

# Omalizumab

Concise evaluated information to support the managed entry of new medicines in the NHS

## Summary

- ◆ Omalizumab is a recombinant humanised monoclonal antibody that selectively binds to human immunoglobulin E (IgE).
- ◆ This novel treatment is licensed as add-on therapy to improve asthma control in adult and adolescent patients with severe persistent allergic asthma who meet specific criteria as listed below. It is given by subcutaneous injection every 2 to 4 weeks.
- ◆ In clinical trials in patients with severe asthma taking continuous inhaled corticosteroids (ICS), omalizumab has been shown to reduce the rate and severity of asthma exacerbations and to improve lung function and quality of life parameters. A significant number of patients were also able to reduce the dosage of ICS. The pivotal INNOVATE trial demonstrated similar benefits for omalizumab in patients taking high-dose ICS plus long-acting  $\beta_2$ -agonists and additional controller medication.
- ◆ The most commonly occurring adverse events in clinical trials were injection site reactions and headaches. Anaphylactic reactions were rare. Facilities to treat anaphylaxis must be available.
- ◆ Omalizumab may be of benefit in a small group of patients with uncontrolled severe persistent allergic asthma despite optimal preventative treatment but at present its role in the stepwise management of asthma is unclear. High acquisition costs may be offset by reductions in exacerbations requiring hospitalisation. Cost-benefit studies are needed to determine if this is the case in clinical practice.

## Introduction

Asthma is a chronic inflammatory disorder of the airways. It often has an allergic component resulting in over-production of human immunoglobulin E (IgE) in response to environmental allergens e.g. pollen, house dust mite. IgE binds to cell membrane receptors resulting in the release of inflammatory mediators.

Omalizumab is a recombinant humanised monoclonal antibody which selectively binds to IgE forming an omalizumab-IgE complex. This prevents IgE binding to receptor sites on mast cells and basophils. Removal of free IgE also results in down-regulation of these receptors. Both these effects are reversible on discontinuation of the drug.<sup>1</sup>

## Evidence

Four key double-blind randomised controlled trials (RCTs)<sup>2,3,4,5</sup> have examined the efficacy of omalizumab in adults and adolescents over 12 years old with allergic asthma. All trials followed a similar design (see Appendix II for further trial details). During a run-in period patients' asthma medication was reviewed and adjustments made. In three of the trials patients were switched to a standard inhaled corticosteroid (ICS), either beclometasone dipropionate<sup>2,3</sup> or fluticasone.<sup>4</sup> Patients were randomised to omalizumab or placebo for the treatment phase. In three trials<sup>2,3,4</sup> this period was split into a steroid stable phase followed by a steroid reduction phase. Two trials<sup>2,3</sup> included a 24 week double-blind extension phase.<sup>6,7</sup>

Omalizumab doses were calculated based on body weight and baseline serum IgE concentration to give a dose between 150mg and 375mg by sc injection every 2 to 4 weeks. The maximum dose in 4 weeks was 750mg.

The primary endpoint in three<sup>2,3,5</sup> trials was the number of clinically significant asthma exacerbations during the treatment phase. An exacerbation was defined as

**Brand Name, (Manufacturer):** Xolair®, (Novartis)

**BNF Therapeutic Class:** 3.3 (provisionally)

**Licensed Indications:** Xolair® is licensed as add-on therapy to improve asthma control in adult and adolescent patients (12 years and above) with severe persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and reduced lung function ( $FEV_1 < 80\%$ ) as well as frequent daytime symptoms or night-time awakenings and have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled  $\beta_2$ -agonist. Xolair® treatment should only be considered for patients with convincing IgE mediated asthma.

**Dosage and Administration:** 75mg – 375mg by subcutaneous injection every 2 – 4 weeks based on body weight (kg) and baseline IgE (IU/ml) as per dosing tables in the SPC. Only patients with a baseline IgE level  $\geq 30$ -700 IU/ml are suitable candidates. Doses greater than 300mg should be split into two doses given at 2 week intervals.

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**Cost Comparisons:** Cost per 150mg vial is £256.15. For 28 days treatment for a 70kg adult with baseline IgE (IU/ml) >100-200 the cost of omalizumab based on a dose of 300mg (i.e. 2 x 150mg vials) is £512.30.

At present there is no other therapeutically equivalent treatment with which to compare costs.

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worsening of asthma symptoms severe enough to require systemic steroids<sup>5</sup> or a doubling of the patients baseline ICS dose.<sup>2,3</sup> In all three<sup>2,3,5</sup> trials including the INNOVATE trial<sup>5</sup> (see below for further details) the mean number of asthma exacerbations per patient was significantly less in omalizumab treated patients than in patients receiving placebo. This effect was maintained during the steroid reduction phases<sup>2,3</sup> and the extension phases.<sup>6,7</sup>

In the fourth trial<sup>4</sup> the primary outcome was the percentage reduction from baseline in fluticasone dose over 32 weeks which was significantly greater in omalizumab treated patients than in patients receiving placebo. The mean number of asthma exacerbations per patient, a secondary outcome, did not reach statistical significance.

Analysis of pooled data from the steroid stable phases of two trials<sup>2,3</sup> determined that factors indicating more severe asthma were all predictive of a greater probability of response to omalizumab.<sup>8</sup> 87% of patients who responded to omalizumab treatment did so by 12 weeks.

The pivotal study supporting the licensed indication of omalizumab is the INNOVATE trial.<sup>5</sup> This multicentre, double-blind RCT included 419 patients with severe persistent asthma receiving ICS plus long-acting  $\beta_2$ -agonists (LABA) and additional controller medication if necessary. After adjustment for an observed imbalance in baseline exacerbations, the mean exacerbation rate during the 28 week treatment period was 0.68 with omalizumab and 0.91 with placebo ( $p=0.042$ , rate ratio 0.738; 95% CI: 0.552-0.998). Without adjustment a similar magnitude of effect was seen but this did not reach statistical significance. The number needed to treat (NNT) for one year to prevent one clinically significant exacerbation was 2.2.

Among the secondary outcomes, severe exacerbation rate (PEF or

FEV<sub>1</sub> <60% of personal best requiring treatment with systemic corticosteroids) was halved in the omalizumab group compared to placebo. The total number of emergency visits was significantly reduced in the omalizumab group vs. placebo (omalizumab  $n=50$  vs. placebo  $n=93$ ; rate ratio 0.561; 95% CI: 0.325-0.928;  $p=0.038$ ). There were 13 hospital admissions in omalizumab treated patients compared with 25 admissions in the placebo group. Using the Juniper Asthma Quality of Life (QoL) questionnaire a greater percentage of patients receiving omalizumab achieved a  $\geq 0.5$ -point improvement from baseline compared with patients receiving placebo, which is considered clinically meaningful (60.8% vs. 47.8% respectively;  $p=0.008$ ).

Pooled data from seven studies including the INNOVATE study (omalizumab  $n=2,511$  and placebo  $n=1,797$ ) showed a significantly lower annual rate of exacerbations in omalizumab treated patients than in control patients (0.910 vs. 1.474 respectively;  $p<0.0001$ ). Omalizumab also significantly reduced total emergency visits compared with placebo ( $p<0.0001$ ). Omalizumab reduced hospital admissions by 52%, emergency room visits by 61% and unscheduled doctor visits by 47% (no absolute figures given).<sup>9</sup>

### Safety

The most common adverse reactions in patients receiving omalizumab were injection site reactions and headache. More serious adverse events included malignancies and anaphylaxis. A variety of malignancies were observed in 0.5% of patients treated with omalizumab compared with 0.18% control patients. The overall incidence rate of malignancy for omalizumab treated patients was comparable to that in the general population.

Anaphylactic reactions were rare in clinical trials (<1/1000). Facilities to treat anaphylaxis must be available.<sup>10</sup>

### Place in Therapy

Omalizumab is a novel treatment for patients with severe persistent allergic asthma. The licensed

indications are restrictive and reflect the inclusion criteria of the INNOVATE trial which enrolled patients taking high-dose ICS plus LABA and additional controller medication i.e. equivalent to step 4 of the BTS/SIGN asthma management guidelines.<sup>11</sup> Current estimates for peak uptake of omalizumab are 12 patients per 100,000 population.<sup>12</sup>

Omalizumab is expensive. Service delivery implications should also be considered. Patients must have IgE levels measured prior to treatment and a positive skin prick test. Patients with an IgE <76 IU/ml are less likely to experience benefit and unequivocal in vitro reactivity (RAST) to a perennial allergen must be demonstrated before starting treatment.<sup>10</sup> Treatment should be initiated by a specialist and administered by trained staff. Resuscitation facilities must be available. The establishment of omalizumab clinics may avoid product wastage resulting from part-used vials. Acquisition costs may be offset by reductions in hospital admissions but cost-benefit studies to support this are lacking.

Before prescribing omalizumab assess compliance with current therapy, especially ICS.<sup>1</sup> At 16 weeks patients should be reviewed and consideration given to discontinuing treatment if no improvement in asthma control has been seen.<sup>10</sup>

## Appendix I: Bibliography Appendix II: Table of Clinical Trials

### Key Paper:

Humbert M et al. INNOVATE. Allergy 2005; 60: 309-316.

### Risk Management Issues:

Store in a fridge (2°C – 8°C)  
Reconstitution is complex, taking at least 20 minutes. A swirler device to aid reconstitution is available. The reconstituted solution can be stored for up to 4 hours at room temperature or up to 8 hours in the fridge. Work is ongoing on a liquid formulation. Safety in pregnancy has not been established.

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The information contained in this document will be superseded in due course.

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## Appendix I

### Bibliography

#### References

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2. Busse W et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 2001; 108: 184-90
3. Solèr M et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J* 2001; 18: 254 –61
4. Holgate ST et al. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. *Clin Exp Allergy* 2004; 34: 632-38
5. Humbert M 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: 309-16
6. Lanier BQ et al. Omalizumab is effective in the long-term control of severe allergic asthma. *Ann Allergy Asthma Immunol* 2003; 91: 154-59
7. Buhl R et al. Omalizumab provides long-term control in patients with moderate-to-severe allergic asthma. *Eur Respir J* 2002; 20: 73-78
8. Bousquet J et al. Predicting response to omalizumab, an anti-IgE antibody, in patients with allergic asthma. *Chest* 2004; 125: 1378-86
9. Bousquet J et al. The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. *Allergy* 2005; 60: 302-8
10. Xolair® Summary of Product Characteristics. Novartis Pharmaceuticals UK Ltd. Oct 2005
11. The British Thoracic Society and Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. Guideline No 63. Revised Edition Nov 2005. accessible at <http://www.sign.ac.uk/guidelines/fulltext/63/index.html> (accessed Nov 2005)
12. Anon. Personal communication. Novartis Pharmaceuticals UK Ltd. September 2005.

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### Appendix II

**Table of key clinical trials evaluating omalizumab in patients with severe persistent allergic asthma**

Ref No	Trial Design	Common Criteria - all trials	Additional Criteria	Outcome Measures			Results					
				Primary outcome	Omalizumab	Placebo	P value					
Ref 5 INNOVATE	Multicentre, double-blind, RCT over 28 weeks omalizumab vs. placebo 4 phases: <ul style="list-style-type: none"> <li>◆ 1 week screening</li> <li>◆ 8 week run-in</li> <li>◆ 28 week treatment</li> <li>◆ 16 week follow-up (unpublished)</li> </ul>	<b>Inclusion Criteria</b> <ul style="list-style-type: none"> <li>◆ Age 12 – 75 years</li> <li>◆ Positive skin prick test to ≥ 1 perennial allergen</li> <li>◆ Moderate to severe allergic asthma*</li> <li>◆ Duration of asthma ≥ 1 year</li> <li>◆ Total serum IgE ≥ 30 IU/ml to ≤ 700 IU/ml</li> <li>◆ FEV<sub>1</sub> ≥ 40 to ≤ 80% of predicted normal value and continuing asthma symptoms</li> <li>◆ FEV<sub>1</sub> reversibility ≥ 12% from baseline within 30 minutes after administration of inhaled β<sub>2</sub>-agonist</li> </ul>	n=482 at entry n=419 efficacy analyses <b>Additional Inclusion Criteria</b> <ul style="list-style-type: none"> <li>◆ Severe persistent asthma (GINA 2002 step 4<sup>#</sup>), receiving ICS and LABA (100% patients) and additional controller medications including oral corticosteroids (22% patients)</li> <li>◆ At least 2 exacerbations requiring systemic corticosteroids or 1 severe exacerbation resulting in hospitalisation or emergency room treatment in past 12 months</li> </ul> <b>Additional Exclusion Criteria</b> <ul style="list-style-type: none"> <li>◆ Smoker</li> <li>◆ Treatment for an exacerbation within 4 weeks of randomisation</li> </ul>	<b>Primary outcome</b>								
				Rate of clinically significant asthma exacerbations during treatment phase	0.68	0.91	0.042	Rate ratio 0.738 (95% CI: 0.552-0.998)				
				<b>Secondary outcomes</b>								
				Severe exacerbation rate (PEF or FEV <sub>1</sub> <60% requiring treatment with systemic corticosteroids)	0.24	0.48	0.002					
				Total number of emergency visits	50	93	0.038	Rate ratio 0.561 (95% CI 0.325-0.968)				
				Hospital admissions	13	25	Not sig					
				Asthma-related QoL using Juniper AQLQ instrument >0.5-point improvement from baseline	60.8%	47.8%	0.008					
				Improvement in FEV <sub>1</sub>	190ml	96ml						
				Ref 2 Busse et al	Multicentre, double-blind, RCT over 28 weeks omalizumab vs. placebo 4 phases: <ul style="list-style-type: none"> <li>◆ 4-6 week run-in</li> <li>◆ 16 week stable steroid phase</li> <li>◆ 12 week ICS reduction</li> <li>◆ 24 week extension</li> </ul>	<b>Exclusion Criteria</b> <ul style="list-style-type: none"> <li>◆ Prior exposure or sensitivity to omalizumab</li> <li>◆ Elevated IgE levels other than atopy</li> </ul> *See individual trials for further details	n=525 <b>Additional Inclusion Criteria</b> <ul style="list-style-type: none"> <li>◆ Severe allergic asthma requiring daily ICS</li> <li>◆ Treatment with beclometasone dipropionate 420-840mcg/day or equivalent ICS for &gt; 3 months prior to randomisation</li> </ul> <b>Additional Exclusion Criteria</b> <ul style="list-style-type: none"> <li>◆ Acute upper respiratory tract infection within 1 month</li> <li>◆ &lt;3 months stable immunotherapy, regular treatment with β<sub>2</sub> blockers</li> <li>◆ Required dose omalizumab &gt;750mg</li> </ul>	<b>Primary outcome</b>				
Mean number of exacerbation episodes per patient in stable steroid phase	0.28	0.54	0.006									
<b>Secondary outcomes</b>												
% of patients experiencing at least one exacerbation in stable steroid phase	14.6%	23.3%	0.009									
% of patients achieving >50% reduction in beclometasone dipropionate dose	72.4%	54.9%	<0.001									
Mean change in PEF at week 16	18.5L/min	6.9L/min										

#GINA (Global Initiative for Asthma) Guidelines. Step 4 – severe persistent asthma requiring regular treatment with > 1000mcg/day beclometasone dipropionate equivalent and LABA

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Ref No	Trial Design	Common Criteria - all trials	Additional Criteria	Outcome Measures		Results		
				Primary Outcome	Placebo	P value		
Ref 6 Lanier et al	24 week double-blind extension of above study (Ref 2) Patients maintained on randomised treatment (omalizumab or placebo) and the lowest effective dose of beclometasone dipropionate	<b>Inclusion Criteria</b> <ul style="list-style-type: none"> <li>◆ Age 12 – 75 years</li> <li>◆ Positive skin prick test to ≥ 1 perennial allergen</li> <li>◆ Moderate to severe allergic asthma*</li> <li>◆ Duration of asthma ≥ 1 year</li> <li>◆ Total serum IgE ≥ 30 IU/ml to ≤ 700 IU/ml</li> <li>◆ FEV<sub>1</sub> ≥ 40 to ≤ 80% of predicted normal value and continuing asthma symptoms</li> </ul>	n=460 patients completing the core study  Concomitant asthma medication was allowed including switching to other inhaled corticosteroids	<b>Primary Outcome</b>	<b>Omalizumab</b>	<b>Placebo</b>	<b>P value</b>	
				Mean number of exacerbation episodes per patient	0.60	0.83	0.023	
				<b>Secondary Outcomes</b>				
				% of patients experiencing at least 1 exacerbation	31.8%	42.8%	0.015	
				% of patients able to maintain beclometasone dipropionate equivalent dose <50% baseline	46%	33%	0.003	
Ref 3 Solèr et al	Multicentre, double-blind, RCT over 28 weeks Omalizumab vs. placebo 4 phases: <ul style="list-style-type: none"> <li>◆ 4-6 weeks run-in</li> <li>◆ 16 week stable steroid</li> <li>◆ 12 week ICS reduction</li> <li>◆ 24 week extension</li> </ul>	<b>Inclusion Criteria</b> <ul style="list-style-type: none"> <li>◆ FEV<sub>1</sub> ≥ 40 to ≤ 80% of predicted normal value and continuing asthma symptoms</li> <li>◆ FEV<sub>1</sub> reversibility ≥ 12% from baseline within 30 minutes after administration of inhaled β<sub>2</sub>-agonist</li> </ul> <b>Exclusion Criteria</b> <ul style="list-style-type: none"> <li>◆ Prior exposure or sensitivity to omalizumab</li> <li>◆ Elevated IgE levels other than atopy</li> </ul>	n=546 <b>Additional Inclusion Criteria</b> <ul style="list-style-type: none"> <li>◆ Body weight ≤150kg</li> <li>◆ Mean total daily symptom score ≥ 3</li> <li>◆ ICS dose equivalent to 500 – 1200 mcg/day beclometasone dipropionate for ≥ 3months prior to randomisation</li> <li>◆ No acute exacerbation requiring additional corticosteroids for ≥ 1 month prior to screening</li> </ul> <b>Additional Exclusion Criteria</b> <ul style="list-style-type: none"> <li>◆ Patients taking regular oral corticosteroids</li> </ul>	<b>Primary Outcome</b>	<b>Omalizumab</b>	<b>Placebo</b>	<b>P value</b>	
				Mean number of asthma exacerbations per patient in stable steroid phase	0.28	0.66	<0.001	
					95% CI 0.15-0.41	95% CI 0.49-0.83		
				<b>Secondary Outcomes</b>				
				% of patients experiencing at least one exacerbation in stable steroid phase	12.8%	30.5%	<0.001	
	% of patients able to reduce beclometasone dipropionate dose >50% at end of steroid reduction phase	79%	55%	<0.001				
Ref 7 Buhl et al	24 week double-blind extension of above study (Ref 3) Patients maintained on randomised treatment and lowest effective dose of beclometasone dipropionate	*See individual trial data for further details	n=483 patients completing the core study  Concomitant asthma medication was allowed including switching to other asthma medications as necessary	<b>Primary Outcome</b>	<b>Omalizumab</b>	<b>Placebo</b>	<b>P value</b>	
				Mean number of asthma exacerbations per patient	0.48	1.14	<0.001	
					95% CI 0.30-0.66	95% CI 0.81-1.46		
				<b>Secondary Outcomes</b>				
	% of patients experiencing at least one exacerbation	24%	40.6%	<0.001				
Ref 4 Holgate et al	Multicentre, double-blind, RCT <ul style="list-style-type: none"> <li>◆ 6-10 week run-in</li> <li>◆ 16 week stable steroid</li> <li>◆ 16 week ICS reduction</li> </ul>		n=246 <b>Additional Inclusion Criteria</b> <ul style="list-style-type: none"> <li>◆ Severe asthma</li> <li>◆ Inhaled fluticasone &gt;1000mcg/day and LABA</li> </ul> <b>Additional Exclusion Criteria</b> <ul style="list-style-type: none"> <li>◆ Patients taking theophylline or anti-leukotrienes, history of anaphylaxis, recent near-fatal asthma, respiratory infection within 4 weeks of study, parasitic infection</li> </ul>	<b>Primary Outcome</b>	<b>Omalizumab</b>	<b>Placebo</b>	<b>P value</b>	
				Median percentage reduction from baseline in fluticasone dose	60%	50%	0.003	
					95% CI 50.0-75.0	95% CI 33.3-50.0		
				<b>Secondary Outcomes</b>				
				Mean number of exacerbations per patient in steroid stable phase	0.15	0.23	No signif	
	% of patients with clinically detectable improvement in QoL scores	58%	39%	<0.01				