on treatment was £68,995 compared with £35,902 for standard care; the mean QALYs were 13.44 and 12.78 respectively. This resulted in an ICER for omalizumab of £50,181 per QALY gained. As with the hospitalisation subgroup, the Assessment Group estimated that the probability that omalizumab was cost effective at £30,000 per QALY was zero.

4.2.24 The Assessment Group presented results for several scenarios reflecting

different assumptions. This included a scenario that took into account the adverse effects of maintenance oral corticosteroids, following a similar approach taken by the manufacturer. The Assessment Group assumed that:

- patients who do not receive omalizumab continue maintenance oral corticosteroids for the rest of their lives
- the excess relative risk of developing diseases attributable to use of oral corticosteroids does not persist once an individual has stopped taking oral corticosteroids, and
- health losses expressed in disability-adjusted life years (DALYs) are equivalent to health gains expressed in QALYs.

4.2.25 The Assessment Group commented that the key drivers of cost effectiveness were the asthma-related mortality rates, the degree to which omalizumab improves health-related quality of life and, for people who take maintenance oral corticosteroids, whether or not the model included adverse effects from oral corticosteroids. When the model incorporated the higher asthma-related mortality rates reported by Watson et al. and adopted by the manufacturer, the ICERs for omalizumab as an add-on treatment compared with standard care alone for the base-case populations were £46,029 per QALY gained for adults and adolescents, and £98,688 per QALY gained for children. In the subgroup reflecting patients hospitalised in the year before starting therapy, the ICERs for omalizumab were £31,576 per QALY gained for adults and adolescents and £47,430 per QALY gained for children, and in the subgroup taking maintenance oral corticosteroids, the ICER was £29,657 per QALY gained for adults and adolescents and was not estimated for children. Whether the model included the assumption that omalizumab did or did not improve a child's health-related quality of life also had a substantial impact on the ICERs. However, the ICER did not fall below £30,000 per QALY gained in children (the lowest ICER was £42,296 per QALY gained in the subgroup of children hospitalised in the previous year). Incorporating the adverse effects of oral corticosteroids in the maintenance oral corticosteroids subgroup reduced the ICER for omalizumab as an add-on treatment to standard care compared with standard care alone from £50,181 to £44,292.

4.2.26 An additional subgroup consisting of people experiencing 3 or more

exacerbations in the previous year was considered by the Assessment Group. The ICERs for omalizumab in this subgroup were lower than the ICERs for the base-case populations of adults and adolescents (£77,868 per QALY gained compared with £83,822 per QALY gained) and children (£71,513 per QALY gained compared with £78,009 per QALY gained). The Assessment Group commented that using the health-related quality-of-life data from INNOVATE (EQ-5D mapped from Asthma Quality of Life Questionnaire scores) reduced the ICERs in this subgroup to £52,236 per QALY gained in adults and adolescents, and to £50,139 per QALY gained in children.

Additional analyses requested by the Appraisal Committee at the first Appraisal Committee meeting (3 July 2012)

4.2.27 After the first appraisal committee meeting, NICE requested on behalf of the Appraisal Committee that the Assessment Group undertake additional analyses in order to model scenarios with alternative assumptions on:

- mortality rates for very severe asthma
- rates of clinically significant exacerbations for very severe asthma
- treatment duration
- adverse effects of oral corticosteroids, and
- carer benefits.

The Committee requested additional analyses for 3 scenarios including populations who are covered by the marketing authorisation, whose therapy is optimised and who are followed in a specialist centre:

- Population 1: people with very severe persistent allergic asthma maintained on oral corticosteroids and who were hospitalised in the year before treatment.
- Population 2: people with very severe persistent allergic asthma maintained on oral corticosteroids, but who have not necessarily been hospitalised in the year before treatment.

- Population 3: people with very severe persistent allergic asthma who are on maintenance or frequent courses of oral corticosteroids (for example, 4 or more courses per year), but who have not necessarily been hospitalised in the year before treatment.

4.2.28 The Assessment Group requested additional data from the manufacturer for populations 1 and 3, and used data for subgroup 2 available in the manufacturer's submission. The Assessment Group also received additional information requested from clinical specialists about omalizumab use in the UK. The additional analyses conducted by the Assessment Group were presented for the following: children aged 6 to 11 years; adults and adolescents aged 12 years and over; and the overall population consisting of adults, adolescents and children. For adults and adolescents, and the overall population, the results presented were based on a weighted average of the ICERs for different age cohorts to reflect the mortality risk that differs by age. The weighting was based on the percentage of people at each age in the APEX study.

4.2.29 The Assessment Group's additional analyses incorporated the following assumptions in the base case: asthma-related mortality risk from Watson et al.; adverse effects of oral corticosteroids; 5-year treatment duration for children, 10-year treatment duration for adults and adolescents; EQ-5D utility values from EXALT for the subgroup taking maintenance oral corticosteroids (population 2) used for all populations; and the same exacerbation rates at start of treatment, treatment effectiveness, and health-related quality of life assumed for children as for adults and adolescents. The ICER for omalizumab as an add-on treatment to standard care compared with standard care alone for children was £62,945, £61,361 and £61,096 per QALY gained in populations 1, 2 and 3, respectively. The ICER for adults and adolescents was £32,398 and £32,508 per QALY gained in populations 1 and 2 respectively, with the lowest ICER in population 3 (£31,573). The ICER for omalizumab as an add-on treatment to standard care compared with standard care alone for the overall population (adults, adolescents and children) was £33,077, £33,150 and £32,229 per QALY gained in populations 1, 2 and 3 respectively. The Assessment Group commented that the ICERs for the overall population (adults, adolescents and children), and for adults and adolescents alone, were similar because children represent a small proportion of the overall population (2.2%). The Assessment Group further commented that asthma-related mortality risk was the main driver of the cost-effectiveness

results and of the differences in the results between the adult and adolescent population and children.

4.2.30 The Assessment Group presented cost-effectiveness results for populations 1, 2 and 3 based on alternative scenarios, as requested by the Appraisal Committee. Increasing the clinical effectiveness of omalizumab observed in INNOVATE by 10% in all subgroups reduced the ICERs for omalizumab very slightly across all 3 populations, with all the ICERs remaining above £30,000 per QALY gained. Using the improvement in utility (0.1300) from EXALT for the group hospitalised in the year before starting therapy applied to all populations also reduced the ICERs for omalizumab, though they remained above £30,000 per QALY gained for all 3 populations. Increasing the asthma-related mortality risk from Watson et al. by 15% across all age groups also reduced the ICERs slightly. In the overall population, increasing the asthma-related mortality risk from Watson et al. by 15% reduced the ICER to £32,047, £32,134 and £31,159 per QALY gained for populations 1, 2 and 3 respectively. Using asthma-related mortality risk from de Vries et al. and increasing the risk by 15% reduced the ICERs for children in all 3 populations to approximately £53,000 per QALY gained. For adults and adolescents, the ICERs increased to approximately £42,000 per QALY gained for each population. For the overall population, the ICERs increased to £42,613, £42,634 and £41,868 per QALY gained for populations 1, 2 and 3 respectively. The Assessment Group also incorporated an additional QALY burden from non-Hodgkin's lymphoma, adrenal insufficiency and sleep disturbance, which resulted in an annual total QALY loss of 0.04978. This reduced the ICERs for omalizumab slightly across all 3 populations, again with all the ICERs remaining above £30,000 per QALY gained.

4.2.31 The Assessment Group conducted a threshold analysis to estimate the minimum health-related quality-of-life losses associated with oral corticosteroid-related adverse effects that would be needed to achieve an ICER for omalizumab of less than or equal to £30,000 per QALY gained. The Assessment Group's results showed that the QALY loss associated with oral corticosteroids would need to be at least 0.115 QALYs per patient per year for population 1, at least 0.120 QALYs per patient per year for population 2 and at least 0.095 QALYs per patient per year for population 3. To achieve an ICER of £30,000 per QALY gained, identified health consequences would need to be 2.3, 2.4 and 1.9 times their current values in populations 1, 2 and 3 respectively.

4.2.32 The Assessment Group was not aware of any evidence to provide adequate estimates on health-related quality-of-life benefits not currently captured in the economic modelling, including in carers. For patients, the model captured the health-related quality-of-life improvements with omalizumab.

Additional analyses and the patient access scheme submitted by the manufacturer after the second Appraisal Committee meeting (3 October 2012)

4.2.33 In its response to the appraisal consultation document, the manufacturer provided additional analyses for population 2 (people with very severe persistent allergic asthma who require maintenance oral corticosteroids) and population 3 (people with very severe persistent allergic asthma who require maintenance or frequent courses of oral corticosteroids [4 or more per year]). In contrast to its original analyses, the manufacturer assumed that the utility gain from omalizumab for adolescents and adults applied also to children. The manufacturer calculated an asthma-related mortality rate midway between the estimates from Watson et al. and de Vries et al., and increased the result by 15% to represent those patients with the most severe asthma. The manufacturer varied the proportion of children in the age-weighted ICER calculations. The 3 proportions were:

- 2.2%, used in the Assessment Group's weighted average cost-effectiveness analyses
- 7.3%, based on mid-2011 census data for England and Wales; and
- 4.75%, the midpoint value between 2.2% and 7.3%.

4.2.34 The manufacturer agreed a patient access scheme with the Department of Health, in which the manufacturer offers a discount on the list price of omalizumab to the NHS. The resulting ICERs for population 2 were £24,183, £24,591 and £25,010 per QALY gained when the proportions of children were assumed to be 2.2%, 4.75% and 7.3% respectively. The resulting ICERs for population 3 were £23,453, £23,902 and £24,370 per QALY gained with the same proportions of children.

4.2.35 The Assessment Group reviewed the manufacturer's additional analyses and reported that the manufacturer had assumed that the risk of asthma-related mortality reported in Watson et al. and de Vries et al. used the same measure of risk. However, Watson et al. reported a conditional probability of death after hospitalisation for acute severe asthma, and de Vries et al. reported an annual mortality rate for patients treated at BTS/SIGN step 5. The Assessment Group considered that the probability and the rate should have been converted into the same measure of risk before averaging across risks. The Assessment Group also commented that, by averaging the proportion of patients in the overall population for the different age categories to obtain an average midpoint mortality risk by age, then using this risk to calculate the age-weighted ICER, the manufacturer had not accurately weighted the proportion of patients in each age category. The Assessment Group corrected these errors and, using the midpoint mortality estimates increased by 15%, estimated ICERs for population 2 of £23,626, £23,817 and £24,008 per QALY gained when the proportions of children were assumed to be 2.2%, 4.75% and 7.3% respectively. The resulting ICERs for population 3 were £23,011, £23,203 and £23,395 per QALY gained with the same proportions of children.

4.3 Innovation

4.3.1 The manufacturer considered that omalizumab's innovative characteristics included its ability to substantially improve quality of life. The manufacturer highlighted its opinion that omalizumab represents the only significant advance in the management of severe asthma in the past 30 years.

4.4 Consideration of the evidence

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

Management of severe persistent allergic asthma in UK clinical practice

4.4.2 The Committee discussed the clinical need of people with severe persistent allergic asthma. It heard from the clinical specialists and the patient experts that severe exacerbations have a large impact on people with severe persistent allergic asthma and their families. This may include frequent attendance at accident and emergency departments, emergency GP visits, reduced attendance and poor performance at school or work, limitations to social life and inability to exercise. The Committee also heard that the impact on families and carers may include anxiety, sleep deprivation, and emotional and financial pressures. The Committee accepted that severe uncontrolled asthma can severely reduce quality of life among people with the condition, as well as their families and carers.

4.4.3 The Committee discussed the role of omalizumab in UK clinical practice. It heard from the clinical specialists that UK clinical practice is based on the 'British guideline on the management of asthma' (BTS/SIGN) and uses a stepped treatment approach, with drugs added or withdrawn depending on symptoms and control. The Committee heard from the clinical specialists and patient experts that, in current UK clinical practice, the population for which omalizumab would be considered was smaller than that covered by the marketing authorisation. Clinicians currently optimise a person's asthma treatment before considering omalizumab; for those whose asthma remains poorly controlled, and affects their quality of life, omalizumab is considered as an add-on treatment. One clinical specialist estimated that the number of people currently being offered omalizumab in his practice accounts for approximately 1 in 200 people with asthma and approximately 8 in 200 people with asthma are at step 5 of the 'British guideline on the management of asthma'. The Committee concluded that only people with the most severe persistent allergic asthma despite optimised treatment would currently be offered omalizumab.

4.4.4 The Committee was aware that NICE's previous technology appraisal guidance on omalizumab for severe persistent allergic asthma (now replaced by this guidance) required a person to have been hospitalised for a clinically significant severe exacerbation in the year before starting omalizumab. The Committee heard from a patient expert that requiring hospitalisation as a prerequisite for

treatment with omalizumab provides the perverse incentive to let the condition worsen. The Committee heard from the clinical specialists that there are various reasons why people might choose not to go into hospital, and that some people tolerate respiratory distress better than others. It heard from a patient expert that he chose not to go to hospital even when extremely ill, and heard from the clinical specialists that this behaviour is not unusual for people with severe uncontrolled asthma. The Committee noted that the clinical specialists preferred other ways of identifying candidates for treatment with omalizumab, that is, people with asthma at step 5 of the 'British guideline on the management of asthma' (BTS/SIGN) with poorly controlled asthma who are treated with continuous or multiple courses of oral corticosteroids per year, irrespective of whether they had recently been admitted to hospital. The Committee accepted that there are limitations to using the requirement of previous hospitalisation as a criterion for determining clinical need for omalizumab.

4.4.5 The Committee discussed oral corticosteroid use, including the significant physical and psychiatric long-term adverse effects associated with frequent use. The Committee noted that these include bone fracture, diabetes mellitus, peptic ulcer, myocardial infarction, stroke, cataracts, glaucoma, sleep and mood disturbance, and weight gain, and, for children, failure to reach expected adult height. It also noted that the patient experts and clinical specialists highly valued any therapy that would help a person with severe asthma taper or stop oral corticosteroid use. The clinical specialists explained that they would offer omalizumab not only to people on maintenance oral corticosteroids, but also to some people who required frequent courses of oral corticosteroids. The Committee heard from the clinical specialists that omalizumab enables people with severe allergic asthma to reduce their use of high-dose oral corticosteroids, and that patients and their carers are prepared to accept the inconvenience of attending specialist centres to have injections of omalizumab. The Committee accepted that there are significant risks associated with oral corticosteroids, and that frequent use may have a considerable impact on the lives of people with severe asthma.

Clinical effectiveness

4.4.6 The Committee considered the evidence on the clinical effectiveness of

omalizumab from the manufacturer's submission and the assessment report. The Committee noted that omalizumab as an add-on to standard care reduced the rate of clinically significant exacerbations and clinically significant severe exacerbations in adults, adolescents and children, although the effect on clinically significant severe exacerbations was not statistically significant in children. The Committee noted that the conclusions from the double-blind INNOVATE trial were supported by the results from several other clinical trials. The Committee also noted that, in adults, omalizumab reduced total emergency visits (including hospital admissions, emergency department visits and unscheduled visits to the doctor), and reduced hospital admissions in children whose asthma responded to omalizumab compared with children randomised to placebo. The Committee noted that omalizumab treatment resulted in small increases in lung function in adults as measured by percentage of predicted FEV_1 but that no FEV_1 data were collected in the children's trials. The Committee also noted that there was some evidence that adults and adolescents taking omalizumab used rescue medication less frequently and oral corticosteroids in lower doses. The Committee heard from patient experts and clinical specialists, and again from comments received during consultation, that omalizumab has resulted in life-changing improvements in reducing the number of asthma-related clinically significant exacerbations. The Committee concluded that omalizumab as an add-on to optimised standard care is more clinically effective in treating severe persistent allergic asthma than optimised standard care alone.

4.4.7 The Committee understood that health-related quality of life was generally collected using the Asthma Quality of Life Questionnaire, with a paediatric version for children participating in the IA-05 trial. The Committee noted that EXALT was the only trial that also reported EQ-5D scores. The Committee also noted that there were statistically significant improvements in health-related quality of life favouring omalizumab in adults from both INNOVATE and EXALT, but not in children. The Committee agreed with the Assessment Group's suggestion that the IA-05 trial may have been underpowered to detect differences in health-related quality of life in children. The Committee heard from a patient expert that treatment with omalizumab resulted in a marked improvement in her child's health-related quality of life, including the ability to attend school, participate in sports and play in the park. The Committee accepted from the testimonies of the patient experts and the evidence from the clinical studies that omalizumab was likely to improve health-related quality of life in adults,

adolescents and children with severe persistent allergic asthma. The Committee also agreed that there could be additional health-related benefits for carers as a result of omalizumab use, and that these could be included within NICE's reference case if quantifiable.

4.4.8 The Committee noted that the clinical trials included people whose asthma was less severe than those currently being treated with omalizumab in the UK. The Committee concluded that the trial evidence may not be fully applicable to people who would be offered omalizumab in the UK, who, having more severe asthma, might receive more benefit from omalizumab treatment, a conclusion supported by the clinical specialists.

Cost effectiveness

4.4.9 The Committee considered the cost-effectiveness results from the manufacturer's submission and the assessment report, and noted that the main differences between the manufacturer's and the Assessment Group's economic models were the assumptions on asthma-related mortality and how health-related quality of life improvements from omalizumab were incorporated in the models. The Committee discussed which estimates for asthma-related mortality risk were most plausible. The manufacturer's model included mortality rates from Watson et al. for people hospitalised with acute severe asthma, categorised by age. By contrast, the Assessment Group used data from de Vries et al., which stratified people with asthma aged 18 years and over from the General Practice Research Database according to their GINA stage, with GINA step 5 as the Assessment Group's base case. The Committee noted that the mortality rate from de Vries et al. was constant across all ages, and that the Assessment Group assumed that this mortality rate also applied to children. The Committee heard from the clinical specialists that the asthma-related mortality risk in children is much lower than in adults, and that in adults mortality risk increases with age. The Committee concluded that it was inappropriate to accept the same mortality risk across all ages because it did not reflect the natural history of the disease. However, the Committee was concerned that the Watson et al. data were inconsistent with the observation that no deaths attributable to asthma were observed in the APEX trial. On the other hand, the Committee considered that mortality rates may have been underestimated in the de Vries

et al. data, if people offered omalizumab in the UK reflected the more severe end of step 5 with higher mortality rates than those reported for people at step 5 as a whole. Additionally, the Committee was aware that both studies may have overestimated the true mortality rate from asthma by attributing deaths from chronic obstructive pulmonary disease to asthma, although the de Vries et al. study tried to exclude people with chronic obstructive pulmonary disease. The Committee concluded that both the Watson et al. and the de Vries et al. studies had limitations, that considerable uncertainty remained about the mortality associated with severe persistent asthma, and that neither may reflect mortality among the subgroups of people with very severe persistent asthma, to whom omalizumab is offered in clinical practice. The Committee agreed that the asthma-related mortality rates applicable to this appraisal were likely to be between the Watson et al. and de Vries et al. estimates.

4.4.10 The Committee considered that assumptions around the utility gain associated with omalizumab also accounted for some of the differences in the results between the Assessment Group's and the manufacturer's models. Firstly, it noted that the Assessment Group assumed that children experienced the same improvement in health-related quality of life as adults and adolescents, whereas the manufacturer assumed there was no health-related quality of life improvement from omalizumab treatment in children. The Committee concluded that the evidence presented by a patient expert, and the results from an observational study in children, showed that the utility values used in the manufacturer's economic model did not adequately capture the potential health-related quality-of-life benefits of omalizumab for children. The Committee therefore preferred the Assessment Group's approach in which the same utility gain was assumed for adults, adolescents and children. Secondly, the Committee was aware that the manufacturer and the Assessment Group used different methods of estimating health-related quality of life for day-to-day asthma symptoms. The Committee noted that the Assessment Group's approach, using EQ-5D values directly collected in the EXALT trial, resulted in a lower quality-of-life benefit for people whose asthma responded to omalizumab than did the manufacturer's approach of mapping Asthma Quality of Life Questionnaire scores collected in the INNOVATE trial onto EQ-5D values. The Committee preferred the direct estimates of EQ-5D, in line with the NICE reference case.

4.4.11 The Committee considered which discount rates to use in this appraisal, noting

the clarification of the Guide to the methods of technology appraisal issued by the Board of NICE. This states that 'where the Appraisal Committee has considered it appropriate to undertake sensitivity analysis on the effects of discounting because treatment effects are both substantial in restoring health and sustained over a very long period (normally at least 30 years), the Committee should apply a rate of 1.5% for health effects and 3.5% for costs'. The Committee considered that restoring and sustaining health for a very long period equated to a cure. The Committee heard from the clinical specialists that severe persistent asthma is not considered to be curable. It concluded that it did not have evidence that omalizumab cured asthma and that there was no case to apply differential discounting.

4.4.12 The Committee noted that the manufacturer's original probabilistic base-case ICERs (see section 4.2.7; for omalizumab as an add-on treatment to standard care compared with standard care alone, and using the Watson et al. mortality rates) were £33,300 per QALY gained for adults and adolescents and £89,000 per QALY gained for children. By contrast, the Committee noted that the original Assessment Group's base-case ICERs (using the de Vries et al. mortality rates) were £83,800 per QALY gained for adults and adolescents and £78,000 per QALY gained for children, and using the Watson et al. mortality data the Assessment Group's ICERs were £46,000 per QALY gained for adults and adolescents and £98,700 per QALY gained for children. The Committee acknowledged that using the mapped utility values as done in the manufacturer's model would reduce the ICERs from £83,800 to £52,200 per QALY gained for adults and adolescents, but it considered the use of direct EQ-5D values more appropriate (see section 4.4.10). The Committee concluded that the ICERs for omalizumab for the whole population were higher than what can be considered a cost-effective use of NHS resources.

4.4.13 The Committee acknowledged that the analyses carried out for subgroups of people hospitalised in the year before trial entry or on maintenance oral corticosteroids resulted in lower ICERs in both the manufacturer's and Assessment Group's analyses. However, the Committee noted that the Assessment Group's ICERs were still above £30,000 per QALY gained in adults and adolescents even with the use of the more favourable Watson et al. mortality data. The Committee noted that the Assessment Group's analysis had taken into account the disutility from several long-term adverse effects including bone

fracture, diabetes mellitus, peptic ulcer, myocardial infarction and stroke, cataract and glaucoma, weight gain, non-Hodgkin's lymphoma, adrenal insufficiency and sleep disturbance. However, the Committee concluded that other adverse effects, such as obesity, hypertension, mood changes, depression, psychosis, thinning skin, delayed wound healing, reduced growth in children and increased risk of infection were additional important factors that had not been captured when calculating the QALY.

4.4.14 The Committee recognised that omalizumab was an effective therapy, and that the analyses presented may not have been applicable to the population of people with very severe asthma for whom omalizumab is used in clinical practice. The Committee considered whether it was possible to describe more clearly the clinical characteristics of this population and model the use of omalizumab more accurately, thereby identifying people with very severe asthma for whom omalizumab may potentially be cost effective. The Committee requested more information about the clinical characteristics of the population for which omalizumab would be considered, and asked the Assessment Group to carry out additional analysis in 3 high-risk populations with very severe persistent allergic asthma:

- people who are on maintenance oral corticosteroids and who were hospitalised in the year before treatment
- people who are on maintenance oral corticosteroids but who have not necessarily been hospitalised in the year before treatment
- people who are on maintenance or frequent courses of oral corticosteroids (for example, 4 or more courses per year) but who have not necessarily been hospitalised in the year before treatment.

The Committee also asked the Assessment Group to assume higher efficacy for omalizumab and higher asthma-related mortality estimates to reflect people with very severe uncontrolled asthma, as well as analyses incorporating more adverse effects from oral corticosteroids and carer benefits associated with omalizumab. The Committee also requested pooled analyses for the overall population of children, adolescents and adults for which omalizumab is licensed to explore the possibility of developing a single recommendation for all licensed populations.

4.4.15 The Committee considered the additional information and analyses provided by clinical specialists and the manufacturer, who provided the Assessment Group with the information necessary to conduct the further analyses requested by the Committee at the first appraisal committee meeting (see section 4.2.28). The Committee was aware that the new analyses incorporated the Watson et al. asthma-related mortality data, with a sensitivity analysis using the de Vries et al. data, and shorter treatment duration for children (5 instead of 10 years in the Assessment Group's original analyses following the advice of the clinical specialists). The Committee noted that the base-case ICERs were similar across the 3 high-risk populations, that is, £31,600 to £32,500 per QALY gained for adults and adolescents, £61,100 to £62,900 per QALY gained for children and £32,200 to £33,200 per QALY gained for the overall population. The Committee acknowledged that the ICERs for the overall population and for adults and adolescents were similar because children were assumed to represent only a very small proportion of the overall population treated with omalizumab (2.2%). However, the Committee acknowledged that the lower use of omalizumab in children may reflect the recommendation in NICE's previous technology appraisal guidance on omalizumab for the treatment of severe persistent allergic asthma in children aged 6 to 11 (now replaced by this guidance) and therefore the proportion of children who might otherwise be considered for omalizumab treatment may be underestimated. The Committee concluded that, even assuming 15% higher mortality rates because of the severity of the disease, the ICERs in the overall population were still high at £32,000 and £42,000 per QALY gained using the Watson et al. or de Vries et al. data respectively.

4.4.16 The Committee considered the Assessment Group's additional analysis on the health-related quality-of-life losses associated with oral corticosteroid-related adverse effects. The Committee noted that the Assessment Group had conducted a threshold analysis to explore the necessary size of the unidentified health effects of oral corticosteroid use, in addition to those already modelled, to reduce the cost per QALY gained of omalizumab to £30,000. The Committee noted that the additional QALYs from unidentified adverse effects of oral corticosteroids would need to be twice or more of those derived from known adverse effects, and was not persuaded that this was a plausible assumption.

4.4.17 The Committee considered omalizumab to be innovative in its potential to make a significant and substantial impact on health-related benefits, and explored if any

potential significant and substantial health-related benefits have been identified that were not included in the economic model. The Committee recognised that some benefits of avoiding the adverse effects of oral corticosteroid use had not been fully captured in the QALY measure (see section 4.4.13). The Committee also considered the benefits to carers associated with omalizumab, which may not have been captured in the QALY calculations. The Committee noted that the manufacturer included no empirical and quantifiable evidence relating to potential carer benefits in its submission, and the Assessment Group did not include any carer benefits formally in its additional analyses. The Committee concluded that the potential additional health-related benefits for carers as a result of omalizumab use could not currently be quantified. The Committee recognised that the approach to estimate utility gain in light of the lack of evidence taken in NICE's technology appraisal guidance on pharmalgen for the treatment of bee and wasp venom allergy was not appropriate to use here, because omalizumab does not provide a cure for asthma.

4.4.18 The Committee considered the additional analyses, including a patient access scheme, submitted by the manufacturer after consultation on the appraisal consultation document (see section 4.4.14). The Committee noted that the manufacturer calculated an asthma-related mortality rate midpoint between the conditional probability in Watson et al. and the mortality risk in de Vries et al., and increased both by 15% to reflect mortality in people with very severe uncontrolled asthma, acknowledging the Assessment Group's concerns about averaging proportions and rates. The Committee concluded that the 15% increase in mortality risk was an appropriate approximation of the mortality risk in very severe allergic asthma. The Committee also concluded that a more realistic mortality rate likely lay between the midpoint and the estimate from de Vries et al. and that the average rate as corrected by the Assessment Group was a more plausible mortality rate, though some uncertainty remained.

4.4.19 The Committee noted the manufacturer's analyses of different proportions of children in the overall population eligible for omalizumab, which were carried out because of concerns that the 2.2% value assumed in the original Assessment Group's weighted average cost-effectiveness analyses might underestimate the true value (see section 4.4.15). The Committee was aware that increasing the proportion of children from 2.2% to 7.3% in line with 2011 census data did not have a large impact on the ICERs (see section 4.2.35) and it concluded that,

given uncertainties in the true value, it would be reasonable to accept the midpoint value of 4.75%. The Committee also concluded that, because the proportion of children used was very small and it did not have a large impact on the ICERs, it was appropriate to use the pooled analyses presented by the Assessment Group as the basis for a recommendation.

4.4.20 The Committee considered the results of the additional cost-effective analyses using the asthma-related mortality rate midpoint between Watson et al. and de Vries et al. increased by 15%, the 4.75% proportion of children aged 6 to 11 in the overall population eligible for omalizumab, and incorporating the patient access scheme for omalizumab. The Committee concluded that applying the Assessment Group's corrections to the manufacturer's analysis resulted in a most plausible ICER of £23,200 per QALY gained for the combined population of adults, adolescents and children on maintenance or frequent courses of oral corticosteroids, defined as 4 or more courses in the year before receiving omalizumab.

4.4.21 The Committee considered the comments received during consultation on the appraisal consultation document indicating the 'life-changing' effect that omalizumab had on patients' lives and the lives of their families and carers. The Committee noted that many consultees had emphasised the need to acknowledge the uncaptured benefits of reducing dependence on oral corticosteroids and it was persuaded that these uncaptured benefits were sufficient to justify accepting an ICER of £23,200 per QALY gained. The Committee concluded that, with the patient access scheme submitted after consultation on the appraisal consultation document, omalizumab as an add-on to optimised standard therapy is a cost-effective use of NHS resources for treating severe persistent confirmed allergic IgE-mediated asthma in people aged 6 years and over who need continuous or frequent oral corticosteroid treatment (defined as 4 or more courses in the previous year) and should be recommended as an option for treatment in this population.

4.4.22 The Committee noted that optimised standard therapy was specified in NICE's previous technology appraisal guidance on omalizumab for severe persistent allergic asthma (now replaced by this guidance) and that oral beta$_2$ agonists were listed as a component of optimised standard therapy but are now rarely used in clinical practice. For the purposes of this guidance, the Committee agreed that

optimised standard therapy should be defined as a full trial of, and documented compliance with, inhaled high-dose corticosteroids, long-acting $beta_2$ agonists, leukotriene receptor antagonists, theophyllines, oral corticosteroids, and smoking cessation if clinically appropriate.

5 Implementation

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

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

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has severe persistent confirmed allergic IgE-mediated asthma 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.

6 Appraisal Committee members 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, Peninsula Technology Assessment Group (PenTAG), University of Exeter

Dr Ray Armstrong
Consultant Rheumatologist, Southampton General Hospital

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

Dr Peter Barry

Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

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

Dr Mark Chakravarty
External Relations Director, Pharmaceuticals and Personal Health, Oral Care Europe

Mark Chapman
Health Economics and Market Access Manager, Medtronic UK

Professor Fergus Gleeson
Consultant Radiologist, Churchill Hospital, Oxford

Eleanor Grey
Lay member

Professor Jonathan Grigg
Professor of Paediatric Respiratory and Environmental Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University London

Sanjay Gupta
Young physically disabled (YPD) Service Case Manager, Southwark Health and Social Care, Southwark PCT

Professor Daniel Hochhauser
Consultant in Medical Oncology

Dr Neil Iosson
General Practitioner

Anne Joshua
Associate Director of Pharmacy, NHS Direct

Terence Lewis
Lay Member

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 Rubin Minhas
General Practitioner and Clinical Director, BMJ Evidence Centre

Dr Elizabeth Murray
Reader in Primary Care, University College London

Dr Peter Norrie
Principal Lecturer in Nursing, DeMontfort University

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

Dr John Pounsford
Consultant Physician, Frenchay Hospital, Bristol

Dr Danielle Preedy
Lay Member

Dr John Rodriguez
Assistant Director of Public Health, NHS Eastern and Coastal Kent

Alun Roebuck
Consultant Nurse in Critical and Acute Care, United Lincolnshire NHS Trust

Roderick Smith
Finance Director, West Kent Primary Care Trust

Cliff Snelling
Lay Member

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

David Thomson
Lay Member

Tom Wilson
Director of Contracting and Performance, NHS Tameside and Glossop

NICE project team

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

Richard A. Diaz
Technical Lead(s)

Zoe Charles
Technical Adviser

Jeremy Powell
Project Manager

7 Sources of evidence considered by the Committee

The assessment report for this appraisal was prepared by the Centre for Reviews and Dissemination, Centre for Health Economics Technology Assessment Group, University of York:

- Norman G, Faria R, Paton F et al. Omalizumab for the treatment of severe persistent allergic asthma: a systematic review and economic evaluation, April 2012

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

Manufacturers or sponsors:

- Novartis

Professional or specialist and patient or carer groups:

- Asthma UK
- British Society for Allergy and Clinical Immunology
- British Thoracic Society
- Primary Care Respiratory Society
- Royal College of Nursing
- Royal College of Paediatrics and Child Health
- Royal College of Pathologists
- Royal College of Physicians

- Royal Pharmaceutical Society

Other consultees:

- Department of Health
- Welsh Government

Commentator organisations (without the right of appeal):

- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Medicines and Healthcare products Regulatory Agency
- MRC and Asthma UK Centre in Allergic Mechanisms of Asthma

The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer or sponsor consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on omalizumab by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Shuaib Nasser, Consultant Physician in Allergy and Asthma, nominated by the British Society for Allergy and Clinical Immunology – clinical specialist
- Professor Graham Roberts, Professor and Honorary Consultant in Paediatric Allergy and Respiratory Medicine, nominated by the British Society for Allergy and Clinical Immunology – clinical specialist
- Emily Humphreys, Policy and Public Affairs Manager, Asthma UK nominated by Asthma UK - patient expert
- Stewart Thompson, nominated by Asthma UK – patient expert
- Nicola Whitehead, nominated by Asthma UK – patient expert

Representatives from the following manufacturers or sponsors attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific

issues and comment on factual accuracy.

- Novartis

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