Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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omalizumab 150mg solution for injection (Xolair®) SMC No. (1017/14)

Novartis Pharmaceuticals UK Ltd

05 December 2014

The Scottish Medicines Consortium (SMC) 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 full submission

omalizumab (Xolair®) is accepted for restricted use within NHS Scotland.

Indication under review: as add-on therapy for the treatment of chronic spontaneous urticaria in adult and adolescent (12 years and above) patients with inadequate response to H1 antihistamine treatment.

SMC restriction: use in adults and adolescents with chronic spontaneous urticaria who have an inadequate response to combination therapy with H1 antihistamines, leukotriene receptor antagonists (LTRA) and H2 antihistamines, used according to current treatment guidelines.

The addition of omalizumab to combination therapy with H1-antihistamines, and/or leukotriene receptor antagonists and/or H2-antihistamines was more effective than placebo in reducing the weekly itch severity score (ISS) at 12 weeks.

This advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of omalizumab. This advice is contingent upon the continuing availability of the Patient Access Scheme in NHS Scotland or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

As add-on therapy for the treatment of chronic spontaneous urticaria in adult and adolescent (12 years and above) patients with inadequate response to H1 antihistamine treatment.

Dosing Information

300mg by subcutaneous injection every four weeks. Prescribers are advised to periodically reassess the need for continued therapy. Clinical trials experience of long-term treatment beyond six months in this indication is limited.

There is limited experience with self-administration of omalizumab. Therefore treatment is intended to be administered by a healthcare provider only.

Omalizumab treatment should be initiated by physicians experienced in the diagnosis and treatment of chronic spontaneous urticaria.

Product availability date

28 February 2014

Summary of evidence on comparative efficacy

Omalizumab is a recombinant DNA-derived humanised monoclonal antibody that selectively binds to immunoglobulin E (IgE), reducing the amount of free IgE. There is also down-regulation of IgE receptors on cells but the mechanism of action of omalizumab in chronic spontaneous urticaria (CSU) is not completely understood.[1,2]

Omalizumab was initially licensed for the treatment of allergic asthma but the marketing authorisation has been extended to include CSU. It is the first medicine licensed for use in CSU when H1-antihistamines provide an inadequate response. The submitting company has requested that the Scottish Medicines Consortium (SMC) considers omalizumab when positioned for use for adults and adolescents who have previously been treated unsuccessfully with combinations of up to four times the licensed dose of H1-antihistamines, leukotriene receptor antagonists (LTRA) and H2-antihistamines, and who have an inadequate response to these combination therapies. This positioning is in line with standard treatment guidelines for CSU.

The key evidence to support the use of omalizumab in the patient population proposed by the submitting company comes from the GLACIAL study.[2,3] This was a randomised, double-blind, placebo-controlled, phase III study in 336 patients with chronic idiopathic/spontaneous urticaria (CIU/CSU). It was primarily designed to assess the safety of omalizumab but efficacy outcomes were assessed as a secondary objective. Eligible patients remained symptomatic despite H1-antihistamines (at up to four times the licensed dose) plus H2-antihistamines or LTRA or both for at least three consecutive days immediately before screening. Patients were considered symptomatic if they had an urticaria activity score over seven days (UAS7) (range 0 to 42) of ≥16 and a weekly itch severity score (ISS) (range 0 to 21) of ≥8 during the seven days before randomisation, as well as an UAS (range 0 to 6) ≥4 when assessed by the physician in clinic. Eligible patients were randomised in a ratio of 3:1 to receive omalizumab 300 mg (n=252) or placebo (n=84) by subcutaneous (SC) injection every 4 weeks for 24 weeks (i.e. 6 doses). Randomisation was stratified by baseline ISS, weight and study centre. Patients remained on stable doses of their pre-randomisation treatment (H1

antihistamine, H2 antihistamine and/or LTRAs) throughout the study period. Rescue medication with diphenhydramine (up to 75 mg/day) was allowed for symptom relief. The 24-week treatment period was followed by a 16-week treatment-free period to 40 weeks.

The key efficacy outcome was change in weekly ISS from baseline at week 12. In the omalizumab group, this reduced from a baseline of 14.0 by -8.6 compared with a reduction from baseline of 13.8 by -4.0 in the placebo group: least square mean (LSM) difference of -4.52 (95% confidence interval [CI]: -5.97 to -3.08), p<0.001 (using baseline observation carried forward [BOCF] for missing data at week 12).

There were statistically significant differences between omalizumab and placebo in each of the following additional outcomes: change from baseline in UAS7 at week 12 (-19.0 versus -8.5 respectively: LSM difference -10.0 [95% CI: -13.2 to -6.9]), change from baseline in weekly number of hive score at week 12 (-10.5 versus -4.5 respectively; LSM difference -5.9 [95% CI: -7.7 to -4.1]), median time to minimally important difference in weekly ISS, (2.0 weeks versus 5.0 weeks respectively), patients with a UAS7 ≤6 at week 12 (52% versus 12%), patients with change from baseline in mean ISS of ≤5 (70% versus 40%), proportion of angioedema-free days from weeks 4 to 12 (91% versus 88%), change from baseline in weekly size of largest hive score at week 12, (-8.8 versus -3.1: LSM difference -5.6 [95% CI: -7.3 to -4.0] and patients itch and hive-free (UAS7=0) at week 12, (34% versus 4.8%).[3]

Quality of life was measured using the Dermatology Life Quality Index (DLQI: a 10-item questionnaire producing a total score of 0 to 30 with a higher score indicating a reduced quality of life) and the change from baseline at week 12 was -9.7 with omalizumab versus -5.1 with placebo: LSM difference -4.7 (95% CI: -6.3 to -3.1). The Chronic Urticaria Quality of Life Questionnaire (CU-Q_2oL: a 23-item questionnaire producing a total score of 0 to 100 with a higher score indicating an improved quality of life) was an exploratory outcome, and change from baseline at week 12 was -29.3 versus -16.3 respectively: LSM difference -13.4 (95% CI: -18.2 to -8.6).[3]

There were two other key randomised, placebo-controlled, phase III studies (ASTERIA I and II) which support the licensed indication of patients with symptomatic CSU despite treatment with the licensed doses of H1-antihistamines.[4,5] Eligible patients met the same inclusion criteria as in the GLACIAL study with the exception that they had background therapy of H1-antihistamines only at licensed doses for at least eight weeks. Patients were randomized equally to receive omalizumab 75 mg, 150 mg, or 300 mg or placebo, by SC injection every four weeks during the 24-week double-blind treatment period in ASTERIA I (n=319) and the 12-week double-blind treatment period in ASTERIA II (n=323). The primary outcome in both studies was the change from baseline to week 12 in weekly ISS. In ASTERIA I, omalizumab 300mg reduced ISS from 14.4 by -9.40 compared with from 14.4 by -3.63 with placebo and in ASTERIA II, from 13.7 by -9.77 compared with from 14.0 by -5.14 with omalizumab and placebo respectively. The LS differences for omalizumab 300mg versus placebo were -5.80 and -4.81 in ASTERIA I and II respectively using BOCF. The differences between omalizumab and placebo were statistically significant in both studies.

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

Summary of evidence on comparative safety

No comparative safety data are available. Refer to the summary of product characteristics for details.

Summary of clinical effectiveness issues

CSU is the daily, or almost daily, occurrence of pruritic wheals for at least 6 weeks without identifiable aggravating factors. Itch is the most distressing symptom for patients with the greatest impact on quality of life. In more than 40% of patients, there is angioedema or deep tissue swelling which can occur anywhere in the body including the upper respiratory tract.[2] CSU is managed symptomatically with H1-antihistamines (e.g. cetirizine or loratadine) and current guidelines recommend that the dose can be increased up to fourfold if symptoms persist, followed by a trial of ciclosporin (off-label), the leukotriene receptor antagonist, montelukast (off-label), or omalizumab, when symptoms remain.[6] Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area, namely in the small group of patients who fail to respond to H1-antihistamines. The submitting company has requested that SMC considers omalizumab when positioned for use in adults and adolescents with CSU who have had an inadequate response to treatment with combinations of up to four times the licensed dose of H1-antihistamines, LTRA and H2-antihistamines.

Although two pivotal studies, ASTERIA I and II, support the licensed indication of patients who have an inadequate response to H1-antihistamines, key evidence for the proposed positioning (inadequate response despite combinations of up to four times the licensed dose of H1-antihistamines +/- LTRA +/- H2-antihistamines) comes from results of the GLACIAL study.[3,4,5] All patients had previously received H1-antihistamines, 89% had received H2-antihistamines and 58% had received LTRAs. At baseline in the GLACIAL study, 27% (89/335) of patients were receiving H1-antihistamines + H2-antihistamines + LTRA; 56% (186/335) were receiving H1-antihistamines + H2-antihistamines and 14% (47/335) were receiving H1-antihistamines + LTRA. In addition, 37% (123/335) of patients were receiving standard doses of H1-antihistamines; 35% (116/335) two times standard doses of H1-antihistamines; 11% (37/335) three times standard doses of H1-antihistamines and 16% (53/335) four times standard doses of H1-antihistamines. It is not clear what the relative doses of H1-antihistamines that were used within each of the H1-antihistamines +/- H2-antihistamines +/- LTRA combinations. The GLACIAL study was primarily designed to assess the safety of omalizumab and a number of efficacy outcomes were assessed as secondary objectives. The study was powered to detect a difference between omalizumab and placebo in change in weekly ISS at week 12, and this difference between omalizumab and placebo was statistically significant. However, during the 16 week treatment-free period to week 40, the treatment effect diminished.[3] An additional, unpublished, subgroup analysis in patients receiving H1-antihistamines + LTRA + H2-antihistamines during the study (i.e. the most refractory patients) found similar results to the total population. Although the subgroup analysis did not include the main clinical outcome (change in weekly ISS) or details of the proportions of patients who were on more than the standard dose H1-antihistamines, the submitting company considered that this was sufficient to support using the full GLACIAL results in the economic analysis.

There are no comparative data for omalizumab versus other agents used off-label for patients with CSU who fail to respond to increased doses of H1-antihistamines. Although alternative agents are recommended by current guidelines, the company suggested that there was a lack of good clinical evidence on which to conduct an indirect comparison with omalizumab. In the GLACIAL study, patients could have previous received treatment with a LTRA.

Omalizumab offers a licensed treatment option for patients with CSU which responds inadequately to standard treatments. The dosing of omalizumab for CSU is fixed at 300mg every four weeks and each dose requires two SC injections of 150mg. The SPC notes that there is limited experience with self-administration of omalizumab and that treatment should be administered by a healthcare provider only. As well as limited clinical trial experience beyond six months, the SPC notes that there is limited experience of retreatment with omalizumab for CSU. There is no recommendation about stopping

criteria.[1] Clinical experts consulted by SMC considered that omalizumab for CSU is a therapeutic advancement due to its efficacy in refractory patients and that its place in therapy would be after the failure of conventional treatment.

Summary of comparative health economic evidence

The company submitted a de novo cost-utility analysis which used a Markov model to compare the costs and health outcomes of omalizumab as an add-on treatment to background medication (up to 4 times licensed dose H1-antihistamines +/- LTRA +/- H2-antihistamines) compared with background medication alone. Patients with CSU and inadequate response to H1 antihistamine-based treatment enter the model with moderate or severe urticaria and all receive background medication. The disease states are defined using UAS7 scores (a function of number of hives and severity of itching). Patients receive either omalizumab 300 mg or remain on background medication. Those receiving omalizumab are reviewed at 16 weeks and, if responding, (well-controlled or urticaria-free) remain on the medication until week 24. Non-responders (mild, moderate and severe urticaria) stop omalizumab at 16 week but remain on background medication. At end of treatment (16 or 24 weeks), all are at risk of spontaneous remission and death and are on background medication. Patients who are in well-controlled or urticaria-free health states relapse to either a moderate or severe state and are re-treated with a 24-week course of omalizumab.

Patients in the "no further pharmacological treatment" arm are treated continuously with background medication throughout the 10-year time horizon. Those in moderate or severe urticaria health states at 24 weeks remain in those health states for the remainder of the time horizon, with a risk of spontaneous remission and death. Responders are at risk of relapse, remission and death.

Clinical efficacy and safety data for the first 24 weeks for both arms are taken from the pivotal clinical study. Resource use data are from an observational burden-of-illness study, with appropriate unit costs applied. Utility values are derived from the pooled values from 3 clinical studies of omalizumab, adjusted for population-based weights. The resulting utility values used in the model ranged from 0.712 for patients with severe urticaria to 0.897 for the uticaria-free health state.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple confidential discount was offered on the list price. With the PAS, the ICER was estimated to be £19,632 per QALY, based on an incremental cost of £7,459 and a QALY gain of 0.38. Probabilistic sensitivity analysis (PSA) reported a 52% probability of the ICER being less than £20,000 and 100% probability of less than £30,000 with the PAS. The results are sensitive to the acquisition cost of omalizumab, the cumulative relapse for patients who are urticaria-free after initial treatment, utility values, responses to re-treatment, cost of background medication and adopting a treatment period of 12 weeks.

Strengths of the submission include choice of health states in model, good correlation between model and clinical data at week 24, and use of a literature review to search for evidence of efficacy, resource use and utilities. The clinical study also included some appropriate patient groups and relevant clinical endpoints.

Weaknesses include:

- In clinical practice in Scotland, a range of treatments is used in addition to antihistamines and LTRAs, including immunosuppressants, oral steroids, anti-TNF-α inhibitors and ultraviolet B phototherapy, and these would potentially be displaced by omalizumab. The company

acknowledged this but argued that inadequate evidence would not allow a cost-effectiveness comparison.

- The assumption that background medication (cost £405 per year plus appointments) is maintained for 10 years with no clinical benefit is not consistent with guidelines and Scottish clinical practice. However, a scenario analysis was provided where it was assumed that patients in the omalizumab arm require less background therapy and this reduced the ICER to £15k per QALY with the PAS.

- The clinical study data reported at week 40 indicate the UAS7 scores for the omalizumab arm converged to the absolute levels observed for those on background treatment. The company was unable to compare the distribution of patients, by health state for each arm at 40 weeks as modelled and as reported in the clinical study because some patients in the omalizumab arm in the model had been re-treated. It did provide mean re-treatment rates with omalizumab which were 0.49 (an extra 12 weeks treatment) for those well-controlled at 24 weeks, and 1.49 re-treatments (36 weeks) for urticaria–free patients from week 24 to year 5. Given the clinical study results and this level of re-treatment, one would anticipate the distribution of health states to be identical at year 5. However, 28.6% in the omalizumab were disease free or well-controlled compared to 0.7% in the group receiving only background therapy. The assumptions adopted to extrapolate the data beyond week 24 are thus not consistent with the observed data at week 40. The company provided a sensitivity analysis which models only the 40 weeks data from the clinical study and reports an ICER of £73,782 per QALY with the PAS. This was considered to be a particularly conservative analysis as it is based only on the 40 week study data and did not allow for patients to be retreated following relapse, which would be likely to happen in practice.

- A review of patients at 16 weeks with all non-responders, including those judged to now have 'mild' disease, stopping medication may be difficult to achieve in practice. Moreover, stopping treatment in responders at 24 weeks may also be difficult clinically, given symptoms return quickly. However, sensitivity analysis showed that the ICER increased only marginally when all patients were treated for 24 weeks.

- There is limited evidence on the effectiveness of re-treatment with omalizumab and the results are sensitive to the values assumed for this parameter. Sensitivity analysis using more conservative assumptions around retreatment increased the ICER to £24k per QALY.

- No rationale to support choice of sensitivity analyses is provided. No sensitivity analyses are provided to evaluate the impact of the outcomes for both arms converging at 40 weeks or for longer treatment periods. Given the medicine does not modify disease and so the disease returns, some clinicians may prescribe for more than 24 weeks.

Although there were weaknesses with the analysis as outlined above, the sensitivity analysis showed the ICER remained acceptable in most scenarios. Therefore, the economic case was demonstrated.

Summary of patient and public involvement

The following information reflects the views of the specific patient group.

- A submission was received from Skin Conditions Campaign Scotland (SCCS), which is a registered charity.

- SCCS has received funding from several pharmaceutical companies in the past two years, but not from the submitting company.

- Severe chronic, spontaneous or idiopathic urticaria can be an incapacitating, potentially long-term illness that affects physical and psychological wellbeing, sleep, mood, work, and social life. Continuous itch and unpredictable and alarming swellings are disruptive to all aspects of daily living.

- Current treatments include antihistamines, which are taken continuously in large doses. These can relieve some of the itch and may reduce the extent of swelling, but do not reduce the frequency of attacks and have no effect on redness and often little effect on the pain of weals on hands and feet. Oral or injected corticosteroids can control the disease, but often in high maintenance doses. It is the continuous wearing effect of ongoing itch, visible weals and swellings that are not fully responsive to current treatments.

- Omalizumab can have a life-changing benefit. It is combined with existing antihistamines to produce more complete control of itch, weals and new attacks. It may possibly be a safer short-term and longer-term option than steroids, ciclosporin or pooled immunoglobulin.

Additional information: guidelines and protocols

European Academy of Allergology and Clinical Immunology (EAACI), Global Allergy and Asthma European Network (GALEN), European Dermatology Forum (EDF) and World Allergy Organization (WAO) published the EAACI/GAL2EN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria: the 2013 revision and update.[6] This recommends that the aim of treatment is complete symptom control as safely as possible. First-line treatment with modern second generation H1-antihistamines is recommended. If symptoms persist after two weeks, second-line treatment involves increasing the dose of modern second generation H1-antihistamines up to fourfold. If symptoms persist after one to four further weeks, it is recommended that a trial of omalizumab, ciclosporin or montelukast as third-line treatment is added.

The British Association of Dermatologists (BAD) published guidelines for evaluation and management of urticaria in adults and children in 2007.[7] This recommends that:

- it has become common practice to increase the dose of second-generation H1-antihistamines above the licensed dose for patients when the potential benefits are considered to outweigh any risks.
- combinations of nonsedating H1-antihistamines with other agents, such as H2-antihistamines, sedating antihistamines at night or the addition of antileukotrienes, can be useful for resistant cases.
- oral corticosteroids should be restricted to short courses for severe acute urticaria or angio-oedema affecting the mouth, although more prolonged treatment may be necessary for delayed pressure urticaria or urticarial vasculitis.
- immunomodulating therapies for chronic autoimmune urticaria should be restricted to patients with disabling disease who have not responded to optimal conventional treatments.

An update to this guideline is in progress.

The British Society for Allergy and Clinical Immunology (BSACI) published guidelines for the management of chronic urticaria and angio-oedema in 2007.[8] This guideline recommends the following stepped management:

- a standard dose non sedating H1-antihistamine
- a higher dose of H1-antihistamine
- adding a second non sedating H1-antihistamine (regular or as required)
- considering a sedating antihistamine at night

- considering adding or substituting with a second line agent, e.g. anti-leukotriene (or tranexamic acid if angio-oedema is present)
- adding or substituting other second line agents, such as ciclosporin or low dose corticosteroid

Additional information: comparators

There are no licensed alternative agents for patients with CSU who fail to respond to increased doses of H1-antihistamines, although off-label use of alternative agents is recommended by current guidelines.

Cost of relevant comparators

Drug	Dose Regimen	Cost per 4 weeks (£)
Omalizumab	300mg by subcutaneous injection every four weeks	512

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on date 3 September 2014. During the GLACIAL study treatment continued for 24 weeks. This would cost £3,074. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated the population eligible for treatment is about 1,270 patients, assuming a prevalence of 0.75% of chronic urticaria of whom 60% have CSU. Of these, 77% are treated with H1-antihistamines, with 7.9% having an inadequate response to combinations of up to four times the licensed dose of H1 +/- H2 receptor anatagonists +/- LTRAs.

With the PAS, the gross impact on the medicines budget was estimated at £337k in year 1, rising to £2.76m in year 5. As other medicines were assumed to be displaced, the net medicines budget impact was estimated to be £335k in year 1, rising to £2.48m in year 5.

References

The undernoted references were supplied with the submission.

1. Novartis Pharmaceuticals UK Ltd. Summary of product characteristics, Xolair®, 1 September 2014.

2. European Medicines Agency. Public Assessment Report: omalizumab (Xolair®), procedure number EMEA/H/C/000606/II/0048. www.ema.europa.eu [accessed 1 September 2014]

3. Kaplan A, Ledford D, Ashby M, et al. Omalizumab in patients with symptomatic chronic Idiopathic/spontaneous urticaria despite standard combination therapy. J Allergy Clin Immunol 2013;132:101-9.

4. Saini SS, Bindslev-Jensen C, Maurer M, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1-antihistamines: A randomized, placebo-controlled study. J Investigative Dermatology 2014; doi 10.1038/jid.2014.306

5. Maurer M, Rosen K, Hsieh HJ, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. N Engl J Med 2013;368:924-35.

6. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA^{2}LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. Allergy 2014:69:868-87.

7. Grattan CE, Humphreys F. Guidelines for evaluation and management of urticaria in adults and children. Br J Dermatol 2007;157:1116-23.

8. Powell RJ, Du Toit GL, Siddique N et al. BSACI guidelines for the management of chronic urticaria and angio-oedema. Clinical and Experimental Allergy 2007;37:631-50.

This assessment is based on data submitted by the applicant company up to and including 14 November 2014.

**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/About_SMC/Policy_Statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that

has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

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.