Scottish Medicines Consortium

Re-Submission

omalizumab 150mg powder and solvent for injection (Xolair®) **No. (259/06)**

Novartis Pharmaceuticals UK Ltd.

7 September 2007

The Scottish Medicines Consortium has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a second re-submission

omalizumab (Xolair®) is accepted for restricted use within NHS Scotland as add-on therapy to improve asthma control in adult and adolescent patients (12 years of age and above) with severe persistent allergic asthma.

It is restricted to initiation and monitoring by hospital physicians experienced in the diagnosis and treatment of severe persistent asthma. It is restricted to patients who are prescribed chronic systemic steroids and in whom all other treatments have failed. The response to omalizumab treatment should be assessed in all patients at 16 weeks and treatment should be discontinued in patients who have not shown a marked improvement in overall asthma control.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Omalizumab is indicated as add-on therapy to improve asthma control in adult and adolescent patients (12 years of age and above) with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and who have reduced lung function (FEV_1 <80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids (ICS), plus a long-acting inhaled beta2-agonist (LABA). Omalizumab treatment should only be considered for patients with convincing immunoglobulin E (IgE) mediated asthma.

Dosing information

Dose range: 75mg every 4 weeks to 375mg every 2 weeks as a subcutaneous injection(s). The dose and dosing frequency is determined by baseline IgE (IU/ml), measured before the start of treatment, and body weight (kg).

Product availability date

31 October 2005

Summary of evidence on comparative efficacy

Omalizumab is a recombinant humanised anti-immunoglobulin E (anti-IgE) antibody. It prevents human IgE from binding to its receptor on mast cells and basophils, thus inhibiting the histamine release response normally triggered by exposure to allergens. In this second resubmission, the company are suggesting that omalizumab should be restricted to those patients on maintenance oral corticosteroid therapy.

One randomised, placebo-controlled, double-blind, multi-centre trial was conducted in 419 patients with severe persistent asthma (Global Initiative for Asthma (GINA) definition) requiring regular treatment with inhaled corticosteroids (>1000mcg/day of beclometasone dipropionate or equivalent) and a long-acting beta-agonist (LABA). In addition, patients were required to have a forced expiratory volume in one second (FEV_1) ≥ 40% to <80% of predicted normal value and at least two exacerbations requiring systemic corticosteroids or one severe exacerbation requiring hospitalisation or emergency room treatment in the past 12 months. Patients also had a positive skin prick test to at least one perennial allergen and a total IgE level ≥ 30 to ≤ 700 IU/ml. Additional asthma medications taken regularly from > 4 weeks prior to randomisation were permitted as were oral corticosteroids (≤20mg/day) provided at least one of the exacerbations in the previous 12 months had occurred whilst on this therapy. Patients were randomised (1:1) with stratification for country and concomitant asthma therapy to receive omalizumab (dose based on patient's bodyweight and total serum IgE level at screening) or matching placebo, given every 2 or 4 weeks by subcutaneous injection for 28 weeks.

The primary efficacy variable was the rate of clinically significant asthma exacerbations (defined as a worsening of asthma symptoms requiring treatment with systemic corticosteroids). Secondary efficacy variables included severe exacerbation rate (defined as peak expiratory flow (PEF) or FEV_1 <60% of personal best, requiring treatmentwith systemic corticosteroids), symptom measurement and emergency visits for exacerbations. Quality of life (QoL) was assessed using the Juniper Adult Asthma Quality of Life Questionnaire (AQLQ) which assesses responses to 32 individual questions in four domain scores: symptoms, activities, emotions and environmental exposure.

For the primary efficacy variable a *post-hoc* adjustment for baseline exacerbation history was undertaken because at baseline patients who subsequently received omalizumab had experienced more frequent exacerbations and more multiple exacerbations than those in the placebo group. The primary intent-to-treat population used in the efficacy analyses consisted of patients randomised after the protocol amendment advising this analysis. After including history of exacerbations (in the year prior to screening and the run-in period) as a covariate, the rate of clinically significant asthma exacerbations over the 28-week treatment period was 0.68 and 0.91 for the omalizumab and placebo groups respectively (rate ratio 0.74, 95% confidence interval (CI) 0.55-1.00, p=0.04). The unadjusted clinically significant asthma exacerbation rate ratio was 0.81 (p=0.15). Omalizumab was superior to placebo for the secondary efficacy variables; severe exacerbation rate, total emergency visits, changes in PEF and FEV_1 and the AQLQ measure.

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

The safety population comprises over 5300 patients exposed to omalizumab in controlled and open label studies. Adverse effects that were observed more frequently in the omalizumab group compared with placebo/standard therapy control were injection site reactions, exanthema/urticaria, gastrointestinal disorders (e.g. gastroenteritis, nausea and vomiting) and infections (sinusitis). Injection site reactions caused less than 1% of patients to discontinue treatment, and, overall in the placebo controlled studies, <2% patients in both groups discontinued treatment due to adverse events or abnormal laboratory values. In the pivotal randomised controlled trial described previously the incidence of injection site reactions was 5.3% and 1.3% for the omalizumab and placebo groups respectively.

There was an increased incidence of malignancy in the overall safety population exposed to omalizumab (25 cases in 5015 patients; 0.5%) compared with the control group (5 cases in 2854 patients; 0.18%), although the malignancies were considered unlikely to be related to treatment. A pharmacovigilance plan includes an ongoing 5-year comparative observational prospective cohort study in which all serious adverse events (including malignancies) will be monitored and followed up.

Summary of clinical effectiveness issues

There is limited experience of self-administration of omalizumab. The Summary of Product Characteristics (SPC) recommends that omalizumab is administered by a health care provider. To administer the omalizumab dose, up to three injections may be required due to a single strength being available and limitations on the volume that can be injected via the subcutaneous route.

In the randomised controlled trials omalizumab was assessed as an add-on therapy to inhaled corticosteroids (and Long Acting Beta 2 Agonists (LABAs) in the pivotal study). While

it has been shown that omalizumab is useful as an adjunctive treatment, it has not been determined whether or not it is any more clinically beneficial or cost-effective than other medications such as slow release theophyllines or anti-leukotriene agents. Comparative studies with these drugs have yet to be performed. It is noted that in the pivotal trial one third of patients were not receiving any additional controller medication.

Since only two-thirds of patients respond to omalizumab, the resubmission is accompanied by a proposed assessment protocol designed with input from Scottish asthma specialists to identify non-responders after 16 weeks of treatment, to allow treatment to be stopped. The assessment of response is based on defined improvements in mini-AQLQ and the asthma control test (ACT) as well as excellent or good improvement in the physicians' overall evaluation of treatment response.

Omalizumab is an innovative treatment which may be life saving for a small number of patients with severe persistent disease.

*Other data were also assessed but remain commercially confidential.**

Summary of comparative health economic evidence

The manufacturer presented a re-analysis of the pivotal trial based around those receiving oral corticosteroids: 22% of the trial population. The modelling of cost-effectiveness of omalizumab as an add-on therapy to standard care in this group assumed a cohort of 40 year olds which was simulated over a 40 year period. This used a Markov model, implemented through a 3-month cycle. Non-responders to omalizumab discontinued treatment at week 16. Responders to omalizumab continued treatment for 5 years then stopped. The comparator was standard care, which was appropriate. General mortality and mortality due to severe exacerbations was applied.

The proportion of responders and exacerbations rates were drawn from the pivotal trial. Exacerbation rates among omalizumab responders were assumed to remain constant at the 28 week level over the 5 years of treatment, with there being no drop-outs or any requirement to change dose during the 5 years of treatment. Supporting evidence for these assumptions from prospectively collected data was not presented. For all other patients and periods the exacerbation rates from the subset of patients using oral corticosteroids within the standard care arm were applied.

Quality of life values for day-to-day living were collected during the trial and differentiated by treatment. The quality of life effects of exacerbations were drawn from a separate study within the literature.

The base case estimated a gain of 0.84 QALYs at an additional cost of £25,982 to yield a cost effectiveness estimate of £30,995 per QALY.

Weaknesses of the analysis included:

- the 3.1% likelihood of dying during a severe exacerbation episode which may be an overestimate for the population modelled.
- the assumption of no drop-outs with maintained efficacy over five years for responders at 28 weeks may have been optimistic.
- the base case assuming divisible vial dosing which may not always be feasible in clinical practice

Summary of patient and public involvement

Patient Interest Group Submission: Asthma UK Scotland

Additional information: guidelines and protocols

The SIGN/BTS published the *British Guideline on the Management of Asthma* in 2003 and it was updated in 2005. The updated guidance includes the following advice; omalizumab may be of benefit in highly selected patients with severe persistent allergic asthma, but at present its role in the stepwise management of asthma is unclear.

The Global Initiative for Asthma (GINA) updated their *Global strategy for asthma management and prevention* in 2004. The treatment strategy for the management of severe persistent asthma (step 4) is a high dose inhaled glucocorticosteroid plus LABA plus one or more of the following if needed; sustained release theophylline, leukotriene modifier, long acting oral beta 2 agonist, oral glucocorticoid or omalizumab.

An updated Cochrane Collaboration review, *Anti-IgE for chronic asthma in adults and children*, was published in 2006 and includes the pivotal trial.

Additional information: previous SMC advice

SMC originally issued advice in May 2006, following a full submission. This stated that "Omalizumab (Xolair®) is not recommended for use within NHS Scotland as add-on therapy to improve asthma control in adult and adolescent patients (12 years of age and above) with severe persistent allergic asthma. The economic case for omalizumab has not been demonstrated."

SMC issued advice in December 2006, following a resubmission. This stated that "Omalizumab (Xolair®) is not recommended for use within NHS Scotland as add-on therapy to improve asthma control in adult and adolescent patients (12 years of age and above) with severe persistent allergic asthma. The economic case for omalizumab has not been demonstrated. The licence holder has indicated their decision to resubmit."

Additional information: comparators

The licensed indication for omalizumab reflects step 4 of the SIGN/BTS *British Guideline on the Management of Asthma* which includes a trial of a leukotriene receptor antagonist, SR theophylline or oral beta-2-agonist in addition to a drug regimen already including an inhaled corticosteroid and a long acting beta-2-agonist. This second resubmission suggests a restricting use to patients requiring maintenance oral corticosteroid therapy in line with step 5 of the guideline. There are mo direct comparators to omalizumab at this stage. Consideration should be given to other treatments e.g. unlicensed use of immunosuppressants (methotrexate, ciclosporin and oral gold) to minimise corticosteroid use.

Additional information: costs

Drug	Dose Range	Cost per year (£)*
Omalizumab	**75mg every 4 weeks to 375mg every 2 weeks**	**3330-19980**
Zafirlukast	20mg twice daily	367
Montelukast	10mg once daily	351
salbutamol SR (Ventmax SR®)	8mg twice daily	134
SR theophylline (Slo-Phyllin®)	250-500mg twice daily	56-113
SR theophylline (Nuelin SA 250®)	250-500mg twice daily	54-108
SR theophylline (Nuelin SA®)	175-350mg twice daily	39-77
SR theophylline (Uniphyllin Continus®)	200-400mg twice daily	41-73

*Cost from eVADIS drug dictionary accessed on 22/6/07.
Doses are shown for general comparison and do not imply therapeutic equivalence

Additional information: budget impact

Based upon an eligible population of 427 patients and a market share of 2.6% in year 1 (11 patients) rising to 18.6% by year 5 (79 patients), the manufacturer estimated a gross drug cost of £62k in year 1 rising to £403k by year 5. There are significant service implications which have not been included in the budget impact estimate.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 17 August 2007.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

** Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/*

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

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; 60:309-16.

Bousquet J, Cabrera P, Berkman N, 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(3): 302-8.

Walker S, Monteil M, Phelan K et al. Anti-IgE for chronic asthma in adults and children (Review). The Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.: CD003559. DOI: 10.1002/14651858.CD003559.pub3.

Anon. Omalizumab for severe asthma Drug Therap Bull 2006: 44; 86-88.