

Omalizumab for the Treatment of Severe Persistent Allergic Asthma in Children Aged 6–11 Years

A NICE Single Technology Appraisal

Jane Burch,¹ Susan Griffin,² Claire McKenna,² Simon Walker,² James Paton,³ Kath Wright¹ and Nerys Woolacott¹

1 Centre for Reviews and Dissemination (CRD), University of York, York, UK

2 Centre for Health Economics (CHE), University of York, York, UK

3 Royal Hospital for Sick Children, Glasgow, UK

Contents

Abstract	992
1. The Decision Problem	993
2. The Independent Evidence Review Group (ERG) Review	994
2.1 Clinical Evidence	994
2.1.1 Critique of the Evidence	994
2.2 Cost-Effectiveness Evidence	996
2.2.1 Critique of the Evidence	997
2.3 Conclusions of the ERG Review	998
2.4 Key Methodological Issues	998
2.4.1 Clinical Effectiveness	998
2.4.2 Cost Effectiveness	998
3. The National Institute for Health and Clinical Excellence (NICE) Appraisal Committee:	
Consideration of All Available Evidence	998
3.1 How the Evidence Related to the NHS in England and Wales	999
3.2 The Impact of Severe Persistent Allergic Asthma on Children and Their Carers	999
3.3 Clinical Effectiveness	1000
3.4 Cost Effectiveness	1000
3.4.1 Treatment Duration	1000
3.4.2 Treatment Response	1000
3.4.3 Asthma-Related Mortality	1000
3.4.4 Omalizumab Costs	1001
3.4.5 Plausibility of the Incremental Cost-Effectiveness Ratios Presented	1001
3.5 Budgetary Impact	1001
3.6 Equalities Considerations	1001
3.7 The Appraisal Committee's Recommendations	1001
4. NICE Guidance	1002
5. Interpretation of the Guidance	1002

Abstract

Following a licence extension to include those aged 6–11 years, the National Institute for Health and Clinical Excellence (NICE) invited the manufacturer of omalizumab (Novartis Pharmaceuticals UK) to submit evidence for the clinical and cost effectiveness of this drug for patients with severe persistent allergic asthma in this age bracket. NICE had previously considered the use of omalizumab in patients aged 12 years and over. The Centre for Reviews and Dissemination (CRD) and the Centre for Health Economics (CHE) at the University of York were commissioned as the Evidence Review Group (ERG) to critically appraise the evidence presented by the manufacturer. This article summarizes that review of the evidence, the deliberations of the NICE Appraisal Committee and the resulting NICE guidance.

The ERG critically reviewed the evidence presented in the manufacturer's submission and identified areas requiring clarification, for which the manufacturer provided additional evidence. The relevant patient population was patients aged 6–11 years of age with severe persistent allergic immunoglobulin E-mediated asthma whose condition remained uncontrolled despite best standard care with high-dose inhaled corticosteroids and a long-acting inhaled β_2 -agonist. The main clinical effectiveness data were derived from a pre-planned subgroup analysis of a single randomized controlled trial comparing omalizumab plus standard therapy against standard therapy alone. At a 52-week follow-up, the only outcome to show a statistically significant benefit of omalizumab compared with placebo was the number of exacerbations defined as 'clinically significant' [CS] (relative risk [RR] 0.504; 95% CI 0.350, 0.725; $p < 0.001$). At the ERG's request, the manufacturer provided analyses stratified by baseline exacerbation rate, which indicated the effect of omalizumab on CS exacerbations was statistically significant only for those children with ≥ 3 exacerbations as baseline. The ERG identified a number of issues relating to the clinical effectiveness results: it was unclear whether the pre-planned subgroup analysis had sufficient power; the definition of CS exacerbation was less severe than that used in UK clinical practice; and the method for imputing exacerbations for those who withdrew from treatment may have underestimated the exacerbation rate.

The incremental cost-effectiveness ratio based on the manufacturer's results was considerably above the threshold range stated in the NICE *Guide to the Methods of Technology Appraisal*. The ERG identified numerous issues relating to the cost-effectiveness results, which included the following: the 10-year time horizon for treatment may exceed that in clinical practice; the assumption of constant exacerbation rates over a lifetime given that adolescence is expected to impact on the severity of asthma; and whether it is appropriate to use health-related quality-of-life data collected in adults for children.

The ERG concluded that omalizumab appears to reduce CS exacerbations but there was no evidence of improvement in daily symptoms, CS severe (CSS) exacerbations or hospitalization rates. The main driver of cost effectiveness was the reduction in asthma-related mortality associated with a reduction in CSS exacerbations. As the number of CSS exacerbations avoided was low, as is asthma-related mortality in children, the potential small gain in QALYs associated with omalizumab was not sufficient to compensate for the

high treatment cost even under the most favourable scenario analyses. The Appraisal Committee recommended that omalizumab should not be routinely provided for the treatment of severe persistent allergic asthma in children aged 6–11 years.

Key points for decision makers

- The number of clinically significant severe exacerbations avoided with omalizumab is low, as is asthma-related mortality in children; the potential small gain in quality-adjusted life-years (QALYs) associated with omalizumab was not sufficient to compensate for the high treatment cost
- The Appraisal Committee recommended that omalizumab should not be routinely provided for the treatment of severe persistent allergic asthma in children aged 6–11 years
- The key driver for the decision was the most plausible incremental cost-effectiveness ratio, even in a high-risk subgroup, being at least £65 900 per QALY
- Omalizumab may be an efficacious alternative to oral corticosteroids (OCS) in children with more severe asthma, but an OCS-sparing trial would need to be conducted to confirm this

The National Institute for Health and Clinical Excellence (NICE) is an independent organization responsible for providing national guidance to the NHS in England and Wales on the use of selected new health technologies. Single technology appraisals (STAs) evaluate a single product, device or other technology that has a single indication, for example a new pharmaceutical product or licensed indication.^[1] The manufacturer (or sponsor of the technology) submits the principal evidence supporting the clinical and cost effectiveness of the product, and an external independent academic organization (the evidence review group [ERG]) is commissioned to produce a review and critique of the evidence submitted.^[2,3] Clinical specialists, NHS commissioning experts and patient experts also provide evidence for consideration by the NICE Appraisal Committee in formulating their guidance.^[2] Once published, NICE technology guidance provides a legal obligation for NHS providers to reimburse technologies that have been approved.^[2] This article presents a summary of the ERG report and subsequent development of NICE guidance for the use of omalizumab in the treatment of severe persistent allergic asthma in patients aged between 6 and 11 years. This is one in a series of

STA summaries being published by *Pharmacoeconomics*.^[4–18]

Full details of the relevant appraisal documents, including the appraisal scope, manufacturer submission, ERG report, Appraisal Consultation Document (ACD), Final Appraisal Determination (FAD) and responses to these documents, can be found on the NICE website.^[19]

1. The Decision Problem

Approximately 1.1 million children in the UK (1 in 11) are currently receiving treatment for asthma.^[20] In the UK, of 1204 deaths from asthma in 2008, 29 were in children aged 14 years or under,^[20] and of 79 794 emergency hospital admissions for asthma in 2008–9, 30 740 were children aged 14 years or under; this equates to a child being admitted to hospital every 17 minutes.^[20] Omalizumab (Xolair[®], Novartis Pharmaceuticals UK) is a monoclonal antibody licensed as an add-on to existing therapy in patients aged 6–11 years with severe persistent allergic immunoglobulin E (IgE)-mediated asthma whose condition remains uncontrolled despite best standard care with high-dose inhaled corticosteroids (ICS) and an inhaled long-acting β_2 -agonist (LABA).

The scope for the appraisal specified by NICE was the clinical and cost effectiveness of omalizumab, within this licensed indication, compared with standard therapy without omalizumab. The manufacturer of omalizumab estimates that just over 300 children in the UK fall into the licensed indication of the drug.^[21]

2. The Independent Evidence Review Group (ERG) Review

The manufacturer provided a submission to NICE on the use of omalizumab as an add-on treatment for children with severe IgE-mediated allergic asthma (within the licensed indication). The ERG critically reviewed the evidence presented in the manufacturer's submission by (i) assessing whether the submission conformed to NICE methodological guidelines; (ii) assessing whether the manufacturer's interpretation and analysis of the evidence were appropriate; and (iii) indicating the presence of other evidence or alternative interpretations of the evidence. In addition, the ERG identified areas requiring clarification, for which the manufacturer provided additional evidence.^[3]

2.1 Clinical Evidence

The manufacturer submitted a systematic review of controlled studies of omalizumab in patients aged 6–11 years with allergic asthma. A pre-planned subgroup of children ($n=235$) who were receiving high-dose ICS and LABAs, from a single randomized controlled trial (RCT) comparing omalizumab plus standard therapy with standard therapy alone, met the inclusion criteria. This trial subgroup was referred to as the European Union Population from the Novartis IA-05 study (IA-05 EUP).^[21,22] Children included in the IA-05 trial population (total $n=628$) who did not receive the required concomitant medications were excluded from the effectiveness evaluation but were included in the drug safety evaluation. Two further trials were identified that did not meet the review's inclusion criteria, but provided additional data: one was conducted in children with stable asthma from

which data on adverse events were derived^[23] and the other was conducted in adults (INNOVATE; Investigation of Omalizumab in seVere Asthma TrEatment), from which data on hospitalization rates, emergency visits and quality of life were derived.^[24]

After a 52-week double-blinded trial period, the only outcome in the IA-05 EUP population to show a statistically significant benefit of omalizumab compared with placebo was the number of clinically significant (CS) exacerbations (relative risk [RR] 0.504; 95% CI 0.350, 0.725; $p<0.001$). A large proportion of the children in both the omalizumab (57%) and placebo (42%) arms did not experience an exacerbation during the trial. When the analyses were stratified by baseline exacerbation rate (≤ 2 vs ≥ 3 exacerbations in the year prior to randomization), there was a statistically significant decrease in the rate of exacerbations with omalizumab in children who had ≥ 3 exacerbations at baseline (RR 0.39; 95% CI 0.25, 0.59; $p<0.001$) but not in children with ≤ 2 exacerbations at baseline (RR 1.06; 95% CI 0.59, 1.90; $p=0.842$).

There were no statistically significant benefits of omalizumab compared with placebo in terms of the following: CS severe (CSS) exacerbations; the proportion of children experiencing symptom-free days and nights; hospitalization rates; accident and emergency (A&E) visits; unscheduled doctor visits; total emergency visits; ICS use; quality of life; or overall rate of adverse events. Change in oral corticosteroid (OCS) use was not assessed during the trial.

Limited evidence for the effect of omalizumab on OCS use was available from a survey of UK specialist paediatric respiratory centres conducted by the manufacturer.^[21] Of 18 children receiving maintenance OCS and omalizumab for at least 16 weeks, four (22%) stopped OCS treatment, and 14 (78%) reduced their OCS dose (absolute reduction 15.42 mg [mean reduction ranged from 22.96 to 6.54]).

2.1.1 Critique of the Evidence

The ERG concluded that there is very limited evidence for the clinical effectiveness of omalizumab in children aged between 6 and 11 years

eligible to receive omalizumab under its current licensed indication. The one RCT identified was generally well conducted and was considered to be of good quality.^[22] However, there were a number of factors that needed to be considered when interpreting the results of the IA-05 trial, outlined in the following paragraphs.

It was unclear whether a sample size calculation was undertaken for the pre-planned IA-05 EUP subgroup; analyses based on data from this subgroup may lack sufficient power to identify statistically significant differences between the omalizumab and placebo groups.

The definition of CS exacerbations was worsening of asthma symptoms requiring doubling of the baseline ICS dose and/or treatment with OCS for at least 3 days. This definition does not reflect that used to classify CS exacerbations in clinical practice. The definition used for CSS exacerbations (requiring treatment with OCS and a peak expiratory flow [PEF] or forced expiratory vol-

ume in 1 second [FEV₁] of <60% of personal best) was more representative of the definition for CS exacerbations used in clinical practice; no significant benefit of omalizumab on CSS exacerbations was demonstrated.

Two outcomes, the Paediatric Asthma Quality of Life Questionnaire (PAQLQ) and the Global Evaluation of Treatment Effectiveness (GETE), may have been subject to recall bias.

The method for imputing the number of exacerbations for patients who discontinued treatment may have resulted in an underestimation of the exacerbation rate in the follow-up year in the intention-to-treat analyses.

In addition, the manufacturer used data from two trials^[23,24] that did not meet the inclusion criteria to support the data from the IA-05 trial;^[22] the populations included in these trials were not comparable with that of the IA-05 trial or the population defined in the NICE scope (table I).

Table I. Comparison of the populations in the trials utilized by the manufacturer with the target population specified in the NICE scope

NICE scope: target population	IA-05 EUP ^[21,22]	INNOVATE ^[24]	Milgrom et al. ^[23]
Aged 6–11 years	✓	12–79 years	5–12 years
Severe persistent allergic asthma	✓	✓	Well controlled with ICS
Positive skin test/ <i>in vitro</i> reactivity to perennial aeroallergen	✓	✓	✓
Frequent daytime symptoms/night-time awakenings	✓	Not reported	Mean (median) asthma scores: Day OMA 0.52 (0) Day PL 0.57 (0) Night OMA 0.21 (0) Night PL 0.25 (0)
Multiple severe asthma exacerbations	23.4% had severe exacerbation in prior year 82.9% had exacerbation requiring OCS	16% had 1 or 0 severe exacerbations in prior 14 months	8% hospitalized prior year
Weight range 20–150 kg	Mean (SD) kg: 37.7 (13.4)	Mean (SD) kg: OMA 81.2 (19.8) PL 79.2 (17.5)	Mean (SD) kg: not reported Children must be <90 kg to be eligible
Total serum IgE at least 200 IU/mL and unequivocal <i>in vitro</i> reactivity [RAST]	31–1327 IU/mL	21–607 IU/mL	>30 to <1300 IU/mL
High-dose [$\geq 800 \mu\text{g/d}$] ICS [beclomethasone equivalent]	1000–3760 $\mu\text{g/d}$	900–8000 $\mu\text{g/d}$	168–672 $\mu\text{g/d}$
Long-acting inhaled β_2 -agonist	✓	✓	ICS to achieve control and rescue medication; other asthma medication prohibited
OMA as an add-on therapy	✓	✓	

ICS = inhaled corticosteroids; IgE = immunoglobulin E; OCS = oral corticosteroids; OMA = omalizumab; NICE = National Institute for Health and Clinical Excellence; PL = placebo; RAST = radioallergosorbent test; SD = standard deviation; ✓ indicates that variable is the same in the trial as for the target population specified in the NICE scope.

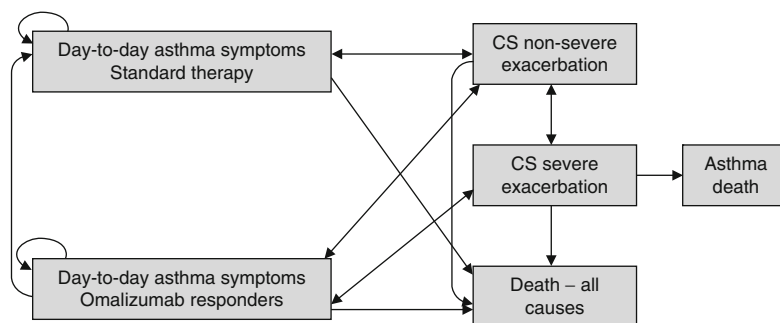


Fig. 1. Schematic of the economic model used in the manufacturer's submission. **CS** = clinically significant.

2.2 Cost-Effectiveness Evidence

The manufacturer's submission included a *de novo* economic evaluation of the cost effectiveness of omalizumab in children aged 6–11 years with severe persistent allergic asthma who remain inadequately controlled despite high-dose ICS plus a LABA. A Markov model was used in which omalizumab plus standard therapy was compared with standard therapy alone. The model contained six states including asthma-related death and death from other causes. The structure of the model is presented in figure 1.

Treatment effectiveness was based on a reduction in the rate of exacerbations for those who responded to treatment with omalizumab, and differing quality of life as a result of day-to-day symptoms for those aged 12 years and older. Movement between states was derived from the IA-05 EUP population.^[21] Data from a further three studies were also used in the economic evaluation: a database analysis provided mortality rates associated with CSS exacerbations;^[25] the INNOVATE trial of omalizumab in adults provided preference-based health-related quality-of-life (HR-QOL) data for day-to-day symptoms;^[24] and a prospective study conducted in asthma centres was included to establish the impact of asthma exacerbations on HR-QOL.^[26] Adverse events were not included in the model. Costs for drugs, treatment initiation and exacerbations were included and a discount rate of 3.5% per annum was applied to both costs and benefits. Detailed deterministic univariate and probabilistic sensitivity analyses were undertaken.

Briefly, the key assumptions used in the manufacturer's economic evaluation were as follows:

- The observed response rate to omalizumab therapy at 52 weeks in the trial was representative of that which would be observed in UK clinical practice where response rate to treatment is evaluated at 16 weeks.
- Treatment duration of omalizumab was 10 years, at which point patients return to standard care only.
- Exacerbation rates remain constant for the duration of the model at the level observed in the IA-05 EUP population.
- There was no HR-QOL difference for day-to-day symptoms between omalizumab with standard therapy and standard therapy only for patients aged 6–11 years; from 12 years of age onwards, responders to omalizumab receive a higher day-to-day HR-QOL based upon the results of the INNOVATE trial than those on standard therapy.^[24]
- HR-QOL decrements for CS (0.572) and CSS (0.326) exacerbations taken from a prospective study in adults using the EQ-5D conducted in four UK specialist asthma centres were applicable to children under 12 years of age.^[26]
- Exacerbations were assumed to last for an average of 17.1 days, based on data from the IA-05 EUP population.^[21]
- Omalizumab responders reverted to the exacerbation rates of those on standard therapy alone once they discontinued treatment.
- Adverse events do not differ across treatments.

The base-case results suggested a cost per QALY of £91 169, which was reduced to £65 911 for a subgroup of the IA-05 EUP population who had been recently hospitalized. Several of the scenarios considered in the one-way sensitivity analysis had a large impact on the incremental cost-effectiveness ratio (ICER), but none reduced it to below £56 350 per QALY. Results of the probabilistic sensitivity analysis showed that the probability of omalizumab plus standard therapy being cost effective at the generally accepted NICE threshold of £20 000–30 000 per QALY was 0%. However, the manufacturer presented a case that, despite this, the number of children with severe persistent allergic IgE-mediated asthma at step 5 of the British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN) guidelines^[27] who would be eligible to receive omalizumab would be so few that the budgetary impact of allowing the use of omalizumab in these children would be small and a recommendation for its use appropriate.

2.2.1 Critique of the Evidence

In general, the ERG considered the manufacturer's economic evaluation to be of satisfactory quality, using an appropriate Markov model structure and meeting the requirements of the NICE reference case. However, the ERG had concerns about some of the assumptions used in the model, and these are discussed below.

Quality of Life

The PAQLQ results for the IA-05 EUP population found no HR-QOL improvement for day-to-day symptoms with omalizumab relative to standard therapy.^[22] However, the INNOVATE trial (aged 12 years and over) had estimated an improvement in HR-QOL for omalizumab relative to standard therapy (0.779 vs 0.669). Therefore, the manufacturer used the HR-QOL for standard therapy from the INNOVATE trial (0.669) for all children under 12 years old, and the HR-QOL improvement observed for omalizumab responders relative to standard therapy from age 12 years onwards. The ERG was unclear whether it was reasonable not to consider two distinct health states in children under 12 years of

age, especially given the challenges of collecting HR-QOL data in children. The ERG noted that the manufacturer also used HR-QOL decrements for CS and CSS exacerbations from a study in adults for all children from age 6 years.^[26]

Response to Omalizumab

The ERG noted that in UK clinical practice and in the licensed indication continued treatment with omalizumab relies upon demonstrating a treatment response at 16 weeks, after which non-responders return to standard therapy alone. In the submitted model, treatment response was based on a GETE assessment at 52 weeks; the results were assumed to be the same as would be observed at 16 weeks. The ERG was uncertain whether this assumption could be considered reasonable. However, when responder rates were increased and decreased by 10% from the base-case rate of 74.2%, there was little impact on the ICER (+10%: £90 711; −10%: £91 770).

It was assumed non-responders had exacerbation rates equivalent to those receiving standard therapy alone; the ERG noted that the manufacturer did not undertake a comparison of omalizumab non-responders and those randomized to standard therapy. In addition, exacerbation rates for the model were derived from the absolute numbers of CS and CSS exacerbations in the IA-05 EUP population, rather than the Poisson regression rates used in the intention-to-treat clinical analysis; this was because omalizumab responders were analysed separately and the results of non-responders were discarded. The ERG had concerns whether using the data in this way biased the results of the model.

Mortality

No deaths occurred in either the IA-05^[22] or INNOVATE^[24] trials. The submitted model assumed that asthma-related death could only occur as a result of a CSS exacerbation; mortality rates following a CSS exacerbation were taken from an observational study (which appears to have been sponsored by the manufacturer)^[25] that did not appear to have been identified through a systematic review of the literature on asthma mortality. The ERG had concerns that the definition of asthma exacerbation for which

the mortality rate was estimated in the observational study did not match the definition of CSS as used in the IA-05 clinical trial.

Time Horizon

The model assumed that treatment with omalizumab would continue for 10 years, and the ERG expressed a concern that this was considerably longer than is likely to occur in clinical practice. In a one-way sensitivity analysis, shorter treatment durations were shown to increase the ICER.

2.3 Conclusions of the ERG Review

The ERG concluded that omalizumab appeared to reduce CS exacerbations, but that there was no clear evidence of improvement in daily symptoms, CSS exacerbations or hospitalization rates.^[3] Additional analysis of the main RCT on which the clinical evidence was based suggested that the reduction in CS exacerbations was primarily in children experiencing more frequent exacerbations at baseline. The ERG considered that omalizumab may be an efficacious alternative to OCS in children with more severe asthma who were not being optimally treated according to UK guidelines, but that this would need to be confirmed by conducting an OCS-sparing trial. The ERG's investigation of the submitted cost-effectiveness evidence revealed that the main driver of cost effectiveness was the reduction in asthma-related mortality associated with a reduction in CSS exacerbations. However, the absolute reduction in the number of exacerbations was low, as is asthma-related mortality in children, and so the absolute gain in QALYs associated with omalizumab therapy was therefore also low, while the additional cost of treatment is high. The cost per QALY gained with omalizumab was estimated to be above £30 000 even under the most favourable scenario analyses.

2.4 Key Methodological Issues

2.4.1 Clinical Effectiveness

The three main areas of uncertainty in terms of clinical effectiveness and drug safety were (i) the potential benefit of omalizumab on CSS exacerbations, emergency visits and hospitalization rates in the IA-05 EUP subgroup with three or more

exacerbations a year at baseline; (ii) the relative efficacy and safety of omalizumab compared with OCS in children at step 5 of the BTS/SIGN guidelines;^[27] and (iii) the longer-term safety of omalizumab in a paediatric population.

2.4.2 Cost Effectiveness

Seven main areas of uncertainty in terms of the cost effectiveness of omalizumab were identified as:

- the appropriateness of the use of a GETE assessment at 52 weeks as a proxy for response at 16 weeks;
- the comparability of omalizumab non-responders and those receiving standard therapy;
- the potential change in exacerbation rates over time given that the paediatric population would undergo adolescence within the modelled time horizon, during which the severity of their asthma symptoms and exacerbation rates could be expected to alter;
- whether the data for post-hospitalization death by age group in an acute severe asthma UK population were suitable for informing the risk of death following CSS exacerbations;
- whether the application of a single average cost of CS and CSS exacerbations to both types of exacerbations in the model was appropriate;
- the use of HR-QOL decrements for exacerbations based on a study in an adult population for describing the impact on children;
- the potential cost effectiveness of omalizumab in a subgroup of children with more severe asthma symptoms.

3. The National Institute for Health and Clinical Excellence (NICE) Appraisal Committee: Consideration of All Available Evidence

The NICE Appraisal Committee considered the evidence presented in the manufacturer's submission and ERG report and from a range of additional sources, including: clinical experts; related health professionals; representatives from patient, professional and specialist groups; and health economists. Representatives of the manufacturer were also in attendance at the Committee

meeting in order to provide further detail in response to any queries on the analysis they had undertaken. The main aims of the NICE Appraisal Committee were to consider whether:

- all relevant evidence had been taken into account;
- the summaries of clinical and cost effectiveness were reasonable interpretations of the evidence;
- recommending omalizumab would be an effective use of NHS resources;
- the provisional recommendations were sound and a suitable basis for guidance to the NHS;
- any aspects of the recommendations needed particular consideration to ensure unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief was avoided.^[28]

The main areas discussed by the Committee and recorded in the ACD^[29] along with the recommendations of the Committee are summarized in the following sections.

3.1 How the Evidence Related to the NHS in England and Wales

The evidence presented to the Appraisal Committee indicated that the management of asthma in the NHS used a stepped treatment approach as recommended in the BTS/SIGN guidelines, with drugs added or withdrawn depending on symptoms and control.^[27] The current licensed indication for omalizumab would apply to children at steps 4 and 5 of the BTS/SIGN guidelines.^[27] However, both the clinical experts and the manufacturer's submission indicated that in clinical practice the population for whom omalizumab would be most appropriate would be children at step 5 of the BTS/SIGN guidelines. This represents a more narrowly defined population than the marketing authorization, the target population in the NICE scope and the IA-05 EUP population. The IA-05 EUP population included a proportion of children at step 4 of the BTS/SIGN guidelines, but approximately 60% of the children had a high exacerbation rate at baseline (three or more exacerbations in the year prior to randomization) and it was suggested that these children may corresponded more closely with step 5 of the BTS/SIGN guidelines.

3.2 The Impact of Severe Persistent Allergic Asthma on Children and Their Carers

The potential impacts of severe allergic asthma on children, particularly attendance at A&E departments, emergency GP visits, potentially reduced attendance at school, limited social life and inability to undertake exercise, were highlighted. Several consultees raised the issues of the impact of severe asthma on a child's education, career prospects and social life, and the potential benefit of omalizumab on these outcomes. The wider impacts on a child's family were identified as anxiety, sleep deprivation, and emotional and financial pressures; however, no evidence was presented to support the existence or magnitude of these impacts. In addition, the Committee acknowledged how long-term OCS use can impact upon a child, potentially predisposing a child to osteoporotic fractures and inhibiting growth.

In the *Guide to the Methods of Technology Appraisal* produced by NICE in 2004,^[30] the primary cost-effectiveness evaluation (reference case) had to be from an NHS and personal social services perspective; costs to social and economic budgets outside of the health sector are generally not considered within the reference case.^[30,31] There is some debate over the most appropriate perspective for cost-effectiveness assessments of treatments provided by health systems. Some health technology assessment (HTA) organizations (German Agency for Health Technology Assessment, the Dental and Pharmaceutical Benefits Agency [Tandvårds-och läkemedelsförmånsverket; TLV] in Sweden, Canadian Agency for Drugs and Technologies in Health and the Health Insurance Review Agency [Korea]) use a wider societal perspective during technology appraisals, but there is no consensus across HTA organizations.^[32] The use of a wider societal perspective allows benefits outside of the healthcare system to be considered; therefore, a technology that is not cost effective from the perspective of the healthcare system may not be rejected if it offers significant benefits to other public and private sectors.^[31] In 2008, the NICE *Guide to the Methods of Technology Appraisal* was updated and non-reference-case analyses could be considered in the Appraisal Committee's

deliberative process, if identified during the scoping process, were agreed with the Department of Health and were detailed in the final scope for the technology appraisal.^[1] Some of the wider benefits suggested for omalizumab, such as impacts on education and the HR-QOL of carers, lie outside the bounds of the benefits that would be routinely included in a NICE reference-case analysis. However, these were not identified at the scoping stage. In the case of omalizumab, the submitted cost-effectiveness evidence and the Committee's considerations were based on the NICE reference case.

3.3 Clinical Effectiveness

The overall conclusion of the Committee regarding the clinical effectiveness of omalizumab was that omalizumab, as an add-on to optimized standard therapy, was more clinically effective than optimized standard therapy alone in terms of reducing exacerbations for children with severe persistent allergic asthma who have experienced three or more CS exacerbations in the previous year. However, the Committee concluded that there was currently insufficient evidence to support a beneficial impact of omalizumab in those with less severe asthma or on CSS exacerbations, hospitalization rates, A&E visits, symptom-free days and nights, or HR-QOL regardless of asthma severity.

3.4 Cost Effectiveness

The Committee considered both the economic model provided in the manufacturer's submission and the additional exploratory sensitivity analyses performed by the ERG. The Committee discussed the key factors determining the cost effectiveness of omalizumab (response to treatment, treatment duration, asthma-related mortality risk from CSS exacerbations and the estimation of omalizumab drug costs) in the IA-05 EUP population and the defined 'hospitalization' subgroup. They also considered what the most plausible ICER for omalizumab compared with standard therapy would be in the primary target population being treated in the NHS in England and Wales.^[28]

3.4.1 Treatment Duration

The clinical experts advised the Appraisal Committee that a 5-year treatment duration might be more representative of UK clinical practice. Reducing the treatment duration in the economic model substantially increased the ICER. The Committee considered that the 10-year treatment duration utilized in the model was not representative of UK clinical practice and that this had caused the ICER to be underestimated.

3.4.2 Treatment Response

The Committee heard that the decision to stop or continue treatment after 16 weeks is based on indicators of treatment response such as daily symptoms, quality-of-life assessment, frequency of exacerbations, spirometric and PEF measurements, and the number of unplanned consultations for asthma; clinical experts confirmed that there was no standardization as to the magnitude of improvement required to define an adequate response to omalizumab. The main discussion point was whether a GETE assessment at 52 weeks was an appropriate proxy for treatment response at 16 weeks. No evidence was presented to support this assumption, which resulted in uncertainty of the ICERs in the manufacturer's model. The Committee considered that the use of exacerbations from responders only and the exclusion of data from non-responders in informing the manufacturer's model were reasonable, although a comparison of characteristics between non-responders and children receiving standard therapy would have been useful.

3.4.3 Asthma-Related Mortality

The manufacturer's base-case analysis incorporated annual mortality rates of 0.097% for children aged under 12 years, 0.319% for people aged 12–16 years, 0.383% for people aged 17–44 years and 2.478% for people aged older than 44 years. An exploratory analysis conducted by the ERG showed that, by applying the adult mortality rates that had been used in the previous assessment of omalizumab in adults (TA133^[33]) to all patients aged 12 years and above in the manufacturer's 'hospitalization' subgroup, the ICER would decrease to £31 700 and £34 000 per

QALY gained for mortality rates of 3.109% and 2.478%, respectively. However, the Committee heard that asthma-related mortality in children is rare. It was also considered that the mortality rates used in the manufacturer's model derived from the study by Watson et al.^[25] may have been overestimated due to the inclusion of deaths due to viral illness and wheezes misclassified as asthma. Given the evidence, the Committee concluded that assuming such a high rate of mortality that would be required to reduce the ICER to the £30 000 threshold would be unrealistic and inappropriate.

3.4.4 Omalizumab Costs

The manufacturer's model assumed that the dose of omalizumab would not change over time for a given patient. However, dosing of omalizumab is weight based (in combination with baseline IgE) and so it was considered that this assumption may be unrealistic in a paediatric population, and the true costs of treatment may be underestimated. The prescribed dose of omalizumab can range from 75 mg to 600 mg; omalizumab is currently available in single-use vials containing 150 mg of omalizumab powder. Unless centres have more than one patient attending for treatment, partially unused vials must be discarded. The base case in the manufacturer's model used the actual cost of omalizumab administered, and therefore presumed the ability to share vials between patients without wastage. When the cost per vial was used (unused omalizumab was wasted) in a sensitivity analysis, the ICER rose to £105 480 per QALY. The manufacturer asserted that the introduction of pre-filled syringes containing 75 mg or 150 mg omalizumab is planned, which has the potential for reducing wastage in centres that do not have the capability to vial share.

3.4.5 Plausibility of the Incremental Cost-Effectiveness Ratios Presented

After discussing the appropriateness of the main assumptions and impacts of the main drivers on the estimates of cost effectiveness, the most plausible ICER for omalizumab compared with standard therapy was considered. The Com-

mittee concluded that due to optimistic assumptions regarding the treatment duration and the non-varying treatment cost of omalizumab over time meant that the most plausible ICERs would be higher than the base-case estimates of £91 200 and £65 900 for the IA-05 EUP population and the 'hospitalization' subgroup, respectively.

3.5 Budgetary Impact

The Appraisal Committee acknowledged that the small number of children who would be eligible for treatment with omalizumab would mean a low budget impact of the treatment; however, the Committee referred to the NICE *Guide to the Methods of Technology Appraisal*,^[1] which states, "the potential budget impact of the adoption of a new technology does not determine the Appraisal Committee's decision."

3.6 Equalities Considerations

The Committee heard that adherence to asthma treatment in children may be affected by socioeconomic or cultural reasons or through the lack of understanding of carers. However, these factors were thought to apply equally to all treatment options. Omalizumab had previously been recommended by NICE for use in adults (aged 12 years and older). However, the asthma-related mortality rate in adults is much higher than in children, which means that omalizumab is more cost effective in adults due to a greater impact on mortality.

3.7 The Appraisal Committee's Recommendations

The NICE Appraisal Committee did not recommend omalizumab for the treatment of severe persistent allergic asthma in children aged 6–11 years.^[28] The key driver for the decision was stated as being that the most plausible ICER, even in a high-risk subgroup, was at least £65 900 per QALY. Such an ICER is substantially higher than those normally considered to be an acceptable use of NHS resources.^[28] The response to the preliminary guidance summarized in the ACD^[29] was considered during a second meeting

in which the Committee produced an FAD. The FAD forms the basis of the NICE guidance for the use of omalizumab in the NHS in England and Wales.^[28]

4. NICE Guidance

The Committee considered that the responses to the preliminary guidance did not contain any evidence that would alter the preliminary conclusions. The FAD^[28] states that,

“Omalizumab is not recommended for the treatment of severe persistent allergic asthma in children aged 6–11 years. Children currently receiving omalizumab for the treatment of severe persistent allergic asthma should have the option to continue treatment until it is considered appropriate to stop. This decision should be made jointly by the clinician and the child and/or the child’s parents or carers.”

5. Interpretation of the Guidance

The Appraisal Committee rejected the manufacturer’s position that only a small number of children in this age group would be eligible for treatment, and therefore the budgetary impact would be low. They stated that their judgement was based on cost effectiveness, not the prevalence of the condition as stated in the NICE *Guide to the Methods of Technology Appraisal*.^[1] The Scottish Medicines Consortium approved the use of omalizumab in these children in NHS Scotland in March 2010.^[20,34]

When NICE chooses not to recommend a technology, generally the NHS providers have no obligation to make the technology available.^[35] Both the Royal College of Paediatrics and Child Health^[36] and the Primary Care Respiratory Society^[37] had requested that the drug should be available on a ‘named-patient’ basis, which allows doctors to prescribe medications that are not licensed in the UK to patients in whom they are considered to be the most appropriate option, and where alternative treatments have been unsuccessful.^[38] It also covers the prescription of a treatment on the NHS that is considered to be

‘low priority’.^[39] However, omalizumab does not fall into either of these categories.

NICE’s negative recommendation does not preclude the use of omalizumab in the NHS in England and Wales.^[40] In fact, a large proportion of drugs prescribed to children on the NHS are used off licence/off label (for example, the drug has a licence in a different age group or at a different dose), without the patients having to be named as per the named-patient policy.^[41] It therefore remains unclear how the decision by NICE not to recommend omalizumab for children aged 6–11 years will impact on the availability of the treatment to these children. It may be the case that children with the same severity of illness are able to receive the drug in some primary care trusts in England and Wales but not others.

This project highlighted some of the potential inconsistencies that can arise when the STA process is applied to a subset of the eligible population, in this case one covered by a license extension. A key finding during this appraisal was the relationship between the mortality associated with CS exacerbations and the patient’s age, and the impact this had on the assessment of cost effectiveness. However, it was noted that this relationship had not been explored fully in the previous appraisal of omalizumab that considered the original licensed population of patients aged 12 years and older. The analysis for that appraisal focused on those represented in the key clinical trial that had a mean age of 45 years; the implications of providing omalizumab to patients as young as 12 years old were not specifically addressed. Despite identifying this, the appraisal of the use of omalizumab in patients aged 6–11 years could not be used to determine guidance in patients aged 12 years and above due to restrictions within the NICE process. As part of the NICE process to review recommendations, it was noted that the adult and children populations should be considered jointly on the basis of a single, common technology appraisal (which is now scheduled^[42]). This review is deemed to be necessary not because of the emergence of new evidence but due to the potential inconsistency and equality issues that arose from appraising the two age groups sepa-

rately. It is possible, therefore, that reviewing the entire relevant patient population initially rather than undertaking an appraisal solely of the license extension could have been a more efficient use of NICE resources.

Acknowledgements

This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (project number 09/98/01) and will be published as part of a compendium of ERG articles in *Health Technology Assessment*. See the HTA programme website (<http://www.hta.ac.uk>) for further project information. This summary of the ERG report was compiled after the Appraisal Committee's review and incorporates additional information and comment from the authors on the STA process and iterations of the NICE guidance not covered by the HTA report. This summary has not been externally peer reviewed by *PharmacoEconomics*.

The views and opinions expressed herein are those of the authors and do not necessarily reflect those of NICE or the Department of Health. The authors have no conflicts of interest that are directly relevant to the content of this summary. They would like to thank Jonathan Minton for his assistance during the production of the ERG report.

This work is Crown copyright (UK).

Author contributions:

Jane Burch: Researcher responsible for reviewing the clinical evidence submitted, and the writing of the manuscript.

Susan Griffin: Researcher responsible for reviewing the cost-effectiveness evidence submitted and provided comments on drafts of the manuscript.

Claire McKenna: Contributed to the review of cost-effectiveness evidence and provided comments on drafts of the manuscript.

Simon Walker: Contributed to the review of cost-effectiveness evidence and provided comments on drafts of the manuscript.

James Paton: Provided clinical advice throughout the project and comments on drafts of the manuscript.

Kath Wright: Reviewed the search strategies, conducted additional searches, and provided comments on drafts of the manuscript.

Nerys Woolcott: Took overall managerial responsibility for the project, contributed to all aspects of the review of the evidence submitted, and provided comments on drafts of the manuscript.

References

1. National Institute for Health and Clinical Excellence. Guide to the methods of technology appraisal. London: NICE, 2008
2. National Institute for Health and Clinical Excellence. Guide to the single technology appraisal (STA) process. London: NICE, 2006
3. Walker S, Burch J, McKenna C, et al. Omalizumab for the treatment of severe persistent asthma in children aged 6 to 11 years. London: NICE, 2010
4. Sculpher M. Single technology appraisal at the UK National Institute for Health and Clinical Excellence: a source of evidence and analysis for decision making internationally. *PharmacoEconomics* 2010; 28 (5): 347-9
5. Rodgers M, Griffin S, Paulden M, et al. Alitretinoin for severe chronic hand eczema: a NICE single technology appraisal. *PharmacoEconomics* 2010; 28 (5): 351-62
6. Bagust A, Greenhalgh J, Boland A, et al. Cetuximab for recurrent and/or metastatic squamous cell carcinoma of the head and neck: a NICE single technology appraisal. *PharmacoEconomics* 2010; 28 (6): 439-48
7. Stevenson M, Pandor A. Febuxostat for the management of hyperuricaemia in patients with gout: a NICE single technology appraisal. *PharmacoEconomics* 2011; 29 (2): 133-40
8. Scotland G, Waugh N, Royle P, et al. Denosumab for the prevention of osteoporotic fractures in post-menopausal women: a NICE single technology appraisal. *PharmacoEconomics* 2011; 29 (11): 951-61
9. Dickson R, Bagust A, Boland A, et al. Erlotinib monotherapy for the maintenance treatment of non-small cell lung cancer after previous platinum-containing chemotherapy: a NICE single technology appraisal. *PharmacoEconomics* 2011; 29 (12): 1051-62
10. McKenna C, Maund E, Sarowar M, et al. Dronedarone for the treatment of atrial fibrillation: a NICE single technology appraisal. *PharmacoEconomics* 2012; 30 (1): 35-46
11. Holmes M, Carroll C, Papaioannou D. Dabigatran etexilate for the prevention of venous thromboembolism in patients undergoing elective hip and knee surgery: a NICE single technology appraisal. *PharmacoEconomics* 2012; 30 (2): 137-46
12. Yang H, Craig D, Epstein D, et al. Golimumab for the treatment of psoriatic arthritis: a NICE single technology appraisal. *PharmacoEconomics* 2012; 30 (4): 257-70
13. Boyers D, Jia X, Jenkinson D, et al. Eltrombopag for the treatment of chronic immune or idiopathic thrombocytopenic purpura: a NICE single technology appraisal. *PharmacoEconomics* 2012; 30 (6): 483-95
14. Whyte S, Pandor A, Stevenson M. Bevacizumab for metastatic colorectal cancer: a NICE single technology appraisal. *PharmacoEconomics*. In press
15. Kilonzo M, Hislop J, Elders A. Pazopanib for the first-line treatment of patients with advanced and/or metastatic renal cell carcinoma: a NICE single technology appraisal. *PharmacoEconomics*. In press
16. Craig D, Rice S, Paton F, et al. Retigabine for the adjunctive treatment of adults with partial onset seizures in epilepsy with and without secondary generalization: a NICE single technology appraisal. *PharmacoEconomics*. In press
17. Simpson EL, Fitzgerald P, Evans P, et al. Bivalirudin for the treatment of ST-segment elevation myocardial infarction: a NICE single technology appraisal. *PharmacoEconomics*. In press
18. Armstrong N, Manuela J, van Asselt T, et al. Golimumab for the treatment of ankylosing spondylitis: a NICE single technology appraisal. *PharmacoEconomics*. In press
19. National Institute for Health and Clinical Excellence. Omalizumab for the treatment of severe persistent allergic asthma in children aged 6 to 11 years [NICE technology appraisal guidance no. TA201]. London: NICE, 2010

- [online]. Available from URL: <http://publications.nice.org.uk/omalizumab-for-the-treatment-of-severe-persistent-allergic-asthma-in-children-aged-6-to-11-years-ta201> [Accessed 2012 Aug 13]
20. Asthma UK. Facts for journalists [online]. Available from URL: http://www.asthma.org.uk/news_media/media_resources/for_journalists_key.html [Accessed 2010 Sept 16]
 21. Novartis Pharmaceuticals UK Ltd. Single technology appraisal (STA) manufacturer submission of evidence: Xolair® (omalizumab) for severe persistent allergic asthma in children aged 6-12 years. London: NICE, 2009
 22. Lanier B, Bridges T, Kulus M, et al. Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma. *J Allergy Clin Immunol* 2009; 124 (6): 1210-6
 23. Milgrom H, Berger W, Nayak A, et al. Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). *Pediatrics* 2001; 108 (2): E36
 24. Humbert M, Beasley R, Ayres J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy* 2005; 60 (3): 309-16
 25. Watson L, Turk F, James P, et al. Factors associated with mortality after an asthma admission: a national United Kingdom database analysis. *Respir Med* 2007; 101: 1659-64
 26. Lloyd A, Price D, Brown R. The impact of asthma exacerbations on health-related quality of life in moderate to severe asthma patients in the UK. *Prim Care Resp J* 2007; 16 (1): 22-7
 27. Scottish Intercollegiate Guidelines Network, British Thoracic Society. British guideline on the management of asthma: a national clinical guideline. Edinburgh: SIGN, 2009
 28. National Institute for Health and Clinical Excellence. Final appraisal determination: omalizumab for the treatment of severe persistent allergic asthma in children aged 6 to 11 years. London: NICE, 2010 Aug [online]. Available from URL: <http://www.nice.org.uk/nicemedia/live/12266/50295/50295.pdf> [Accessed 2010 Sep 15]
 29. National Institute for Health and Clinical Excellence. Asthma (in children): omalizumab. Appraisal consultation document (ACD). London: NICE, 2010 [online]. Available from URL: <http://guidance.nice.org.uk/TA/Wave22/9/Consultation/DraftNICEGuidance> [Accessed 2012 Aug 13]
 30. National Institute for Health and Clinical Excellence. Guide to the methods of technology appraisal. London: NICE, 2004
 31. Claxton K, Walker S, Palmer S, et al. Appropriate perspectives for health care decisions. York: Centre for Health Economics, 2010
 32. Neumann PJ, Drummond M, Jonsson B, et al. Are key principles for improved health technology assessment supported and used by health technology assessment organizations? *Int J Technol Assess Health Care* 2010; 26 (1): 71-8
 33. National Institute for Health and Clinical Excellence. Omalizumab for severe persistent allergic asthma [NICE technology appraisal guidance no. TA133]. London: NICE, 2007
 34. Scottish Medicines Consortium. Omalizumab 150 mg powder and solvent for injection (Xolair®) [online]. Available from URL: http://www.scottishmedicines.org.uk/SMC_Advice/Advice/Omalizumab_Xolair_omalizumab_150mg_powder_and_solvent_for_injection_Xolair_1 [Accessed 2010 Sep 15]
 35. NHS. NHS Constitution [online]. Available from URL: <http://www.nhs.uk/choiceintheNHS/Rightsandpledges/NHSConstitution/Pages/Overview.aspx> [Accessed 2010 Sep 30]
 36. Royal College of Paediatrics and Child Health. NICE omalizumab for the treatment of severe persistent allergic asthma in children aged 6 to 11 years: appraisal consultation document (ACD) – Royal College of Paediatrics and Child Health response [online]. Available from URL: <http://www.nice.org.uk/nicemedia/live/12266/50304/50304.pdf> [Accessed 2010 Sep 15]
 37. Primary Care Respiratory Society UK. Appraisal consultation document: omalizumab for the treatment of severe persistent allergic asthma in children aged 6 to 11 years – comments from Primary Care Respiratory Society UK. 2010 [online]. Available from URL: <http://www.nice.org.uk/nicemedia/live/12266/50302/50302.pdf> [Accessed 2010 Sep 15]
 38. Andrews S. Named patient medicines: a pharmacist's perspective. *Oncology News* 2006; 1 (3): 10-11 [online]. Available from URL: http://www.oncologynews.biz/pdf/oct_nov/ON_ON06_08.pdf [Accessed 2010 Sep 28]
 39. Herefordshire NHS Primary Care Trust. Policy on individual funding requests. 2009 Jun [online]. Available from URL: http://www.herefordshire.nhs.uk/docs/publications/hpct_ifr_policy_june_2009_-_final.pdf [Accessed 2010 Sep 28]
 40. National Institute for Health and Clinical Excellence. Omalizumab for the treatment of severe persistent allergic asthma in children aged 6-11: response to consultee, commentator and public comments on the appraisal consultation document (ACD). London: NICE, 2010
 41. Conroy S, Choonara I, Impicciatore P, et al. Survey of unlicensed and off label drug use in paediatric wards in European countries. *BMJ* 2000; 320: 79-82
 42. National Institute for Health and Clinical Excellence. Consideration of consultation responses on review proposal: review of TA133 – omalizumab for severe persistent allergic asthma. London: NICE, 2010 [online]. Available from URL: <http://www.nice.org.uk/nicemedia/live/11894/51714/51714.pdf> [Accessed 2012 Aug 13]

Correspondence: Dr Jane Burch, Centre for Reviews and Dissemination (CRD), University of York, Heslington, York YO10 5DD, UK.
E-mail: jane.burch@york.ac.uk

Copyright of PharmacoEconomics is the property of ADIS International Limited and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.