NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA278; Omalizumab for the treatment of severe persistent allergic asthma

This guidance was issued in April 2013.

The review date for this guidance is March 2016.

1. Recommendation

The guidance should be transferred to the 'static guidance list'. That we consult on this proposal.

2. Original remit(s)

To appraise the clinical and cost effectiveness of omalizumab within its licensed indications for the treatment of severe persistent allergic asthma.

3. Current guidance

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

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

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

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

4. Rationale[1]

Follow-up data from the INNOVATE study originally included in the appraisal, an additional study observing omalizumab add-on therapy and 3 systematic reviews

[1] A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

have been published. These additional data are not inconsistent with the results used for the appraisal and would not be expected to change the decision.

5. Implications for other guidance producing programmes

There is no proposed or ongoing guidance development that overlaps with this review proposal.

6. New evidence

The search strategy from the original Evidence Review Group report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from September 2011 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

7. Summary of evidence and implications for review

The marketing authorisation for omalizumab at the time of developing technology appraisal 278 was as add-on therapy to improve control of asthma in adults and adolescents 12 years and over (hereafter referred to as adults and adolescents) and children aged 6 to 11 years (hereafter referred to as children) with severe persistent allergic asthma who have:

- a positive skin test or in vitro reactivity to a perennial aeroallergen
- reduced lung function (forced expiratory volume at 1 second [FEV1] less than 80% (in adults and adolescents)
- frequent daytime symptoms or night-time awakenings
- multiple documented severe exacerbations despite daily high-dose inhaled corticosteroids plus a long-acting inhaled beta2 agonist.

The marketing authorisation also stated that omalizumab treatment 'should only be considered for patients with convincing IgE (immunoglobulin E) mediated asthma'. The marketing authorisation is currently the same and the company has confirmed there are no planned extensions to the licence.

Since the development of technology appraisal 278 (a review of technology appraisals 202 and 133) no potential comparators have received a marketing authorisation as an add-on treatment to standard asthma therapy for treating severe persistent allergic asthma.

The literature search identified 5 relevant references, since the development of technology appraisal 278. Three of the studies were systematic reviews including adults, young people and children (Hwa O. S. et al., 2014, Normansell R. et al., 2014 and Neffen H., 2015). The systematic reviews concluded that omalizumab was effective in reducing asthma exacerbations and had an acceptable safety profile. One of the studies was observing omalizumab as an add-on therapy to high-dose

inhaled corticosteroids and long-acting beta(2)-agonists in patients aged 12 to 75 years. It concluded that omalizumab significantly reduced the rate of clinically significant asthma exacerbations, severe exacerbations and emergency visits (Zakaria M. et al., 2013). The final study was a follow-up to the INNOVATE trial observing patients from week 28 onwards (Bousquet J., 2014). The study concluded that a significant improvement in the rate of clinically significant and severe exacerbations was evident among responders to omalizumab add-on therapy compared with placebo. The Committee had no specific uncertainties during the technology appraisal 278 other than noting that the population in the INNOVATE trial were less severe than those treated in the UK. The populations in the studies were no more severe than in the INNOVATE trial and therefore cannot provide data on whether this patient group would have a greater response to omalizumab, as the Committee had concluded was likely to happen.

The clinical effectiveness evidence identified from the literature searches, registered trials and current list prices of the technologies do not suggest the recommendations of technology appraisal 278 need reviewing.

The current list price for omalizumab has not altered since the development of technology appraisal 278 and the company has indicated that it intends to continue the current patient access scheme for omalizumab.

Based on the above information, it is proposed that technology appraisal guidance 278 is transferred to the 'static guidance list'.

8. Adoption and Impact

No submission was received from the Adoption and Impact team.

9. Equality issues

During the draft scope consultation consultees noted that people from certain ethnic groups are not accessing health care support as much as other ethnic groups and that people from rural locations may not have equal access to treatment. Both of these potential equality issues related to service configuration or implementation of health care and cannot be addressed in a Technology Appraisal.

It was also raised that overweight people are not included in dosing table in the SPC. This issue cannot be addressed by Appraisal Committee as it can only appraise a technology within the marketing authorisation.

GE paper sign off: Melinda Goodall, Associate Director. 9th February 2016

Contributors to this paper:

Information Specialist:	Tom Hudson
Technical Lead:	Caroline Hall
Project Manager:	Andrew Kenyon

Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	**Consequence**	**Selected – 'Yes/No'**
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the [specify STA or MTA] process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline.	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

i. The technology falls within the scope of a clinical guideline (or public health guidance)

ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement

iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;

- Spending on a treatment for the indication which was the subject of the appraisal continues to rise
- There is evidence of unjustified variation across the country in access to a treatment
- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed

- The treatment is excluded from the Payment by Results tariff

v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

Asthma (2013) NICE quality standard QS25.

Bronchial thermoplasty for severe asthma (2012) NICE interventional procedure guidance 419.

In progress

Asthma management. NICE guideline. Publication expected: June 2017.

Asthma - diagnosis and monitoring. NICE guideline. Publication expected: TBC.

Mepolizumab for treating severe eosinophilic asthma. NICE technology appraisal. Publication expected: July 2016.

Details of changes to the indications of the technology

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
Add-on therapy to improve control of asthma in adults and adolescents 12 years and over and children aged 6 to 11 years with severe persistent allergic asthma who have: • a positive skin test or in vitro reactivity to a perennial aeroallergen • reduced lung function (forced expiratory volume at 1 second [FEV_1] less than 80% in adults and adolescents) • frequent daytime symptoms or night-time awakenings • multiple documented severe exacerbations despite daily high-dose inhaled corticosteroids plus a long-acting inhaled $beta_2$ agonist. Omalizumab treatment should only be considered for patients with convincing IgE (immunoglobulin E) mediated asthma. The list price of omalizumab stated in the original appraisal was £256.15 for a 150-mg vial and £128.07 for a 75-mg vial (excluding VAT; 'British national formulary' [BNF] edition 63).	The indication for the appraisal remains unchanged. The list price for omalizumab remains unchanged (Chemist + Druggist Data, accessed 11/1/2016); however note that the current NICE recommendation for omalizumab is conditional on a discount agreed as part of a patient access scheme.

Details of new products

Drug (company)	Details (phase of development, expected launch date)	In topic selection
Budesonide (Vectura) New formulation based on a novel inhalation system.	Phase II as add-on therapy in oral corticosteroid-dependent asthma. EU regulatory filings anticipated in 2017.	N
Dupilumab (Sanofi)	Phase III as add-on therapy for moderate-to-severe asthma. UK launch estimated around 2019.	N
Interferon beta-1a aerosol (AstraZeneca)	Phase III for the treatment of asthma exacerbations associated with common cold virus infections. UK launch estimated around 2019.	Y
Lebrikizumab (Genentech)	Phase III for asthma which is uncontrolled on high-dose inhaled corticosteroids, in adolescents. UK launch estimated around 2017.	Y
Masitinib (AB Science)	Phase III for severe persistent oral corticosteroid-dependent. UK launch estimated around 2018.	Y
Mepolizumab (GlaxoSmithKline)	Approved in the EU for asthma with airway eosinophilia: oral corticosteroid-dependent or with a history of exacerbations.	In appraisal
Reslizumab (Teva)	Filings made in the EU for allergic eosinophilic asthma which remains uncontrolled on high-dose inhaled corticosteroids	Y

Tralokinumab (AstraZeneca)	Phase III for oral corticosteroid-dependent asthma. UK launch estimated around 2019.	N

Registered and unpublished trials

Trial name and registration number	Details
Study to Evaluate the Effect of Omalizumab on Improving the Tolerability of Specific Immunotherapy in Patients With Persistent Allergic Asthma NCT00267202; CIGE025AUS23	Placebo-controlled RCT N = 275 Completed ~2008 Results available in clinicaltrials.gov
Safety and Efficacy Study of Omalizumab to Treat Allergic Asthma NCT01976208; AA007	Placebo-controlled RCT in Chinese population N = 630 Completed ~ 2015
Efficacy of Omalizumab in Adults (18-60 Years of Age) With Moderate-Severe, Persistent Allergic Asthma, Despite Receiving Inhaled Corticosteroids and Long Acting Beta-agonists NCT00670930; CIGE025A2432, Eudra-CT 2007-004653-29	Placebo-controlled RCT N = 36 Completed ~ 2011 Results in clinicaltrials.gov
Study of the Prednisone Sparing Effect of Xolair (Omalizumab) in Patients With Prednisone-dependent Asthma With Eosinophilic Bronchitis NCT02049294; RP 14-008	Placebo-controlled RCT N = 24 Currently recruiting Estimated completion date: March 2016
Study to Assess the Efficacy and Safety of Omalizumab Treatment on ICS Reduction for Severe IgE-mediated Asthma NCT01912872; CIGE025AMX02	RCT N = 138 Currently recruiting Estimated completion date: June 2016

Trial name and registration number	Details
Effect of Xolair on Airway Hyperresponsiveness NCT00208234	Placebo-controlled RCT N = 22 Recruitment status unknown Estimated completion date: September 2011
The Effect of Xolair (Omalizumab) on Allergy Blood Cells NCT00657891; IgE 025 US22	Placebo-controlled RCT N = 49 Completed ~2009
Non-invasive Ways to Evaluate Lung Disease After Treatment With Xolair NCT00139152; Xolair ENO EBC Study	Placebo-controlled study with exhaled nitric oxide and leukotriene levels as primary endpoints N = 65 Completed ~2009
Omalizumab in non-atopic asthma ISRCTN90016959; NCT01113437; XONAA	Placebo-controlled RCT N = 40 Estimated completion date: 2012

Relevant services covered by NHS England specialised commissioning

Omalizumab treatment is commissioned by NHS England as part of its commissioning of specialist respiratory and allergy services for children and adults (see: Manual for Prescribed Specialised Services, 2013/2014)

References

Zakaria M, Abu-Hussein S, Abu-Hussein A et al. (2013) The effect of omalizumab in treatment of inadequate controlled severe persistent asthma patient. *Chest* 144 (4 MEETING ABSTRACT).

Bousquet J, Humbert M, Rao S et al. (2014) Omalizumab reduces asthma exacerbations among responders at 28 weeks: The INNOVATE study. *Allergy: European Journal of Allergy and Clinical Immunology* 69: 519-.

Hwa OS, Bousquet J, Balwin M et al. (2014) Systematic review of observational studies and RCTS of omalizumab in severe persistent allergic asthma and meta-analysis feasibility assessment. *Value in health* 17 (7): A589-.

Normansell R, Walker S, Milan SJ et al. (2014) Omalizumab for asthma in adults and children. *Cochrane Database of Systematic Reviews* (1).

Neffen H (2015) Systematic review on the use of omalizumab for the treatment of asthmatic children and adolescents Rodrigo G.J. *Pediatric Allergy and Immunology* 26 (6): 551-556.