# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Overview

## Omalizumab for treating severe persistent allergic asthma (review of technology appraisal guidance 133 and 201)

This overview is a summary of:

- the evidence and views submitted by the manufacturers, the consultees and their nominated clinical specialists and patient experts and
- the assessment report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal. Please note that this document is a summary of the information available before comments on the assessment report have been received.

# Key issues for consideration

### Clinical effectiveness

- While there is substantial randomised evidence relating to the short and medium-term efficacy of omalizumab in adults in terms of exacerbations, need for unscheduled care, day-to-day symptoms and lung function, randomised data relating to children between the ages of 6 and 12 years are limited to a single subgroup (defined a priori) of a placebo-controlled trial which showed efficacy in reduced exacerbations and hospitalisations. What is the Committee's view on the strength of the evidence in both licensed populations?
- There is no randomised evidence relating to long-term efficacy in either adults or children and only very limited evidence from observational studies relating to the adult population. What is the Committee's view on this lack of evidence for the long-term efficacy of omalizumab?
- While there is some evidence that omalizumab reduces oral corticosteroid use, the evidence is considerably more robust in adults than in children.

What is the Committee's view on the generalisability and strength of the available evidence?

- There is evidence from randomised studies that omalizumab improves health-related quality of life in adults. However, there is a lack of evidence on symptom and quality of life improvement in children, and the Assessment Group commented that the randomised study in children may have been underpowered to detect differences between treatment groups. What is the Committee's view on the strength of the available evidence? Can the results from the studies of adults be generalised to children?
- There is some evidence available for the short-term safety of omalizumab but there is a lack of data for long-term treatment. What is the Committee's view on the uncertainty around the long-term safety of omalizumab?

**Cost effectiveness**

- Asthma-related mortality risk was a major driver of cost-effectiveness in both the Assessment Group's and the manufacturer's models. However, the different estimates used by the manufacturer and the Assessment Group account for a large proportion of the difference in the results between the models. Which estimates for asthma-related mortality risk are most plausible, those from Watson et al (2007) derived from people hospitalised for acute severe asthma, or those from de Vries et al. (2010) which used data from the General Practice Research Database?
- Health-related quality of life improvement with omalizumab was also a major driver of cost-effectiveness in the models.
  - In the Assessment Group's model, children under 12 years were assumed to experience the same health-related quality of life improvement as those aged 12 years and older, while in the manufacturer's submission, children under 12 years were assumed not to experience any health-related quality of life improvement with omalizumab until they reached the age of 12 years. What is the Committee's view on which approach is most plausible?

  - The manufacturer and the Assessment Group used different methods of estimating health-related quality of life for day to day asthma symptoms. 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, relative to the manufacturer's approach of mapping Asthma Quality of Life Questionnaire scores collected in the INNOVATE trial onto EQ-5D values. What is the Committee's view on the methods and estimates used?
- The incremental cost-effectiveness ratio (ICER) estimates were more favourable towards omalizumab in the more severe subgroup populations compared with the overall severe persistent allergic asthma population (that is, those admitted to hospital in the year before trial entry; those receiving maintenance oral corticosteroids at trial baseline; and those experiencing three or more exacerbations in the previous year). However, the ICERs estimated by the Assessment Group remained outside the range normally considered a cost-effective use of NHS resources in all populations, including the severe subgroup populations. What is the Committee's view on these results?
- The Assessment Group and the manufacturer each carried out a scenario analysis that incorporated the adverse effects of oral corticosteroids in the maintenance oral corticosteroids subgroup. The costs and health losses associated with oral corticosteroid-related adverse effects had a major impact on the cost-effectiveness estimates. The analysis assumed that people who do not receive omalizumab will continue to receive maintenance oral corticosteroids for the rest of their life, that health losses expressed in disability-adjusted life years (DALYs) are equivalent to health losses expressed in QALYs, and that the excess relative risk attributable to oral corticosteroids is based solely on current exposure. The Assessment Group cautioned that these assumptions may favour omalizumab. What is the Committee's view on the appropriateness of estimating the costs and health losses associated with oral corticosteroid-related adverse effects using these assumptions?

# 1 Background: Clinical need and practice

1.1 Asthma is a long-term inflammatory disorder of the airways characterised by symptoms such as breathlessness, chest tightness, wheezing, sputum production and cough associated with variable airflow obstruction and airway hyper-responsiveness. Asthma symptoms vary in frequency and severity, from mild and intermittent to severe and difficult to control, both between people and within a person over time. Distinctions are made between allergic and non-allergic asthma. Allergic asthma results from the over-production of immunoglobulin E (IgE) in response to environmental allergens such as house dust mite, pollen and moulds. Non-allergic asthma is triggered by factors such as anxiety, stress, exercise, cold air, smoke and viruses, and does not involve the immune system.

1.2 The Quality and Outcomes Framework (2008) estimated that 5.9% of the UK population receive treatment for asthma. Prevalence is highest in children aged between 5 and 15 years, and it decreases in adulthood until the ages of 55–64 years, when it starts to rise again. In 2008/09 there were over 67,077 emergency hospital admissions for asthma in the UK, with more than 40% of these (27,970) for children aged 15 years or under. People with asthma may have a severely impaired quality of life, with symptoms leading to fatigue, absence from school or work and psychological problems including stress, anxiety and depression. These psychological problems may be up to six times more common than in the general population. It is estimated that 14–41% of people with asthma have depression. Depression is 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. In 2008, the rate of premature death from asthma was 1.5 times higher in the UK than in Europe.

1.3 There is no cure for asthma and the aim of treatment is to control the condition 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 Global Initiative for Asthma (GINA) pathway. Control is maintained by stepping up treatment as necessary and stepping down when control is good. Good asthma control is characterised by the absence of symptoms, by normal lung function and no exacerbations with minimal treatment. Severe persistent allergic asthma is poorly controlled despite the elimination of modifiable factors (for example, house dust mite, pollen and moulds) and the correct use of optimised standard treatment.

1.4 Step 1 (for mild intermittent asthma) recommends occasional use of inhaled short-acting beta-2 agonists and step 2 recommends introducing inhaled corticosteroids at 200–400 micrograms per day in children aged 5–12 years and 200–800 micrograms per day in those over 12 years. Step 3 recommends adding an inhaled long-acting beta-2 agonist and, if control remains inadequate and they are not already on these dosages, increasing the dosage of inhaled corticosteroids to 800 micrograms per day in those over 12 years and to 400 micrograms per day in children aged 5–12 years. If there is no response to a long-acting beta-2 agonist, a leukotriene receptor antagonist, theophylline or slow-release beta-2 agonist tablet may be considered instead. Step 4 recommends increasing the dosage of inhaled corticosteroids up to 2000 micrograms per day in those over 12 years and up to 800 micrograms per day in children aged 5–12 years. Adding a leukotriene receptor antagonist, theophylline or beta-2 agonist tablet may also be considered at this stage. Before moving to step 5, people whose asthma is inadequately controlled should be referred to specialist care. Step 5 recommends daily steroid tablets at the lowest dose

that provides adequate control alongside the high-dose inhaled steroids. Treatments that may minimise the use of steroid tablets may also be considered. The adverse effects of long-term oral steroids are significant and include adrenal suppression, decreased bone mineral density, cataracts and glaucoma, and growth failure in children

1.5 NICE technology appraisal guidance 133 recommends omalizumab as an option for the treatment of severe persistent allergic (IgE-mediated) asthma as add-on therapy to optimised standard therapy in adults and adolescents (12 years and older) who have been identified as having severe unstable disease. Technology appraisal guidance 201 does not recommend omalizumab for the treatment of severe persistent allergic asthma in children aged 6–11 years.

1.6 Routine measures to assess asthma control include: monitoring of symptoms either through simple questioning or using questionnaires; monitoring of lung function by spirometry ($FEV_1$) or peak expiratory flow (PEF); and measuring exhaled nitric oxide (FeNO) which is related to eosinophilic airway inflammation and eosinophil differential count in induced sputum (a raised sputum eosinophil count is associated with responsiveness to corticosteroids in adults).

# 2 The technology

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

- a positive skin test or in vitro reactivity to a perennial aeroallergen

- reduced lung function ($FEV_1$ less than 80%) (this criterion applies only to adults and adolescents aged 12 years and over)
- 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.

The marketing authorisation states that omalizumab treatment 'should only be considered for patients with convincing IgE (immunoglobulin E) mediated asthma'. It also recommends that at 16 weeks after the start of therapy physicians should assess patients for the effectiveness of treatment before administering further injections, and that the decision to continue omalizumab should be based on whether a marked improvement in overall asthma control is seen.

2.2 Omalizumab is administered subcutaneously every 2 or 4 weeks. The dosage is determined by the concentration of serum IgE before the start of treatment (measured in international units per millilitre [IU/ml]) and body weight. (See the summary of product characteristics.)

2.3 The summary of product characteristics lists the following adverse reactions for omalizumab treatment in people aged 12 years and older: bruising, erythema and pain at the site of injection. The summary of product characteristics lists the following adverse reactions for omalizumab treatment in children under 12 years: headache, pyrexia and upper abdominal pain. Rare adverse effects in children and adults include parasitic infections and anaphylactic reactions. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.4 The price of omalizumab is £256.15 for a 150-mg vial and £128.07 for a 75-mg vial (excluding VAT; 'British national formulary' [BNF]

edition 63). The dosage administered is 75–600 mg every 2 or 4 weeks, up to a maximum dosage of 600 mg every 2 weeks. The cost of omalizumab ranges from approximately £1665 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.

# 3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost effectiveness of omalizumab within its licensed indications for the treatment of severe persistent allergic asthma.

| | **Final scope issued by NICE** | **Additional comments or specifications in the Assessment Group's protocol** |
|---|---|---|
| **Population** | Adults, adolescents and children (6–12 years of age) with severe persistent allergic (IgE-mediated) asthma under the conditions specified in the marketing authorisation | Adults and adolescents (12 years and over) and children aged 6–11 years with severe persistent allergic asthma who meet the following criteria:<br>• a positive skin test or in vitro reactivity to a perennial aeroallergen<br>• reduced lung function ($FEV_1$ < 80%) (this criterion applies only to adults and adolescents aged 12 years and over)<br>• frequent daytime symptoms or night-time awakenings<br>• multiple documented severe exacerbations despite daily high-dose inhaled corticosteroids plus a long-acting inhaled beta-2 agonist. |
| **Intervention** | Omalizumab | Omalizumab given parenterally as a subcutaneous injection every 2–4 weeks depending on dose in addition to optimised standard step 4 or step 5 treatment |

| | Final scope issued by NICE | Additional comments or specifications in the Assessment Group's protocol |
|---|---|---|
| | | (dose and frequency of administration is determined by baseline IgE measured before the start of treatment, and body weight). |
| **Comparators** | Standard treatment without omalizumab | The direct comparator which will be considered is optimised standard treatment. The decision problem differs depending on whether step 4 or step 5 is considered. For step 4, omalizumab is considered as an alternative to frequent or continuous oral corticosteroids; in step 5 it is given in addition to frequent or continuous oral corticosteroids but it may allow a reduction in dose of oral corticosteroids. Optimisation of standard treatment is considered to include the elimination of modifiable factors in addition to treatment adherence. |
| **Outcomes** | • asthma symptoms<br>• incidence of clinically significant acute exacerbations, including those which need unscheduled contact with healthcare professionals or hospitalisation<br>• use of oral corticosteroids<br>• mortality<br>• time to discontinuation<br>• adverse effects of treatment<br>• health-related quality of life | • asthma symptoms<br>• incidence of clinically significant exacerbations<br>• incidence of severe exacerbations which need unscheduled contact with healthcare professionals or hospitalisations<br>• mortality<br>• use of oral corticosteroids<br>• time to discontinuation<br>• adverse effects of treatment including allergic reactions (anaphylaxis)<br>• health-related quality of life. |
| **Economic evaluation** | The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY).<br>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and personal social services perspective. | A new decision-analytic model will be developed to estimate the cost effectiveness of adding omalizumab to optimised standard treatment for severe persistent allergic asthma. The model will be developed in accordance with the NICE reference case. The perspective will be that of the NHS and personal social services. Productivity costs are not included within this perspective but may be included as a secondary analysis. Both costs and QALYs will be discounted at 3.5%. |

# 4 Clinical-effectiveness evidence

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

4.2 The Assessment Group identified 11 randomised controlled trials for inclusion in the efficacy review, which compared omalizumab with placebo or no additional treatment. Nine of the randomised controlled trials were relevant only to those over 12 years, one was relevant only to children aged under 12 years and one was relevant to both groups (age 6–20 years). Three of the randomised controlled trials had populations that met or closely approximated the criteria in the marketing authorisation for those aged 12 years and over (INNOVATE [n = 419], EXALT [n = 404] and a study by Chanez [n = 31]). An additional two randomised controlled trials had populations that were broader than those specified in the UK marketing authorisation but contained relevant subgroups that were defined a priori (IA-04 in adults [n = 164] and IA-05 EUP subgroup in children [n = 235]). The Assessment Group also identified six studies as supportive evidence in which an unknown proportion of the population met the criteria in the marketing authorisation (Hanania [n = 850], Bardelas [n = 271], Vignola [SOLAR, n = 405], Hoshino [n = 30] and Ohta [n = 327] and the trial by Busse [n = 419] for children and young adults). Table 1 summarises the characteristics of the randomised controlled trials in the Assessment Group's efficacy review.

**Table 1 Characteristics of included randomised controlled trials**

| Study (n) | Duration (weeks) | Licence* | Multicentre/ Location | Design/ Randomisation ratio | Comparator | Overall risk of bias |
|---|---|---|---|---|---|---|
| **Adults** | | | | | | |
| Ayres 2004<br>ETOPA / IA-04 (n = 312)<br>EU population subgroup (n = 164) | 52 | 2<br><br><br>1 | Yes / Multinational 5 European countries | Open-label / 2:1 | No additional treatment | High |
| Bardelas 2012 (n = 271) | 52 | 3 | Yes / NR | Double-blind / 1:1 | Placebo | Unclear |
| Bousquet 2010 EXALT (n = 404) | 52 | 1 | Yes / Multinational -14 countries | Open-label / 2:1 | No additional treatment | High |
| Humbert 2005<br>INNOVATE (n = 419) | 52 | 1 | Yes / Multinational -14 countries | Double-blind / 1:1 | Placebo | Low |
| Hanania 2011 (n = 850)<br>M2 subgroup<br>M3 subgroup | 48 | 3 | Yes / USA and Canada | Double-blind / 1:1 | Placebo | Low |
| Vignola 2004<br>SOLAR (n = 405) | 28 | 3 | Yes / NR | Double-blind / 1:1 | Placebo | Low |
| Hoshino 2012 (n = 30) | 16 | 3 | NR / Japan | Open-label / 1:1 | No additional treatment | High |
| Ohta 2009 (n = 327) | 16 | 3 | Yes / Japan | Double-blind / 1:1 | Placebo | Low |
| Chanez 2004 (n = 31) | 16 | 1 | No / France | Double-blind / 2:1 | Placebo | Low |
| **Children and young adults** | | | | | | |
| Busse 2011 (n = 419) | 60 | 3 | Yes / USA | Double-blind / 1:1 | Placebo | Unclear |
| **Children aged 12 years and under** | | | | | | |
| Lanier 2009<br>IA-05 (n = 628))<br>EU population subgroup (n = 235) | 24 + 28 steroid reduction | 2 | Yes / Multinational 7 countries | Double-blind / 2:1 | Placebo | Low |

*1) Entire population meets criteria in the marketing authorisation
2)Defined subgroup meets criteria in the marketing authorisation
3) Undifferentiated proportion meet criteria in the marketing authorisation

4.3 The duration of the adult trials ranged from 16 to 52 weeks. Trials in which the entire population met the criteria in the marketing authorisation ranged from 16 weeks (Chanez et al.) to 32 weeks (EXALT); the duration of INNOVATE was 28 weeks. For children, the total duration of IA-05 was 52 weeks, of which the final 28 weeks constituted a steroid-sparing phase. The study by Busse et al, included in the review by the Assessment Group as supporting evidence, had a duration of 60 weeks.

4.4 There was some variation in the inclusion criteria and actual treatment regimen even among trials in which the whole population or a defined subgroup met the criteria in the marketing

authorisation. For example, EXALT included people taking a lower dose of inhaled corticosteroids (800 micrograms or more of beclomethasone dipropionate [BDP] equivalent) than the IA-04 subgroup or INNOVATE (both 1000 micrograms or more of BDP equivalent) and the mean dose for included patients reflected this at approximately 2000 micrograms compared with 2300 micrograms for INNOVATE and 2850 micrograms for IA-04. In all of these trials a long-acting beta-agonist was used but the use of concomitant treatments such as leukotriene antagonists and theophyllines varied between the studies. The proportion of people on oral corticosteroids was comparable between EXALT, INNOVATE and the trial of Chanez et al. at just over 20%; oral corticosteroid use was not reported in IA-04. In the IA-05 EUP subgroup, children were all taking 500 micrograms or more of fluticasone or equivalent plus a long-acting beta-agonist. The mean dose of fluticasone was 743 micrograms and 58% were taking an additional drug, with the overwhelming majority receiving a leukotriene antagonist. Six children were on maintenance oral corticosteroids. The Assessment Group considered that the quality of the included randomised controlled trials was generally high, with all of the studies of the licensed population or with defined subgroups of the licensed population having adequate allocation concealment and randomisation. Most trials included in the review were double-blind placebo controlled and were considered by the Assessment Group to be at low risk of bias, including INNOVATE, the trial by Chanez et al. of adults meeting the criteria in the marketing authorisation and the IA-05 trial of a subgroup of children in the licensed population. The Assessment Group considered that the EXALT and IA-04 trials in adults were at high risk of bias because of their open-label designs and that this precluded the possibility of pooling data with the double-blind INNOVATE trial, except for the purposes of informing an exploratory sensitivity analysis in the economic evaluation.

4.5 In addition to the trial data presented, the Assessment Group also considered data from observational studies as supporting evidence and in particular to provide data on longer-term response and steroid sparing. These included open-label continuation studies, non-comparative cohort studies and post-marketing studies and are summarised in table 2.

**Table 2 Observational studies included in review**

| Study | n | Follow-up duration | Population (licence) | Design | Review questions addressed |
|---|---|---|---|---|---|
| APEX(AIC) | 136 | 12 months | Adult (3) | Retrospective one-group | 1,3 |
| eXpeRience | 876 | 8 months | Adult (3) | Post-marketing surveillance | 1,3 |
| Brodlie | 34 | 16 weeks | Children & adolescents (3) | Prospective one-group | 1,3 |
| Kirk 2010** | 18 | 16 weeks | Children (3) | Retrospective one group | 3 |
| PERSIST | 158 analysed (53 retrospective follow-up) | 52 weeks (120 weeks) | Adult (1) | Prospective one-group | 1,2,3 |
| Cazzola 2010 | 142 | 12 months | Adult (2) | Prospective one-group | 1,2,3 |
| Costello 2011 | 93 analysed | 6 months | Adult (2) | Retrospective one-group | 1,3 |
| Deschildre 2010 | 104 | 4–6 months | Children & adolescents (3) | Non-comparative cohort | 1 |
| Domingo 2011 | 31 analysed | Mean 17 months | Adult (3) | Prospective one-group | 3 |
| Gutierrez 2007 | 284 | 18 months | Adult (3) | Retrospective comparative | 2 |
| Korn 2009 | 280 (102 Maintenance OCS subgroup) | 6 months (>16 weeks) | Adult (1) | Post-marketing surveillance | 1, 3 |
| Molimard 2008 | 146 analysed (64 Maintenance OCS subgroup) | >5months (>16 weeks) | Adult (2) | Prospective one-group | 3 |
| Ohta 2010 | 133 (37 Severe uncontrolled subgroup) | 48 weeks | Adult (3) | Prospective one-group | 1 |
| Randolph 2010 | 29 analysed | ≤6 years, mean 2.1 years | Adults and children (3) | Prospective one-group | 1,2 |

| Study | n | Follow-up duration | Population (licence) | Design | Review questions addressed |
|---|---|---|---|---|---|
| Stukus 2008 | 45 analysed | NR | Adult (3) | Retrospective one-group | 3 |
| PAX-LASER | 767 (486 allergic patients) | ≥12 months | Adult (3) | Prospective controlled | 1,2 |
| **Significant overlap of the population with Brodlie. Only includes patients who continued treatment beyond 16 weeks responder assessment.<br>Review question: 1 = Clinical efficacy, 2 = Long term efficacy, 3 = OCS sparing<br>Licence: 1 = entire population meets licence criteria , 2 = Defined subgroup meets licence criteria, 3 = Undifferentiated proportion of patients meet licence criteria | | | | | |

## Efficacy results

### Response to treatment

4.6 Four of the randomised controlled trials for the adult population reported global evaluation of treatment effectiveness (GETE) ratings (INNOVATE, EXALT, SOLAR and Bardelas) and one randomised controlled trial reported treatment effectiveness in children (IA-05 EUP subgroup). The proportions of people receiving omalizumab and standard care with physician-rated GETE scores of good or excellent are shown in table 3.

**Table 3 Response to treatment assessed using the global evaluation of treatment effectiveness (GETE) ratings**

| Trial | Time point | Percentage of patients with good/excellent GETE rating | | RR (95% CI) |
|---|---|---|---|---|
| | | Omalizumab | Comparator | |
| | **Adults: licensed population** | | | |
| INNOVATE | 28 weeks | 56.5* | 41.0* | 1.38 (1.13 to 1.69) |
| EXALT | 16 weeks | 70.0* | 28.2* | 2.24 (1.71 to 2.92) |
| **Adults: Supportive trials** | | | | |
| Bardelas 2012 | 24 weeks | 55.1 | 48.1 | 1.15 (0.91 to 1.44) |
| SOLAR | 28 weeks | 59.3 | 41.3 | 1.44 (1.17 to 1.76) |
| | **Children: licensed population** | | | |
| IA-05 EUP subgroup | 52 weeks | 74.0 | 64.5 | 1.15 (0.95 to 1.39) |
| *Numbers calculated using responder/total N; response rates calculated without missing data are higher<br>CI, confidence interval; RR, relative risk | | | | |

4.7 A higher proportion of people in the omalizumab arms compared with the comparator arms of the trials responded to treatment 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, RR = 2.24, 95% CI 1.71 to 2.92) than the double-blinded 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, 55.1% compared with 48.1% [RR = 1.15, 95% CI 0.91 to 1.44]). Response rates in adults measured by the GETE were also reported by four observational studies and were higher than the rate in the double-blind INNOVATE trial and in some cases higher than those seen in EXALT. In children, the proportion of responders receiving omalizumab in the IA-05 EUP subgroup at 52 weeks was 74% compared with 64.5% in the placebo group but this was not statistically significant (RR = 1.15, 95% CI 0.95 to 1.39).

**Exacerbations**

4.8 All of the randomised controlled trials reported data on the outcome of clinically significant exacerbations, with the exceptions of Bardelas and Hoshino. The Assessment Group observed some heterogeneity in the definition of clinically significant exacerbations within trials but the Assessment Group did not consider this to be sufficient to preclude comparability. A number of trials reported data on the number of people experiencing no clinically significant exacerbations, or data from which this information could be calculated. A summary of the total exacerbations in the randomised controlled trials reviewed by the Assessment Group is summarised in table 4.

## Table 4 Randomised controlled trials: total exacerbations

| Trial | Incidence rate | | Rate ratio (95% CI) | Patients with zero exacerbations n (%) | | Relative risk (95% CI) |
|---|---|---|---|---|---|---|
| | Omalizumab | Comparator | | Omalizumab | Comparator | |
| **Adults: licensed population** | | | | | | |
| INNOVATE* | 0.68* | 0.91 | 0.738 (0.552 to 0.998) | NR | NR | NA |
| EXALT* | 0.55 | 0.98 | 0.570 (0.417 to 0.778) | 183 (67) | 64 (50) | 1.35 (1.11 to 1.63) |
| Pooled estimate of INNOVATE and EXALT | | | 0.658 (0.560 to 0.772) | NA | N/A | NA |
| IA-04<br>EU subgroup | 1.26 | 3.06 | 0.41 (0.288 to 0.583) | NR | NR | NA |
| Chanez (2004) | NR | NR | NA | 9 (45) | 7 (64) | 0.71 (0.37 to 1.37) |
| **Adults: supporting trials** | | | | | | |
| Hanania (2011)**<br>ITT | 0.66 | 0.88 | 0.75 (0.61 to 0.92) | 275 (64) | 234 (55) | 1.16 (1.04 to 1.30) |
| M2 group | NR | NR | 0.72 (0.53 to 0.98) | NR | NR | |
| M3 group | NR | NR | 0.95 (0.63 to 1.43) | NR | NR | |
| SOLAR | NR | NR | NA | 171 (82) | 146 (75) | 1.10 (0.99 to 1.22) |
| Ohta | NR | NR | NA | 145 (96) | 146 (89) | 1.08 (1.01 to 1.15) |
| **Children: licensed population** | | | | | | |
| IA-05<br>EUP subgroup | | | | NR | NR | NA |
| Over 24 weeks | 0.42 | 0.63 | 0.662 (0.441 to 0.995) | | | |
| 24-52 weeks | 0.43 | 1.09 | 0.394 (NR) | | | |
| Over 52 weeks | 0.73 | 1.44 | 0.504 (0.350 to 0.725) | | | |
| **Children: supporting trials** | | | | | | |
| Busse (2011)† | NR | NR | NA | 145 (70) | 110 (52) | 1.16 (1.06 to 1.28) |

*Adjusted for baseline exacerbation history: unadjusted data were 0.74 versus 0.92 (rate ratio 0.806, 95% CI 0.600 to 1.083)

† Children and adolescents

**M3 patients probably meet licence criteria (oral corticosteroids maintenance or ≥4 exacerbations/year); M2 patients may meet criteria (ICS + LABA + additional treatment)

CI, confidence interval; ITT, intention-to-treat; NA, not applicable; NR, not reported

4.9 The Assessment Group found a consistent benefit for people receiving omalizumab compared with the comparator group, both in terms of the rate of total exacerbations and the proportion of people who experienced no exacerbations during follow-up. For example, the rate of total exacerbations in the INNOVATE trial 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 was 0.55 for omalizumab compared with 0.98 in the comparator arm (rate ratio = 0.570, 95% CI, 0.417 to 0.778), and in the IA-04 subgroup, the rates were 1.26 and 3.06 respectively (rate ratio = 0.41, 95% CI, 0.288 to 0.583). Only the trial by Chanez showed favourable results for the comparator arm: 7% compared with 9% in the omalizumab arm experienced no exacerbations but this was not statistically significant (relative risk = 0.71, 95% CI, 0.37 to 1.37). The results for children from the IA-05 EUP subgroup showed a statistically significant benefit for omalizumab in the rate of total exacerbations (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, there was also evidence of reductions in the total rate of exacerbations from trials included as supportive evidence and from data reported in observational studies.

4.10 Three of the included trials reported the incidence of clinically significant severe exacerbations and clinically significant non-severe exacerbations separately (INNOVATE and EXALT trials in adults and the IA-05 EUP subgroup in children, summarised in table 5). For adults, the rate of clinically significant severe exacerbations was statistically significantly lower in the omalizumab group compared with the comparator group (INNOVATE, 0.24 compared with 0.48, rate ratio = 0.499, 95% CI, 0.321 to 0.777; EXALT, 0.24 compared with 0.42, rate ratio = 0.562, 95% CI, 0.341 to 0.924). For children, the results from the IA-05 EUP subgroup favoured omalizumab but were not statistically significant (0.14

compared with 0.22 at 24 weeks follow-up, rate ratio = 0.655, 95% CI, 0.302 to 1.421). The Assessment Group commented that this was probably because of a lack of power in this subgroup. Evidence from a single observational study (Deschildre 2010) indicated a substantial reduction in severe exacerbations in children with a mean age of 11.6 years (from 4.4 severe exacerbations per year to 0.51 per year (statistical significance not recorded).

**Table 5 Clinically significant severe exacerbations**

| Trial | Incidence rate | | Rate ratio (95% CI) | Patients with zero exacerbations n (%) | | Relative risk (95% CI) |
|---|---|---|---|---|---|---|
| | Omalizumab | Comparator | | Omalizumab | Comparator | |
| **Adults: licensed population** | | | | | | |
| INNOVATE | 0.24 | 0.48 | 0.499 (0.321 to 0.777) | 174 (83.2) | 155 (73.8) | 1.13 (1.02 to 1.25) |
| EXALT | 0.24 | 0.42 | 0.562 (0.341 to 0.924) | NR | NR | NA |
| Pooled estimate of INNOVATE and EXALT | | | 0.53 (0.41 to 0.68) | NA | NA | NA |
| **Children: licensed population** | | | | | | |
| IA-05 EUP subgroup | | | | NR | NR | NA |
| 24 weeks | 0.14 | 0.22 | 0.655 (0.302 to 1.421) | | | |
| 24–52 weeks | 0.11 | 0.25 | 0.44 (NR) | | | |
| 52 weeks | 0.27 | 0.50 | 0.545 (0.274 to 1.084) | | | |
| CI, confidence interval; NA, not applicable; NR, not reported | | | | | | |

4.11 Rates of exacerbations for post-hoc subgroups were provided by the manufacturer. The sub-groups were: those with a history of hospitalisation; those on oral corticosteroids at baseline; those not on oral corticosteroids at baseline; exacerbation history (≤2 and ≥ 3 exacerbations per year at baseline). The Assessment Group

commented that the data indicated that there may be an increased treatment effect in people on oral corticosteroids maintentance therapy in the INNOVATE trial; the rate of total exacerbations was 0.88 for omalizumab compared with 1.33 in the placebo arm (rate ratio = 0.293) and the rate of clinically significant severe exacerbations was 0.29 for omalizumab compared with 0.81 in the placebo arm (rate ratio = 0.36). Statistical significance was not reported.

4.12 Four trials (INNOVATE, EXALT, the IA-04 subgroup in adults and the IA-05 EUP subgroup in children) reported results for the omalizumab responder subgroup using GETE ratings (see table 3) or Asthma Quality of Life Questionnaire scores (IA-04 subgroup). In these analyses, the rate ratio 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, 0.365 (95% CI 0.244 to 0.546) in the IA-04 subgroup and 0.38 (95% CI 0.15 to 0.91) in the IA-05 EUP subgroup, showing a statistically significant advantage for omalizumab. This pattern in the results for total exacerbations for the omalizumab responder subgroup was also reflected in the results of the responder analysis for clinically significant severe exacerbations.

**Hospitalisation and other unscheduled medical care**

4.13 Six randomised controlled trials (INNOVATE, EXALT, IA-04, Chanez, IA-05 and Busse) presented results for hospitalisation rates. The results were favourable for the omalizumab group but were not statistically significant apart from in the EXALT study (rate ratio = 0.332, 95% CI 0.118 to 0.937). This pattern was mirrored in the three adult studies (INNOVATE, EXALT and IA-04) that presented data for emergency department visits and unscheduled doctor visits. There were however statistically significant reductions in total emergency visits (INNOVATE: risk ratio = 0.561, 95% CI 0.325 to 0.968; EXALT: risk ratio = 0.400, 95% CI 0.244 to 0.654;

IA-04 subgroup: risk ratio = 0.76, 95% CI 0.64 to 0.89). For children, the IA-05 EUP subgroup showed favourable results for the placebo arm for all three outcomes (emergency department visits, unscheduled doctor visits and total emergency visits) but these did not reach statistical significance. The Assessment Group commented that reporting of data from observational studies was limited but showed evidence of substantial reductions across all types of care; where 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 healthcare utilisation outcomes.

4.14 Analyses comparing those with a response to omalizumab and those receiving placebo/standard care for hospitalisation and other unscheduled medical care showed evidence of statistically significant benefit for both INNOVATE and EXALT across the outcomes assessed with the exception of emergency department visits in INNOVATE. Children in the IA-05 EUP subgroup with a response to omalizumab had a statistically significant reduction in hospitalisation rates but non-statistically significant benefits for other unscheduled healthcare measures.

**Asthma symptoms**

4.15 There was considerable heterogeneity in the assessment of asthma symptoms in the included studies; a wide range of scales and individual symptom measures were used to assess response to treatment. In INNOVATE, there was a statistically significant improvement at 28 weeks in the total asthma clinical symptom score in the omalizumab group compared with placebo (change from baseline = –0.66 with omalizumab compared with –0.40 with placebo, p = 0.039). Statistically significant improvements favouring omalizumab were also found in EXALT at 32 weeks using the

Asthma Control Questionnaire (change from baseline = –0.91 with omalizumab compared with –0.04 with no additional treatment, RR = –0.87, 95% CI –1.09 to –0.65) and in the IA-04 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, a non-statistically significant benefit of omalizumab compared with placebo was shown in the IA-05 EUP 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.) found statistically significant increases in the Asthma Control Test following treatment with omalizumab ($p = 0.001$) and limited evidence of efficacy in children. Evidence on the impact of individual symptom measures for children and adults was limited and mixed.

**Use of rescue treatment**

4.16 There was limited evidence of efficacy of omalizumab in reducing the need for rescue treatment. In the licensed population, INNOVATE, the IA-04 subgroup and the trial by Chanez reported data on rescue treatment for adults, and the IA-05 EUP subgroup reported data for children. The IA-04 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 over 14 days was 3.91 in the omalizumab group compared with 5.33 with no additional treatment ($p = 0.008$). Hanania et al., included by the Assessment Group as supporting data, also reported a statistically significant reduction in the use of rescue treatment following omalizumab. There was also limited evidence from observational studies, with two studies reporting reduced use of rescue treatment but with no results of statistical tests. In children the IA-05-EUP subgroup initially showed a

statistically significant benefit but this lost significance following adjustment for multiple testing. There was no additional evidence from supporting randomised controlled trials or observational studies in children.

### $FEV_1$, a pulmonary function test

4.17 Randomised controlled trials of the licensed population reported statistically significant benefits of omalizumab in improving lung capacity as measured by percentage of predicted $FEV_1$, compared with the comparator arm, although these benefits were numerically small. These included INNOVATE at 28 weeks (67.01 with omalizumab compared with 64.18 with no additional treatment, $p = 0.043$), EXALT at 32 weeks (68.1 with omalizumab compared with 63.7 with no additional treatment, $p = 0.007$), and the IA-04 EU subgroup at 52 weeks (71 with omalizumab compared with 60 with no additional treatment, $p < 0.01$). Supporting trials did not indicate a statistically significant benefit, but the Assessment Group commented that these studies were conducted in people with higher mean baseline $FEV_1$. Some observational studies provided additional evidence that omalizumab leads to statistically significant improvements in lung function in adults with uncontrolled severe asthma. In children there was no trial evidence for $FEV_1$ for the licensed population because IA-05 did not assess $FEV_1$. 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.

### Quality of life

4.18 Six adult trials (INNOVATE, EXALT and IA-04 EU subgroup in the licensed population and the supporting studies SOLAR, Hanania 2011 and Hoshino 2012) and one trial in children (the IA-05 EUP

subgroup) reported some measure of asthma-related quality of life. The Asthma Quality of Life Questionnaire or, in the case of the IA-05 EUP subgroup, the paediatric Asthma Quality of Life Questionnaire was employed in all the trials. EXALT also reported EQ-5D scores. Table 6 summarises the quality of life measures captured in these trials.

**Table 6 Quality of life in randomised controlled trials**

| Trial | Time point assessed (weeks) | Change from baseline | | Treatment difference | n (%) with ≥0.5 point increase from baseline | | Treatment difference |
|---|---|---|---|---|---|---|---|
| | | Omalizumab | Comparator | | Omalizumab | Comparator | |
| **Adults: licensed population** | | | | | | | |
| INNOVATE | 28 | 0.91 | 0.46 | P < 0.001 | 124 (61) | 98 (48) | P = 0.008 |
| EXALT | 31 | 1.06 (95% CI 0.88 to 1.24) | -0.07 (95% CI -0.31 to 0.17) | P < 0.001 | 165 (74) | 25 (26) | P < 0.001 |
| IA-04 EU subgroup | 52 | 1.32 | 0.17 | P < 0.001 | 88 (77) | 21 (42)* | P < 0.001 |
| **Adults: supporting trials** | | | | | | | |
| Hanania (2011) | 48 | 1.15 | 0.92 | 0.29 (95% CI 0.15 to 0.43) | NR | NR | NA |
| SOLAR | 28 | NR | NR | NA | 164 (79) | 134 (70) | RR 1.15 (95%CI 1.02 to 1.29)** |
| Hoshino (2012) | 16 | 1.47 (p < 0.001) | 0.28 (P = NS) | NR | NR | NR | NA |
| **Children: licensed population** | | | | | | | |
| IA-05† EUP subgroup | 24 weeks | 0.78 | 0.70 | P = 0.566 | 96 (62) | 42 (58) | P = 0.654 |

*Discrepancy between Niven et al. reported for responder status (71 [62%])

and MS (88 [77%]) for omalizumab; appears because of discrepancy in timepoint (27 compared with 52 weeks); comparator was not reported by Niven et al.

†paediatric Asthma Quality of Life Questionnaire

** calculated by the Assessment Group

CI, confidence interval; NA, not applicable; NR, not reported; RR, relative risk

4.19 In INNOVATE, there was a statistically significant improvement at 28 weeks in the Asthma Quality of Life Questionnaire score in the omalizumab group compared with placebo (change from baseline = 0.91 with omalizumab compared with 0.46 with placebo, p < 0.001; 61% of people receiving omalizumab experienced a 0.5-point or greater increase 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 additional treatment; 74% of people receiving omalizumab experienced a 0.5-point or greater increase compared with 26% with the comparator, $p < 0.001$) and in the IA-04 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 receiving 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 with omalizumab. In children the IA-05-EUP subgroup 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 receiving 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 symptom and quality of life improvement in children may be a consequence of the IA-05 licensed subgroup being underpowered to detect differences.

4.20 Five observational studies reported some measure of quality of life. The Assessment Group commented that APEX, eXpeRience, and PERSIST showed at least a minimally important increase in Asthma Quality of Life Questionnaire scores. In the observational study by Brodlie there was evidence of statistically significant increases in mini-Asthma Quality of Life Questionnaire scores in children dependent on oral corticosteroids in the UK. The score improvements were observed in 92% of the total trial subgroup aged 16 years and under (change from 3.5 [1 to 8.4] at baseline to 5.9 [3.2 to 9.9] at 16 weeks, $p < 0.0001$). Statistically significant score improvements were observed in both children aged 12 and

under (change from 2.3 [1.7 to 4.2] at baseline to 5.2 [3.5 to 6.9], p = 0.019) and in those aged between 12 and 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 represents the only evidence for children with very severe asthma who need oral corticosteroids.

### Discontinuation rates

4.21 Nine randomised controlled trials reported discontinuation rates. 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. However, rates were not always higher in the placebo arm (for example, in INNOVATE 9.3% of those in the placebo group discontinued treatment compared with 12.2% in the omalizumab arm). 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 one trial in children (IA-05 EUP subgroup) the discontinuation rate was approximately 20% in both arms.

### The long-term efficacy of omalizumab

4.22 Three randomised controlled trials and four observational studies reported follow-up data at 52 weeks or longer (summarised in table 7). The Assessment Group commented that there was very limited evidence relating to the effectiveness of omalizumab beyond 12 months in either adults or children. Although the PERSIST observational study reported some follow-up data at 120 weeks, these were limited and related to one-third of the patients in the original study; other studies which appeared to assess longer-term treatment reported only interim results.

**Table 7 Studies presenting data on long-term efficacy**

| **Randomised controlled trials** | | |
|---|---|---|
| **Study** | **Duration** | **Population** |
| IA-04 EU | 52 weeks | Adults, subgroup licensed population |
| IA-05 EUP sub. | 52 weeks | Children, subgroup licensed population |
| Busse 2011 | 60 weeks | Children and adolescents, supporting study |
| **Observational studies** | | |
| **Study** | **Duration** | **Population** |
| PERSIST | 52 weeks + 120 weeks follow-up of single arm | Adults, licensed population |
| Cazzola 2010 | 52 weeks + 52 weeks follow-up | Adults, licensed population |
| Randolph 2010 | Up to 6 years | Adults, supporting study |
| PAX-LASER | ≥ 12 months | Adults, licensed population |

### The steroid-sparing effect of omalizumab

4.23 Two randomised controlled trials provided data on changes in oral steroid use, one in the licensed population (EXALT) and one in a population with controlled asthma (trial 011). Both studies reported data on stratified subgroups of adults on oral corticosteroid maintenance at baseline. The Assessment Group commented that trial 011 was excluded from the other sections of the review because a limited proportion of its population received a long-acting beta-agonist. The Assessment Group included the oral corticosteroid maintenance subgroup of trial 011 in this analysis because of the scarcity of data on changes in oral corticosteroid use from other randomised controlled trials and because all the participants were on oral corticosteroids at baseline.

4.24 The two randomised controlled trials reported very different results. In the EXALT trial at both 16 and 32 weeks, those in the omalizumab group stopped or reduced the use of oral corticosteroids around twice as often as those on no additional treatment and this difference was statistically significant at

32 weeks (62.7% compared with 30.4%, RR = 2.06, 95% CI 1.08 to 3.94). EXALT also found a statistically significant benefit for omalizumab in reducing the oral corticosteroid dose at 32 weeks (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 high in both the omalizumab and the placebo groups (74.0% compared with 73.3%, RR = 1.01, 95% CI 0.79 to 1.28) and the mean dose reduction was smaller with omalizumab than with placebo at both 32 weeks (36.0% compared with a 55.6% reduction, mean difference = 1.70 mg/day, 95% CI –2.17 to 5.57) and at 44 weeks (39.0% compared with a 64.2% reduction, mean difference = 2.30 mg/day, 95% CI –1.75 to 6.35). The Assessment Group commented that evidence from the two randomised controlled trials on the oral steroid-sparing effect of omalizumab is limited by design flaws because of the lack of blinding in EXALT and insufficient oral corticosteroid dose adjustment during the run-in phase of the trial 011. The Assessment Group further commented that because of limited reporting of patient characteristics, the extent to which EXALT and trial 011 are comparable and the extent to which the trial 011 subgroup is representative of the licensed population are unclear. The proportions receiving a long-acting beta-agonist and the rates of exacerbations in the year preceding baseline were not recorded in the trials. No randomised controlled trial data on oral corticosteroid use were available in children.

4.25 Ten uncontrolled observational studies also reported data on oral corticosteroid use following omalizumab treatment. The Assessment Group commented that these studies had significant design flaws (all were uncontrolled and relatively small), and none provided relevant data beyond 12 months, with the exception of one small study. For adults on oral corticosteroid maintenance, oral

corticosteroid withdrawal rates ranged from 25.9% to 71.2% and data from three studies showed that between 49.0% and 65.6% had reduced or stopped taking oral corticosteroids following omalizumab treatment. The outcomes for children on oral corticosteroid maintenance were reported by Brodlie and Kirk in study populations that may overlap, although the extent of overlap is unclear. Both studies showed a significant decrease in oral corticosteroid use after 16 weeks of treatment with withdrawal rates of 13.3% (in the subgroup of children aged 5 to 12 years) and 22.2% (in children aged 6 to 11 years). All participants in the Kirk study either reduced or stopped oral corticosteroid treatment at follow-up with a mean daily oral corticosteroid dose reduction of 14 mg. The baseline daily oral corticosteroid dose in the Brodlie study was 20 mg (range 5–50 mg), which was reduced to 5 mg (range 0–40 mg). Because of significant design flaws, the Assessment Group commented that, overall, the evidence for a clear and clinically significant oral corticosteroid-sparing effect of omalizumab is limited.

**Adverse effects associated with oral corticosteroids**

4.26 The Assessment Group also included a summary of published systematic reviews of the adverse effects of oral corticosteroids. The Assessment Group stated that all the evidence syntheses identified in its review were subject to limitations, and the reliability of the data was unclear. The reviews provided quantitative evidence for the known adverse events of fracture, diabetes, peptic ulcer, cardiovascular events, including myocardial infarction and stroke, cataract and glaucoma, sleep and mood disturbance, and weight gain. Increased fracture risk remains a long-term consequence even when oral corticosteroids are discontinued because of irreversible osteoporosis. There was also some evidence of a relationship between oral corticosteroid treatment during childhood and failure to reach expected adult height.

### Adverse effects associated with omalizumab

4.27 The Assessment Group identified 11 randomised controlled trials and 11 observational studies which reported adverse event data for omalizumab from the publications identified as potentially relevant for the review of omalizumab efficacy. The Assessment Group also identified an additional 10 relevant data sources from the main efficacy search which were included in the review of omalizumab safety.

4.28 Four reviews of adverse events associated with omalizumab were published between 2007 and 2011 and had a sample size ranging from 3429 to 57,300 patients. Two reviews included randomised controlled trials and one included both randomised controlled trials and open-label studies. One review included people with severe persistent allergic asthma, one included people with moderate-to-severe persistent allergic asthma, and the third included people who had received omalizumab but in whom the indication was unclear. The remaining review assessed the incidence of anaphylaxis in people with asthma who had received omalizumab; these data were voluntarily reported to the Adverse Event Reporting System.

4.29 The Assessment Group's review of safety identified no evidence of serious adverse events beyond those identified in the summary of product characteristics. Although the levels of adverse events reported in the included primary studies were high, there were few differences between treatment groups. The key adverse events considered by the Assessment Group were anaphylaxis, for which patients are monitored at the start of treatment, and arterial thrombotic events, where there is a need for further, longer-term data. The Assessment Group stated that both of these are rare and have not been conclusively linked to omalizumab. The evidence on the relationship between omalizumab and the incidence of

malignancy is also subject to great uncertainty and an area in which further data are required. The Assessment Group commented that although there is reasonable evidence for the short-term safety of omalizumab, it is not possible to determine its long-term safety because of lack of data for long-term treatment.

# 5 Comments from other consultees

5.1 Comments were received from Asthma UK, the Association of Respiratory Nurse Specialists, the Royal College of Paediatrics and Child Health, the UK Clinical Pharmacy Association, Royal College of Nursing, the British Thoracic Society and the Royal College of Physicians. Consultees generally agreed that omalizumab should be recommended for a clearly and carefully defined group of adults and children with severe allergic asthma and it should continue to be necessary for people to be properly assessed by a specialist before being given omalizumab. Some consultees agreed that omalizumab should be reserved for use by consultants within tertiary respiratory centres, while one stated that it could be used in secondary or primary care but that training by specialist nurses from secondary care would be essential for ongoing treatment of patients in primary care. Some commentators felt that it should not be necessary to have had a specific number of hospital admissions before a person can be considered for omalizumab, particularly in light of the Outcomes Framework which includes national indicators for hospital admissions in people with long-term conditions and specifically in people under 19 with asthma. Should such a pre-requisite continue to exist, consultees suggested that it may encourage more people to attend hospital in order to become eligible for omalizumab.

5.2 Consultees agreed that omalizumab has been the only significant advance in the management of severe asthma in the past 30 years and that one of the benefits of omalizumab is as an additional

alternative to current treatments. Consultees pointed out that omalizumab treatment was associated with improvements in both quality of life and asthma control score with few significant adverse effects.

5.3 Disadvantages noted by consultees included the fact that omalizumab is expensive and has to be administered by subcutaneous injection every 2–4 weeks. Some consultees noted that although discomfort and anxiety was experienced by people being treated with omalizumab as a result of having injections, this was outweighed by the expectation of substantial improvements in asthma management and consequent improvements in quality of life, including reduced fear of asthma attacks.

5.4 Consultees also agreed that the reduction in regular oral corticosteroid use is an important aspect of omalizumab treatment and noted that oral corticosteroids can have long-term adverse effects such as osteoporosis, psychological symptoms, Cushing's syndrome, adrenal failure, diabetes, growth retardation, high blood pressure, cataracts and Addison's disease. Consultees noted that there could be significant economic benefits from reducing oral corticosteroid use, but these benefits could only be realised over the long term and may be difficult to quantify in QALYs. Consultees commented that this has not been investigated as a primary outcome in any randomised trial to date and has only been investigated as a secondary outcome in small numbers of patients. The consultees noted, however, that there are now a number of 'real-life' studies in larger groups with severe asthma, including data from the UK, which support a substantial steroid-sparing effect in these patientsl.

5.5 One commentator noted that most of the clinical trial data are derived from outside the UK and largely reflect clinical practice in the USA, which is markedly different from that in northern Europe.

Most of the people receiving omalizumab have had asthma of moderate severity, and the number of children with severe asthma dependent on long-term oral corticosteroids was extremely small. In addition, consultees noted the lack of long-term data for omalizumab treatment, especially in children.

5.6 Some consultees noted that because asthma-related mortality in the 6- to 12-year age group is negligible, an economic analysis that relies excessively on death as an outcome measure distorts the analysis in relation to children. It was suggested that for children it would be more appropriate to include educational progress, examination results and life-long outcomes in quality of life assessments, because adult-orientated assessments could lead to unacceptable moral and political discrimination against children.

5.7 One aspect noted by a consultee is the fact that omalizumab is recommended by NICE/SIGN for use only in specialised centres. One consultee suggested that what is meant by specialist centres needs clarification. If it means a tertiary centre, the consultee noted that this could disadvantage many people because of the travelling needed to obtain the drug and could mean a day off work for many people living in rural areas.

5.8 Summaries of comments were received from people living with severe asthma and receiving omalizumab treatment. These summaries pointed out that keeping symptoms under control is the main goal of asthma treatment, but the reality for some people with severe asthma is that this is not possible with current standard treatments. These people experience dangerous and frustrating symptoms which can lead to lack of sleep, social isolation, feelings of despair and depression, low activity levels, weight gain and increased dependence on family and carers. For children, coping with severe asthma can arrest educational and social development, as well as thwarting important life opportunities. People with severe

asthma can often find themselves taking very high doses of oral corticosteroids for a long time, which can lead to very serious adverse effects. Consultees indicated that current evidence supports the continued use of omalizumab in the very small group of people who have severe persistent allergic asthma. The small percentage of people who have asthma that is difficult to treat need very specialised clearly defined approaches, often in tertiary centres. A small number of these people, after careful evaluation, are likely to benefit from omalizumab. A larger number, as a result of receiving proper assessment, will have other successful treatments instituted. The consultees agreed that that omalizumab has been used responsibly by clinicians to date, largely for the population described in TA133. It is clear that it has brought life-changing benefits to the small number of people for whom omalizumab is suitable and in whom other treatment options have been exhausted.

# 6 Cost-effectiveness evidence

6.1 The Assessment Group identified six published studies evaluating the cost effectiveness of omalizumab. All studies reported standard treatment as the comparator, but the definition of standard treatment depended on the patient population and the relevant marketing authorisation. Oba and Salzman (2004), Wu et al. (2007) and Campbell et al. (2010) considered inhaled corticosteroid plus additional rescue treatment (as needed) as standard treatment, whereas Dewilde et al. (2007), Brown et al. (2007) and Dal Negro et al. (2011) considered high-dose inhaled corticosteroids and long-acting beta-agonists as standard treatment. All of the models in these publications assumed that the benefits of omalizumab, compared with standard care, were conferred through a reduction in clinically significant exacerbations. There was marked variation across the studies in cost effectiveness. Five studies used QALYs to estimate incremental cost-effectiveness ratios (ICERs) for

omalizumab compared with standard treatment ranging from approximately £21,700 to £516,500 per QALY gained. Conclusions on the cost effectiveness of omalizumab differed across the studies. Brown et al. concluded that omalizumab is a cost-effective use of healthcare resources, whereas 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 is not cost effective unless its acquisition price is 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 across the studies considered, there were common issues and limitations that precluded reliable conclusions on the cost effectiveness of omalizumab. These included the variability of the populations included in the studies, a lack of consideration of additional risk factors or higher-risk subgroups, the relative efficacy and adverse effects of omalizumab compared with oral corticosteroids, a lack of robust data for asthma-related mortality and health-related quality of life, and a lack of consensus on treatment duration and persistence of treatment effect over time.

**Manufacturer's economic model**

6.2 The manufacturer submitted a de novo economic evaluation which used a model structure identical to that used in TA133 and TA201 and which compared the costs and health outcomes of omalizumab as an add-on treatment to standard care compared with standard care alone. The manufacturer used a Markov model that extrapolates the effects of omalizumab treatment for 10 years (the assumed treatment duration) and follows a hypothetical cohort over a lifetime time horizon (up to age 100 years). People enter the model in the day-to-day asthma symptoms health state on either omalizumab in addition to standard care or standard care alone. At 16 weeks (the end of the first cycle), people on omalizumab are

assessed for response to treatment based on the proportion responding to omalizumab treatment in the trials. People whose asthma responds to omalizumab remain on omalizumab for the treatment duration and are assumed to experience exacerbations at the rates observed for people responding in the clinical trials. People whose asthma does not respond are assumed to discontinue omalizumab, revert to standard care alone and experience the same exacerbation rates as people randomised to the standard care arm of the trials. During each subsequent cycle of the model, people can remain in the day-to-day symptom state or can experience an exacerbation. Asthma-related death is assumed to occur 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 12–16 years, 0.383% for those aged 17–44 years, and 2.478% for those aged 45 years and over (derived from mortality data for people hospitalised for acute severe asthma from Watson et al. [2007] following a search of the published literature). However, people may die from all other causes from any health state of the model. After a non-fatal exacerbation, the person returns to the day-to-day asthma symptoms health state.

6.3 The manufacturer's model included two separate base-case populations: adults and adolescents aged 12 years and over (average age approximately 40 years) and children aged 6–11 years (average age 9 years). The manufacturer approached the decision problem in accordance with the EU/UK marketing authorisation: children aged 6–11 years and adults and adolescents aged 12 years and over with severe persistent allergic asthma uncontrolled despite daily high-dose inhaled corticosteroids plus a long-acting beta-agonist at BTS/SIGN step 4 or above. The model evaluated costs from the perspective of the NHS and personal social services. The manufacturer's model addresses the

impact of omalizumab on clinically significant and severe asthma exacerbations and day-to-day asthma symptoms. Costs and health outcomes were discounted at a rate of 3.5% per annum, in accordance with the NICE reference case.

6.4 The evidence on the clinical effectiveness of omalizumab as add-on treatment in the base case was based on the results of INNOVATE (adults and adolescents) and IA-05 (children), and EXALT and APEX for additional scenario analysis in adults and adolescents. Treatment effectiveness was based on two key components: response rates to omalizumab and clinically significant non-severe and clinically significant severe exacerbation rates. The manufacturer included the costs of the drug itself and the costs of administration and monitoring. The omalizumab dose administered depends on baseline serum IgE and weight and the base-case model assumed an average dose corresponding to the dose distribution of the population in INNOVATE, EXALT, APEX and IA-05. The dosing distribution of omalizumab used in the manufacturer's model refers to the 'standard dose' of treatment that was applied in INNOVATE, EXALT, APEX and IA-05. It does not consider the 'expanded dose' that was included in an update to the marketing authorisation for omalizumab in January 2010 (this raised the maximum dosage to 600 mg every 2 weeks and permitted dosing in people with higher IgE levels). The costs of administration were estimated by assuming 10 minutes of administration time and using the hourly cost of a specialist asthma nurse at £47 per hour. Monitoring costs for anaphylaxis were included up to and including the 16 week assessment. Standard care costs included two routine outpatient appointments per year with a hospital specialist and two extra visits for those people receiving omalizumab. The cost of standard treatment in the model corresponded to the standard treatment 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.

6.5 The manufacturer expressed health-related quality of life in terms of QALYs by quality adjusting the period of time the average person was alive within the model using an appropriate utility score. The two key elements of health-related quality of life were day-to-day asthma symptoms and clinically significant non-severe and severe exacerbations. Utility values for day-to-day symptoms in the base-case analysis were informed by Asthma Quality of Life Questionnaire scores collected in INNOVATE and mapped onto EQ-5D values. The health utility values applied in the manufacturer's model for day-to-day asthma symptoms in the base-case population were 0.669 for those receiving standard care and 0.779 for those whose asthma responded to omalizumab (resulting in a difference in EQ-5D of 0.110). The values applied in the subgroup populations resulted in a difference of 0.138 for the subgroup from INNOVATE needing hospitalisation and 0.106 for the subgroup from INNOVATE needing maintenance oral corticosteroids. Table 8 presents the utility values applied in the manufacturer's model for the base-case populations and the subgroups. Utility decrements for clinically significant non-severe and severe exacerbations were obtained from a prospective study conducted in the UK in four specialist asthma centres (Lloyd 2007). Table 9 presents the manufacturer's values for clinically significant non-severe and severe exacerbations. The mean utility value assigned to a clinically significant non-severe exacerbation was 0.572 and 0.326 for a clinically significant severe exacerbation, compared with 0.889 for no exacerbations. The manufacturer assumed that children under the age of 12 years did not experience any improvement in health-related quality of life with omalizumab.

**Table 8 Health utility values used in the manufacturer's model for day-to-day asthma symptoms (mean and standard deviation), adapted from table 4.11 of the manufacturer's submission**

| Study | Baseline utility (SE) [A] | Utility for ST (SE) [B] | Utility for omalizumab responser + ST (SE) [C] | Utility gain for omalizumab response vs. ST [C]-[B] | Source of data |
|---|---|---|---|---|---|
| INNOVATE randomised controlled trial (Adult and Adolescent Base Case) | 0.590 (0.009) | 0.669 (0.011) | 0.779 (0.013) | 0.110 | AQLQ at week 0 and week 28 mapped to EQ-5D |
| INNOVATE "Hospitalisation" Subgroup | 0.570 (0.015) | 0.634 (0.019) | 0.772 (0.023) | 0.138 | AQLQ at week 0 and week 28 mapped to EQ-5D |
| INNOVATE "Maintenance OCS" | 0.580 (0.019) | 0.639 (0.026) | 0.745 (0.030) | 0.106 | AQLQ at week 0 and week 28 mapped to EQ-5D |
| EXALT randomised controlled trial | 0.653 (0.025) | 0.719 (0.026) | 0.767 (0.020) | 0.048 | EQ-5D utility index, UK population norms at week 0 and week 32 |
| EXALT "Hospitalisation" Subgroup | 0.665 (0.055) | 0.631 (0.061) | 0.761 (0.046) | 0.130 | EQ-5D utility index, UK population norms at week 0 and week 32 |
| EXALT "Maintenance OCS" | 0.657 (0.053) | 0.686 (0.070) | 0.791 (0.032) | 0.105 | EQ-5D utility index, UK population norms at week 0 and week 32 |
| APEX | 0.590 (0.009) | 0.669 (0.011) | 0.779 (0.013) | 0.110 | As per INNOVATE base case |
| APEX"Hospitalisation" Subgroup | 0.570 (0.015) | 0.634 (0.019) | 0.772 (0.023) | 0.138 | As per INNOVATE "hospitalisation" |
| EXALT "Maintenance OCS" | 0.580 (0.019) | 0.639 (0.026) | 0.745 (0.030) | 0.106 | As per INNOVATE "Maintenance OCS" |
| IA-05 EUP randomised controlled trial (Paediatric Base Case) | 0.590 (0.009) | 0.669 (0.011) | 0.779* (0.013) | 0.110 | As per INNOVATE base case |
| IA-05 EUP "Hospitalisation" | 0.570 (0.015) | 0.634 (0.019) | 0.772 (0.023) | 0.138 | As per INNOVATE "hospitalisation" |
| SE, standard error; ST, standard treatment; AQLQ, Asthma Quality of Life Questionnaire | | | | | |

**Table 9 Manufacturer's utility values for severe and non-severe exacerbations, adapted from table 4.12 of the manufacturer's submission**

| | n | Mean | Standard deviation | Std. Error | 95% Confidence interval for mean | |
|---|---|---|---|---|---|---|
| | | | | | Lower bound | Upper bound |
| None, controlled | 74 | 0.889 | 0.1473 | 0.0171 | 0.855 | 0.923 |
| Non-severe (steroids) | 21 | 0.572 | 0.3553 | 0.0775 | 0.411 | 0.734 |
| Severe (hospitalised) | 5 | 0.326 | 0.3921 | 0.1754 | -0.161 | 0.813 |

### Results of manufacturer's economic model

6.6 Table 10 presents the cost-effectiveness results for the manufacturer's base-case populations. The deterministic ICER for the base-case of adults and adolescents aged 12 years and over was £32,076 per QALY gained, and the probabilistic ICER £33,268 per QALY gained. The deterministic ICER for children aged 6–11 years was £80,747 per QALY gained and the probabilistic ICER £88,998 per QALY gained. The probability that omalizumab is cost effective at £20,000 and £30,000 per QALY gained for those aged 12 and over is 0.005 and 0.267 respectively.

**Table 10 Manufacturer's base-case deterministic ICERs, QALYs and costs for omalizumab as add-on treatment compared with standard care alone**

| Scenario | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) (QALYs) |
|---|---|---|---|---|---|---|---|
| **Adults and adolescents aged 12 years and over** | | | | | | | |
| INNOVATE - double-blind randomised controlled trial | 66,571 | 27.62 | 11.24 | 40,748 | 2.12 | 1.27 | 32,076 |
| EXALT – open-label randomised controlled trial | 82,063 | 28.28 | 12.10 | 53,983 | 1.50 | 0.88 | 61,687 |
| APEX – UK observational study | 102,108 | 21.76 | 9.71 | 72,071 | 4.41 | 2.42 | 29,773 |
| **Children aged 6–12 years** | | | | | | | |
| IA-05 EUP – double-blind randomised controlled trial | 94,066 | 55.55 | 16.06 | 54,432 | 0.62 | 0.67 | 80,747 |
| ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year | | | | | | | |

6.7 The manufacturer presented the cost-effectiveness results for the alternative scenarios based on data from the EXALT open-label trial and the observational study APEX. The ICER of £61,687 per QALY gained for the EXALT scenario is approximately double the value for the base-case population, while the ICER of £29,773 per QALY gained for the APEX scenario is slightly lower than the base-case population. The difference in ICER between the INNOVATE

base case and the EXALT scenario is largely a result of two factors:

- the lower treatment effect observed in those whose asthma responded to omalizumab in EXALT compared with INNOVATE, and
- the magnitude of improvement in health-related quality of life for day-to-day symptoms estimated in INNOVATE (based on a mapping between the Asthma Quality of Life Questionnaire and the EQ-5D) and EXALT (based on directly observed EQ-5D data). The reduction in the rate of total exacerbations was more pronounced in INNOVATE (RR = 0.373) than in EXALT (RR = 0.410). Similarly, the health utility improvement for those whose asthma responded to omalizumab was greater in INNOVATE than in EXALT (0.110 compared with 0.048).

6.8 The manufacturer conducted a large number of deterministic sensitivity analyses on the base-case populations (INNOVATE and IA-05 EUP). The manufacturer concluded that the ICER is most 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 discount rate. The key cost-effectiveness drivers in the manufacturer's model are the asthma-related mortality and the improvement in health-related quality of life with omalizumab in children. The ICER for those of 12 years and over (adults and adolescents) increases from £32,076 to £72,113 per QALY gained when the asthma-related mortality risk is set to zero. The effect on the ICER for children is not as pronounced because the asthma-related mortality risk used for this population is much lower. For children, treatment duration and age at treatment initiation have a considerable impact on the cost-effectiveness of omalizumab, reflecting the assumption of no health-related quality of life gain with omalizumab therapy until age 12 years. Assuming 2 years treatment duration instead of

10 years increases the ICER from £80,747 to £662,893 per QALY gained. Similarly, reducing the age at treatment initiation from 9 to 6 years increases the ICER to £130,475 per QALY gained. Assuming an equal health-related quality of life gain with omalizumab in children aged 6–11 years to that seen in those age 12 or older (0.776) reduces the ICER in children aged 6–11 years to £61,731 per QALY gained.

6.9 The manufacturer presented subgroup analyses for two subgroups:

- a subgroup needing hospitalisation and
- a subgroup needing maintenance oral corticosteroids.

The hospitalisation subgroup consisted of people who were hospitalised in the year before trial entry, corresponding to 38.4% of the total INNOVATE trial population, 20.4% of EXALT, 59.7% of APEX and 17% of IA-05 EUP. The maintenance oral corticosteroid subgroup consisted of people who were receiving maintenance oral corticosteroids at trial baseline, corresponding to 19.8% of the INNOVATE population, 17% of EXALT and 65.9% of APEX. Data for the oral corticosteroid subgroup were not available from IA-05 EUP because only 6 participants were on maintenance oral corticosteroids at baseline and these where all in the omalizumab treatment group. The ICERs for the hospitalisation subgroup were £27,928 per QALY gained for adults and adolescents based on INNOVATE, £35,198 per QALY gained for adults and adolescents based on EXALT, £30,407 per QALY gained for adults and adolescents based on APEX and £65,100 per QALY gained for children based on IA-05 EUP. The ICERs for the maintenance oral corticosteroids subgroup for adults and adolescents based on INNOVATE, EXALT and APEX respectively were £26,320, £37,604 and £29,685 per QALY gained. Tables 11 and 12 summarise the results of the manufacturer's subgroup analysis.

**Table 11 Manufacturer's subgroup analysis – omalizumab compared with standard treatment in adults and adolescents aged 12 years and over**

| Trial | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) (QALYs) |
|---|---|---|---|---|---|---|---|
| **Hospitalisation subgroup** | | | | | | | |
| INNOVATE | 65,890 | 24.47 | 9.92 | 40,248 | 2.34 | 1.44 | 27,928 |
| EXALT | 70,838 | 22.66 | 9.35 | 43,613 | 1.85 | 1.24 | 35,198 |
| APEX | 105,930 | 20.88 | 9.14 | 70,251 | 3.93 | 2.31 | 30,407 |
| **Maintenance oral corticosteroids subgroup** | | | | | | | |
| INNOVATE | 57,439 | 22.32 | 9.15 | 34,615 | 2.50 | 1.32 | 26,320 |
| EXALT | 64,331 | 21.35 | 9.43 | 40,181 | 1.63 | 1.07 | 37,604 |
| APEX | 96,638 | 19.89 | 8.72 | 68,670 | 4.38 | 2.31 | 29,685 |
| ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year | | | | | | | |

**Table 12 Manufacturer's subgroup analysis for hospitalisation– omalizumab compared with standard treatment in children aged 6–11 years**

| Trial | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) (QALYs) |
|---|---|---|---|---|---|---|---|
| IA-05 EUP | 82,432 | 51.36 | 14.61 | 39,999 | 0.58 | 0.61 | 65,100 |
| ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year | | | | | | | |

6.10 The manufacturer conducted an exploratory sensitivity analysis incorporating the adverse effects of maintenance oral corticosteroid use. This 'oral corticosteroids-sparing' analysis was conducted for the maintenance oral corticosteroid subgroup of EXALT and APEX because the protocol of INNOVATE did not allow for changes in concomitant treatment during the study period. In EXALT, 41.9% of those whose asthma responded to omalizumab discontinued maintenance oral corticosteroids after 32 weeks, whereas in APEX 45.1% of those whose asthma responded to omalizumab discontinued maintenance oral corticosteroids at follow-up. The annual burden of oral corticosteroids was applied in the model as a reduction in costs and an improvement in QALYs for those whose asthma responded to omalizumab and who discontinued maintenance oral corticosteroids. In the manufacturer's oral

corticosteroids-sparing analysis the ICER was reduced from £37,604 to £28,319 per QALY gained in the EXALT maintenance oral corticosteroid subgroup and from £29,685 to £25,099 per QALY gained in the APEX maintenance oral corticosteroid subgroup.

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

6.11 The Assessment Group carried out a critique of the manufacturer's model. It commented that the manufacturer's approach to continuing omalizumab treatment in people whose asthma had responded was that the response remains unchanged over time. However, evidence from EXALT suggests that this may not be the case. For example, approximately 8.6% of people who had a response at 16 weeks in EXALT were considered not to have an adequate response at 32 weeks. The Assessment Group commented that although these results may have been influenced by the open-label design of the EXALT trial, they demonstrate that a response to omalizumab may not persist. The impact of this was not considered in the manufacturer's model.

6.12 The Assessment Group commented that the direct estimates of EQ-5D would seem a more appropriate choice for informing the health-related quality of life benefit with omalizumab than the manufacturer's method of mapping Asthma Quality of Life Questionnaire scores from INNOVATE onto EQ-5D values. Furthermore, in the manufacturer's model children under 12 years were assumed not to experience any improvement in health-related quality of life with omalizumab until they reached 12 years. The Assessment Group commented that an improvement in asthma-related quality of life in children was observed in IA-05, although this was not statistically significant.

6.13 The Assessment Group found that the manufacturer's exploratory sensitivity analysis which incorporated the adverse effects of maintenance oral corticosteroids in the maintenance oral corticosteroids subgroup was generally reasonable and appropriate, considering the limitation of the evidence available. However, the method used to estimate health utility losses from adverse events related to oral corticosteroids is based on the assumption that DALYs are equivalent to QALYs, which the Assessment Group considered may not be appropriate.

6.14 The Assessment Group commented that some of the uncertainties that had been previously identified in TA133 and TA201 were addressed by the manufacturer; in particular, the relative efficacy and safety of omalizumab compared with oral corticosteroids, the costs and health losses associated with maintenance oral corticosteroid use and an additional subgroup population consisting of people who were hospitalised for asthma in the previous year. However, the Assessment Group highlighted that a number of key uncertainties remained. In particular, there was still uncertainty about the mortality risk associated with asthma and the relationship between mortality, age and severity of exacerbations, the improvement in health-related quality of life with omalizumab in adults and adolescents and children, the influence of age on the cost-effectiveness results; and the overall positioning of omalizumab in the stepwise approach to treatment. The Assessment Group commented that the asthma-related mortality risk applied in the model may have resulted in an over-estimation of asthma deaths because the mortality risk following hospitalisation for acute severe asthma was applied to the clinically significant severe exacerbation state, whereas only about 20% of clinically significant severe exacerbations in INNOVATE involved hospital admissions. In addition, the Assessment Group found that the starting age used in the model masks the distribution of different

ages at treatment initiation both in the trials and in clinical practice. The Assessment Group commented that, because age affects the asthma-related mortality risk, the impact of age at treatment initiation should have been considered, either by presenting subgroups based on age or, if age is not considered an appropriate basis for subgroups, by combining estimates for different ages into a final 'weighted' ICER estimate.

6.15 The Assessment Group further commented that in the manufacturer's systematic review to identify studies that reported mortality from clinically significant severe exacerbations or hospitalisations for asthma, the need to establish a clear link between clinically significant severe exacerbations and death may have resulted in the exclusion of potentially relevant studies reporting on asthma-related mortality.

**Assessment Group's economic model**

6.16 The Assessment Group developed an economic model to assess the cost effectiveness of omalizumab as an add-on treatment to optimised standard care compared with optimised standard care alone from the perspective of the UK NHS. The outcomes of the model are expressed in terms of QALYs and costs are expressed in UK pound sterling at a 2009/10 price base. Both costs and outcomes are evaluated over a lifetime assuming a treatment duration of 10 years and discounted using a 3.5% annual discounted rate, in accordance with the NICE reference case.

6.17 The Assessment Group examined the cost effectiveness of omalizumab as an addition to standard step 4 treatment separately from omalizumab as an addition to standard step 5 treatment, both of which were compared with standard step 4 or 5 treatment alone, respectively. The standard step 4 comparison was evaluated by examining the efficacy and safety result from clinical trials, whereas

the standard step 5 comparison was evaluated using the maintenance oral corticosteroid subgroup from the trials. The Assessment Group commented that in the absence of trials directly comparing omalizumab with oral corticosteroids, the 'optimal' position of omalizumab within the overall stepwise treatment approach to asthma could not be properly assessed. The Assessment Group also considered the steroid-sparing potential of omalizumab by examining the efficacy and safety of long-term oral corticosteroid use.

6.18 The evidence for the overall population used in the Assessment Group's model corresponds to the population in INNOVATE for adults and adolescents 12 years and over, and IA-05 EUP for children aged 6–11 years. The model structure used by the Assessment Group was the same as the manufacturer's, but differed in some input parameters and assumptions employed, particularly for asthma-related mortality and health-related quality of life. In the manufacturer's model, asthma-related deaths are linked directly to a clinically significant severe exacerbation whereas the Assessment Group's model assumes that people in the day-to-day asthma symptoms state have an elevated risk of asthma-related death at each cycle. All asthma-related deaths are assumed to occur because of a clinically significant severe exacerbation, but the Assessment Group's approach does not restrict input parameter estimates for asthma-related mortality to those which can be directly associated with an exacerbation or event as in the manufacturer's model. The Assessment Group undertook a systematic review of asthma-related mortality and considered that the most appropriate data were from de Vries et al. (2010) which used data from the General Practice Research Database of permanently registered patients aged 18 years and older who received a prescription for inhaled short-acting or long-acting beta-2 agonists from 1993. Data from Watson et al. (2007), as used in

the manufacturer's model, were included in a sensitivity analysis. Using data from de Vries et al (2010), the Assessment Group estimated that the probability of death over a 3-month period (the cycle length used in the model) was 0.001 for all ages. The Assessment Group assumed that the mortality of people aged 18 years and older in the de Vries study could be used for children under 12 years (in the absence of data). The Assessment Group also estimated that the probability of asthma-related death over a 3-month period using data reported by Watson et al. was 0.0001 for children under 12 years, 0.0006 for those 12–16 years, 0.0008 for those 17–44 years and 0.0049 for people 45 years and older.

6.19 As with the manufacturer's model, the Assessment Group's model considered health-related quality of life associated with day-to-day asthma symptoms and exacerbations. However, the Assessment Group estimated health-related quality of life for day-to-day asthma symptoms using EQ-5D data from EXALT rather than mapping asthma quality of life questionnaire scores from INNOVATE onto EQ-5D values. It also assumed that children aged 6–11 years experience the same improvement from omalizumab treatment as adults and adolescents, whereas the manufacturer's model assumed no health-related quality of life benefit in children under 12 years. The health utility value applied in the Assessment Group's model for day-to-day asthma symptoms in the base case population was 0.719 for people receiving standard care and 0.767 for those whose asthma responded to omalizumab, resulting in a difference of 0.048 (compared with 0.669 and 0.779, respectively in the manufacturer's model, a difference of 0.110). The values applied in the subgroup populations gave a difference of 0.13 for the hospitalisation subgroup (compared with 0.138 in the manufacturer's model) and 0.105 for the maintenance oral corticosteroid subgroup (compared with 0.106 in the manufacturer's model). Table 13 presents the utility values applied in the

Assessment Group's model for the base-case populations and the subgroups. Utility decreases for clinically significant non-severe and severe exacerbations were obtained from the prospective UK study conducted in four specialist asthma centres (Lloyd et al. 2007) which was also used by the manufacturer. Table 14 presents the decreases in EQ-5D for clinically significant non-severe and severe exacerbations. The loss in utility as a result of an exacerbation was applied in the Assessment Group's model for 4 weeks (28 days). The Assessment Group commented that in the Lloyd study exacerbations needing hospitalisation may have been more severe than the clinically significant severe exacerbations in INNOVATE, and this could lead to an overestimate of the loss in health-related quality of life as a result of an exacerbation.

**Table 13 Health utility values used in the Assessment Group's model for day-to-day asthma symptoms (mean and standard deviation)**

| | **Data source** | **Day-to-day asthma symptoms** | | |
|---|---|---|---|---|
| | | **Standard care** | **Response to omalizumab** | **Difference** |
| **Base-case** | | | | |
| Adult and adolescent | EXALT | 0.719 (0.026) | 0.767 (0.02) | 0.048 |
| Children | EXALT† | 0.719 (0.026) | 0.767 (0.02) | 0.048 |
| **Subgroups** | | | | |
| Adult and adolescent hospitalisation | EXALT hospitalisation | 0.631 (0.061) | 0.761 (0.046) | 0.130 |
| Adult and adolescent maintenance oral corticosteroids | EXALT Maintenance oral corticosteroids | 0.686 (0.07) | 0.791 (0.032) | 0.105 |
| Children hospitalisation | EXALT† hospitalisation | 0.631 (0.061) | 0.761 (0.046) | 0.130 |

†Assumes that children experience the same health utility improvement as adults and adolescents.

**Table 14 Health utility values used in the model for exacerbations**

| | Decrease as a result of clinically significant exacerbations | | Duration in weeks |
|---|---|---|---|
| | Clinically significant non-severe | Clinically significant severe | Used in the model |
| **Base-case and subgroup populations** | | | |
| Adults and adolescents | –0.10 | –0.20 | 4 |
| Children | –0.10 | –0.20 | 4 |

6.20 The Assessment Group included the costs of omalizumab itself and the costs of administration and monitoring. The costs of omalizumab used in the model reflected its use as a subcutaneous injection every 2–4 weeks with the exact dose depending on baseline serum IgE and weight. The unit price of the 75-mg syringe (£128.07) was used to estimate the average omalizumab cost per patient. As in the manufacturer's submission, the model uses an average annual cost of omalizumab per patient. The average annual cost was based on the distribution of doses used in the trials. Data on the dosage distribution were obtained from the manufacturer's submission. For adults and adolescents, the base case uses the dose distribution from INNOVATE, whereas for children the dose distribution corresponds to IA-05 EU-P. The administration and monitoring costs follow the methods and assumptions used by the manufacturer. Administration is assumed to take 10 minutes of a specialist asthma nurse's time at £47/hour. For the first three administrations, monitoring is assumed to take 2 hours with 15 minutes of nurse time at £47/hour. From the fourth administration up to the 16-week assessment, monitoring takes 1 hour. From 16 weeks onwards, no monitoring costs are incurred. The 16-week assessment is assumed to take place during a routine appointment, which is slightly different from the manufacturer's model, which assumed that the assessment occurs during an additional follow-up appointment. The annual average cost of omalizumab for adults and adolescents was calculated to be £8056

plus administration costs of £260 in the first year and £146 in subsequent years; for children the annual average cost of omalizumab was £8455 plus administration costs of £268 in the first year and £151 in subsequent years. Dose distributions for the subgroups were not available; therefore data from the overall patient population were used in the subgroup populations. The costs of standard treatment were taken from the manufacturer's submission and were incurred by both treatment groups. The costs of exacerbations were based on data from the trials as reported in the manufacturer's submission. The key modelling assumptions and data sources used by the Assessment Group and the manufacturer are shown in appendix B.

**Results of Assessment Group's economic model**

6.21 Table 15 summarises the Assessment Group's probabilistic cost-effectiveness results for the base-case population. In addition to the overall population, subgroup analysis is presented for two populations:

- a subgroup of adults and adolescents and children needing hospitalisation, and
- a subgroup of adults and adolescents receiving maintenance oral corticosteroids (data for children were not available from IA-05 EUP).

The hospitalisation subgroup consists of people who were admitted to hospital in the year before trial entry, corresponding to 38.4% of the total INNOVATE population and 17% of IA-05 EUP. The maintenance oral corticosteroids subgroup consists of people who were receiving maintenance oral corticosteroids at trial baseline, corresponding to 19.8% of the INNOVATE population.

6.22 The Assessment Group also presented results for a number of alternative scenarios in which the assumptions used as part of the

base-case results were varied to assess the robustness to variation in the sources of data used to populate the model and alternative assumptions. This included a scenario incorporating the adverse effects of oral corticosteroids in the maintenance oral corticosteroids subgroup, following a similar approach to that taken by the manufacturer. This scenario necessitated a number of assumptions, which the Assessment Group considered may underpin the validity of the estimates obtained. These include:

- people who do not receive omalizumab will continue to receive maintenance oral corticosteroids for the rest of their life
- the excess relative risk attributable to oral corticosteroids is based solely on current exposure to oral corticosteroids, and once people discontinue oral corticosteroids the excess relative risk becomes negligible, and
- health losses expressed in DALYs are equivalent to health losses expressed in QALYs.

**Table 15 Summary of Assessment Group's cost-effectiveness results – probabilistic base-case and subgroup populations and scenario analysis**

| | Analysis | ICER (£/QALY) | |
|---|---|---|---|
| | | Adult and adolescent | Children |
| Overall population | Base-case | 83,822 | 78,009 |
| | Scenario 1: Using baseline exacerbation rates from APEX | 78,484 | - |
| | Scenario 2: Using effectiveness estimates from EXALT | 92,235 | - |
| | Scenario 3: Using pooled effectiveness estimates INNOVATE and EXALT | 89,473 | - |
| | Scenario 4: Asthma-related mortality from Watson et al. (2007) | 46,029 | 98,688 |
| | Scenario 5: Using EQ-5D mapped from AQLQ collected during INNOVATE | 52,236 | 50,319 |
| | Scenario 6: Assuming no health-related quality of life improvement until age 12 years | - | 95,177 |
| | Scenario 7: Lifetime treatment duration | 89,230 | 79,923 |
| | Scenario 8: Using expanded dosing table | 112,033 | - |
| Hospitalisation | Base-case | 46,431 | 44,142 |
| | Scenario 1: Using baseline exacerbation rates from APEX | 43,627 | - |
| | Scenario 2: Using effectiveness estimates from EXALT | 48,892 | - |
| | Scenario 3: Using pooled effectiveness estimates INNOVATE and EXALT | 47,235 | - |
| | Scenario 4: Asthma-related mortality from Watson et al. (2007) | 31,576 | 47,430 |
| | Scenario 5: Using EQ-5D mapped from AQLQ collected during INNOVATE | 44,430 | 42,296 |
| | Scenario 6: Assuming no health-related quality of life improvement until age 12 years | - | 63,908 |
| | Scenario 7: Lifetime treatment duration | 47,590 | 45,025 |
| | Scenario 8: Using expanded dosing table | 62,339 | |

| | Analysis | ICER (£/QALY) | |
|---|---|---|---|
| | | Adult and adolescent | Children |
| Maintenance oral corticosteroids | **Base-case** | **50,181** | **-** |
| | Scenario 1: Using baseline exacerbation rates from APEX | 47,252 | - |
| | Scenario 2: Using effectiveness estimates from EXALT | 57,639 | - |
| | Scenario 3: Using pooled effectiveness estimates INNOVATE and EXALT | 53,454 | - |
| | Scenario 4: Asthma-related mortality from Watson et al. (2007) | 29,657 | - |
| | Scenario 5: Using EQ-5D mapped from AQLQ collected during INNOVATE | 50,068 | - |
| | Scenario 6: Assuming no health-related quality of life improvement until age 12 years | - | - |
| | Scenario 7: Lifetime treatment duration | 51,862 | - |
| | Scenario 8: Using expanded dosing table | 67,363 | - |
| | Scenario 9: Incorporation of long-term effects of oral corticosteroids | 39,509 (scenario 9A); 34,679 (scenario 9B); 33,786 (scenario 9C) | - |
| Scenario 9A adapts the same approach as the manufacturer. The total annual quality of life burden expressed in terms of DALYs is estimated to be 0.02331 per patient and the total annual cost is £205.60 per patient on maintenance oral corticosteroids | | | |
| Scenario 9B uses the same costs as scenario A but uses undiscounted and non-age weighted DALYs | | | |
| Scenario 9C uses the same approach as scenario B but includes an additional health loss for non-Hodgkin's lymphoma, adrenal insufficiency and sleep disturbance | | | |

6.23 For both populations, omalizumab add-on treatment was more costly but also more effective than standard treatment alone. For adults and adolescents (12 years and over), 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 of £83,822 per QALY gained. For children aged 6–11 years 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 of £78,009 per QALY gained. The probability that omalizumab is cost effective at £30,000 per QALY was zero in both populations.

6.24 For the hospitalisation subgroup, omalizumab add-on treatment was more costly but also more effective than standard treatment alone. For adults and adolescents (12 years and over), the mean cost of omalizumab add-on treatment was £75,826 compared with £36,449 for standard care without omalizumab; the mean QALYs were 12.68 and 11.83 respectively. This resulted in an ICER of £46,431 per QALY gained. For children aged 6–11 years the mean cost of omalizumab add-on treatment was £83,145 compared with £44,718 for standard care without omalizumab; the mean QALYs were 15.32 and 14.45 respectively. This resulted in an ICER of £44,142 per QALY gained. The probability that omalizumab is cost effective at £30,000 per QALY was zero in both populations.

6.25 For the maintenance oral corticosteroids subgroup, omalizumab add-on treatment was more costly but also more effective than standard therapy alone. For adults and adolescents (12 years and over , the mean cost of omalizumab add-on treatment was £68,995 compared with £35,902 for standard care without omalizumab; the mean QALYs were 13.44 and 12.78 respectively. This resulted in an ICER of £50,181 per QALY gained. As with the hospitalisation subgroup, the probability that omalizumab is cost effective at £30,000 per QALY was zero.

6.26 The Assessment Group commented that the key drivers of cost effectiveness were asthma-related mortality rates, improvement in health-related quality of life associated with omalizumab treatment; and the incorporation of adverse effects of oral corticosteroids in the maintenance oral corticosteroids subgroup. Using the higher asthma-related mortality rates reported by Watson et al. (2007) (adopted by the manufacturer) instead of those reported by de

Vries et al. (2010) resulted in ICERs for the overall population of £46,029 per QALY gained for adults and adolescents of 12 years and over, and £98,688 per QALY gained for children aged 6–11 years. In the hospitalisation subgroup, the ICERs were 31,576 and 47,430 per QALY gained respectively, and in the maintenance oral corticosteroids subgroup the ICER was £29,657 per QALY gained for adults and adolescents. Changing the assumptions for improvement in health-related quality of life with omalizumab (that is, using EQ-5D mapped from Asthma Quality of Life Questionaire scores collected from INNOVATE and assuming no improvement until children reach 12 years, scenarios 5 and 6) also had a substantial impact on the ICERs. However, the ICER did not fall below £30,000 per QALY gained in any population (the lowest ICER was £42,296 per QALY gained in the hospitalisation subgroup of children aged 6–11 years). Incorporating the adverse effects of oral corticosteroids in the maintenance oral corticosteroids subgroup reduced the ICER from £50,181 to £33,786. However, the Assessment Group concluded that this result should be interpreted with caution because the assumptions used may favour omalizumab. An additional subgroup population consisting of people experiencing three or more exacerbations in the previous year was also considered by the Assessment Group. The ICERs for this subgroup were lower than the ICERs for the base-case population of adults and adolescents aged 12 years and over (£77,686 per QALY gained compared with £83,822 per QALY gained) and children aged 6–11 years (£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 £41,517 per QALY gained in adults and adolescents aged 12 years and over, and £39,893 per QALY gained in children aged 6–11 years.

### Comparison of the Assessment Group and manufacturer's models

6.27 The Assessment Group explored the differences in the results from the two economic models (table 16). The Assessment Group's mean probabilistic base-case ICER for adults and adolescents is £83,822 per QALY gained compared with the manufacturer's base-case ICER of £33,268 per QALY gained. For children aged 6–11 years, the Assessment Group's mean probabilistic base-case ICER for children is £78,009 per QALY gained, compared with the manufacturer's estimate of £88,998 per QALY gained.

**Table 16 Comparison of results from the Assessment Group and manufacturer's base-case probabilistic analysis**

| | ICER (£/QALY) | |
|---|---|---|
| | **Adults and adolescents (12 years and over)** | **Children (6–11 years)** |
| Assessment Group's base case | 83,822 | 78,009 |
| Manufacturer's base case | 33,268 | 88,998 |
| **Alternative parameter estimates varied individually in the Assessment Group's model** | | |
| Using Watson et al. (2007) for asthma-related mortality | 46,029 | 98,688 |
| Using EQ-5D utility values mapped from Asthma Quality of Life Questionnaire scores scores | 52,236 | 50,139 |
| Assuming no improvement in health-related quality of life until 12 years | Not applicable | 95,177 |
| Using the estimates of absolute health-related quality of life for exacerbations from Lloyd et al. (2007) and the duration of an exacerbation from the trials | 84,690 | 77,904 |
| **Cumulative effect of altering the parameters above simultaneously in the Assessment Group's model** | | |
| | 35,972 | £80,540 |

6.28 The Assessment Group commented that the differences in the cost-effectiveness results from the Assessment Group and manufacturer's models were largely a result of differences in two key parameter inputs: asthma-related mortality risk and improvement in health-related quality of life with omalizumab. The cumulative effect of simultaneously changing parameter estimates for asthma-related mortality and health-related quality of life to

those used by the manufacturer changed the Assessment Group's ICERs to £35,972 per QALY gained for adults and adolescents 12 years and over, and £80,540 per QALY gained for children aged 6–11 years (see table 16).

6.29 The Assessment Group highlighted that the asthma-related mortality risk used by the manufacturer (2.478% in adults aged 45 years over derived from Watson et al. [2007]) suggests that 2–3 asthma deaths would have been expected in INNOVATE for the 100 observed clinically significant severe exacerbations; 6–7 asthma deaths would have been expected in APEX for the 261 observed clinically significant severe exacerbations. However, no mortality attributable to asthma was observed in the trials. The Assessment Group concluded that the asthma-related mortality risk used in the manufacturer's submission for adults and adolescents is likely to be an overestimate of mortality. For children, the asthma-related mortality risk was much lower and this resulted in similar ICER estimates from the Assessment Group and the manufacturer.

6.30 The manufacturer's method of estimating utility values from Asthma Quality of Life Questionnaire scores collected in INNOVATE mapped onto EQ-5D values (rather than the Assessment Group's method of using EQ-5D values directly collected in EXALT) resulted in a higher quality of life benefit for people whose asthma responded to omalizumab. This was because the difference in utility between those whose asthma responded to omalizumab and people receiving standard care in the overall EXALT population was less than half of the INNOVATE population. However, values were similar in the hospitalisation and maintenance oral corticosteroids subgroups. In addition, the Assessment Group commented that the different assumptions made for health-related quality of life in children aged 6–11 years (no improvement with omalizumab assumed by the manufacturer; equal improvement to

adults and adolescents aged 12 years and over assumed by the Assessment Group) had a major impact on the cost-effectiveness estimates.

6.31 The Assessment Group concluded that the cost effectiveness of omalizumab depends on the asthma-related mortality risk, health-related quality of life improvements with omalizumab, and the plausibility of assumptions used to estimate costs and health losses associated with adverse effects of oral corticosteroids.

# 7 Equalities issues

7.1 Responses from consultees following consultation on the draft scope suggested that failure to recommend omalizumab for children aged 6–11 years in TA201 was unfair because omalizumab is recommended under specific circumstances for children and young people aged 12 years and over in TA 133. Consultee responses also raised the social, socioeconomic and cultural issues that might affect the incidence and prevalence of asthma as well as social pressure that might affect adherence to treatment by children and adolescents.

# 8 Innovation

8.1 The manufacturer did not present any discussion in its submission of the innovative nature of omalizumab. However, in the manufacturer's previous submission for TA201, it argued that omalizumab represented an innovative approach to proactively targeting IgE, the pathophysiological factor responsible for the development of symptoms in people with allergic asthma. The manufacturer described omalizumab as addressing the unmet need for additional management options in a high-risk population with severe persistent allergic asthma. As evidence of innovation, the manufacturer pointed out that before the first EU approval of

omalizumab in October 2005 no specific treatments were available for people of 12 years or over with allergic asthma.

# 9 Authors

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# Appendix A: Supporting evidence

## *Related NICE guidance*

### Published

- Omalizumab for the treatment of severe persistent allergic asthma in children aged 6 to 11 years. NICE technology appraisal guidance 201 (2011). Available from www.nice.org.uk/guidance/TA201
- Omalizumab for severe persistent allergic asthma. NICE technology appraisal guidance 133 (2007). Available from www.nice.org.uk/guidance/TA133
- Corticosteroids for the treatment of chronic asthma in adults and children aged 12 years and over. NICE technology appraisal guidance 138 (2008). Available from www.nice.org.uk/guidance/TA138
- Corticosteroids for the treatment of chronic asthma in children under the age of 12 years. NICE technology appraisal guidance 131 (2007). Available from www.nice.org.uk/guidance/TA131
- Bronchial thermoplasty for severe asthma. NICE interventional procedure guidance 419 (2012). Available from www.nice.org.uk/guidance/IPG419

# Appendix B: Comparison of key model assumptions and data sources in the Assessment Group and manufacturer models, adapted from table 77 of the assessment report

| Parameter | Assessment Group | Manufacturer |
|---|---|---|
| **Overview** | | |
| **Base-case** | Adults and adolescents (≥ 12years): INNOVATE<br>Children (<12 years): IA-05 EUP subgroup | Same |
| **Alternative base-case** | | Manufacturer's submission presented two alternative scenarios based on the EXALT trial and on the APEX study |
| **Subgroups** | Hospitalisation, maintenance oral corticosteroids, ≥ 3 exacerbations at baseline, <3 exacerbations at baseline. | Manufacturer's submission presents hospitalisation and maintenance oral corticosteroids subgroups for base-case and scenarios |
| **Age at model entry** | Adults and adolescents (≥ 12years): 43 years of age<br>Children (<12 years): 9 years of age<br>Effect of age at model entry evaluated in the sensitivity analysis | Same |
| **Treatment duration** | Assumed 10 years | Same |
| **Cycle length** | 3 months | Same |
| **Time horizon** | Lifetime (age 100 years) | Same |
| **Natural history** | | |
| **Baseline rate of exacerbations** | Assumption: the exacerbation rates observed in the clinical trials are constant throughout time and can be annualised<br>▪ Adults and adolescents (≥ 12years): INNOVATE<br>▪ Children (<12 years): IA-05 EUP subgroup | Same<br><br>Scenarios use rates observed in each study (EXALT and APEX) |
| **Any-cause mortality** | UK life-tables based on years 2008-2010 adjusted by asthma death (based on year 2010). | UK life-tables based on years 2007-2009 unadjusted for asthma deaths. |
| **Asthma-related mortality.** | Base-case: de Vries et al. (2010), death due to asthma using GPRD data.<br><br>Sensitivity analysis:<br>▪ For patients under 18 years of age: Watson et al (2007) mortality from any cause following hospitalisation for acute severe asthma<br>▪ For all patients: Watson et al (2007) mortality from any cause following hospitalisation for acute severe asthma | Assumption: asthma-related death can only occur following a severe exacerbation.<br><br>Base-case: Watson et al (2007), mortality from any cause following hospitalisation for acute severe asthma.<br><br>Sensitivity analysis:<br>▪ Watson et al (2007) for all ages of 0.0858% was used,<br>▪ Lowhagen et al (1997) of 3.108%<br>▪ Gupta et al (2004) of 7.2% for ICU admissions |
| **Clinical effectiveness** | | |
| **Proportion of responders** | Proportion of responders observed in the clinical trials: | Same<br>Scenarios use proportion of responders |

| Parameter | Assessment Group | Manufacturer |
|---|---|---|
| | ▪ Adults and adolescents (≥ 12years): INNOVATE at 28 weeks.<br>▪ Children (<12 years): IA-05 EUP subgroup at 52 weeks. | observed in each study at 16 weeks (EXALT and APEX). |
| **Persistence of response** | Treatment effect and proportion of responders is assumed constant throughout treatment duration. | Same |
| **Omalizumab effect on exacerbations** | Omalizumab reduces the rate of exacerbations as observed in the clinical trials.<br>▪ Adults and adolescents (≥ 12years): INNOVATE.<br>▪ Children (<12 years): IA-05 EUP subgroup. | Same<br>Scenarios use exacerbation rates observed in each study (EXALT and APEX). |
| **Adverse events** | Not considered. | Same |
| **Withdrawals from treatment** | Not considered in the base-case.<br>Tested in the sensitivity analysis. | Same |
| **Resource use and costs** | | |
| **Costs associated with omalizumab add-on therapy** | Costs of omalizumab estimated using the dose distribution observed in:<br>▪ Adults and adolescents (≥ 12years): INNOVATE.<br>▪ Children (<12 years): IA-05 EUP subgroup.<br>▪ Impact of 'extended dosing' table tested in sensitivity analysis.<br><br>Initiation of omalizumab requires one initiation appointment with respiratory consultant.<br><br>Administration by specialist asthma nurse assumed to take 10 minutes.<br><br>Monitoring by specialist asthma nurse assumed to take 15 minutes per hour of monitoring. The duration of monitoring varies as follows:<br>• 2 hours for the first 3 administrations<br>• 1 hour up to the 16 assessment<br>• No monitoring thereafter | Same<br>Scenarios use dosing distributions observed in each study (EXALT and APEX).<br><br>Initiation of omalizumab AND assessment of response require additional appointments with respiratory consultants. |
| **Costs associated with standard care** | Costs of standard care include costs of standard therapy and the costs of routine secondary visits.<br>▪ Costs of standard therapy were obtained from the manufacturer's submission and refer to the standard therapy use observed in INNOVATE and IA-05 EUP subgroup.<br>▪ All patients assumed to have two appointments a year with respiratory consultant. | Same<br>Scenarios use standard therapy observed in each study (EXALT and APEX). |
| **Costs of exacerbations** | Resource use due to exacerbations obtained from the INNOVATE and IA-05 EUP trials.<br>▪ INNOVATE splits by non-severe and severe exacerbation.<br>▪ IA-05 EUP subgroup provides only average resource use any clinically significant exacerbations.<br>Unit costs used in the manufacturer's submission confirmed and used to cost | Same<br>Scenarios use resource use observed in each study (EXALT and APEX). |

| Parameter | Assessment Group | Manufacturer |
|---|---|---|
| | exacerbations. | |
| **Health-related quality of life** | | |
| **Day-to-day symptoms** | Based on the EQ-5D data collected during the EXALT trial. | Same<br>Base-case uses INNOVATE data:<br>▪ INNOVATE: EQ-5D derived from AQLQ.<br>▪ EXALT: EQ-5D collected at trial.<br>▪ IA-05 EUP: = INNOVATE from age 12 years.<br>▪ APEX: = INNOVATE |
| **Exacerbations** | Decrement from baseline reported by Lloyd et al (2007) in:<br>▪ Patients who experienced an exacerbation requiring OCS → health-related quality of lifeL loss due to a clinically significant non-severe exacerbation;<br>▪ Patients who experienced an exacerbation requiring hospitalisation → health-related quality of lifeloss due to a clinically significant severe exacerbation. | Same<br>Health-related quality of lifeobserved at follow-up in patients who experienced exacerbations was subtracted to the health-related quality of lifeof day-to-day symptoms on standard care to obtain health-related quality of lifedecrement associated with exacerbations. |
| **Duration of exacerbations** | Health-related quality of lifeloss associated with an exacerbation assumed to last 4 weeks, corresponding to the follow-up period of Lloyd et al (2007) [93]. | Average duration of an exacerbation as observed in the clinical trials. |
| **Children** | Children experience the same health-related quality of lifeimprovement from omalizumab therapy as adults and adolescents. | Assumed no improvement due to omalizumab until 12 years of age. |