Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Omalizumab for previously treated chronic spontaneous urticaria [ID707]

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted], on behalf of the British Association of Dermatologists' Therapy & Guidelines sub-committee

Name of your organisation: British Association of Dermatologists and British Society of Allergy and Clinical Immunology

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? ✓
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? ✓
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? ✓ Consultant Dermatologist, National Health Service
- other? (please specify) N/A

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? H1 antihistamines are used in all patients with or without short courses of oral corticosteroids as rescue medication. A diverse range of pharmacological treatments may also be used off-licence to manage highly symptomatic patients, including off-licence doses of antihistamines, leukotriene antagonists, dapsone and immunosuppressives

Is there significant geographical variation in current practice? There are no known geographical variations in disease prevalence or severity. Most chronic urticaria is managed adequately in primary care with H1 antihistamines. An unknown proportion is referred to Dermatology, Allergy or Immunology clinics in secondary and tertiary care. The availability of these services will vary across England and Wales. It is unknown what proportion of patients is seen by the different specialties but it is likely that more are referred to Dermatology because of relatively higher national service provision.

Are there differences of opinion between professionals as to what current practice should be? The currently accepted view by Dermatologists is that chronic spontaneous urticaria is a mast cell-mediated illness that is NOT due to allergy although patients usually refer to 'my allergy' and often expect an allergy work up from an Allergist. The management of urticaria is, however, similar across specialties with Dermatologists generally being more comfortable with using dapsone or immunosuppressive drugs, whereas Allergists may be more likely to use tranexamic acid for angioedema when it is a prominent feature of the illness and less likely to prescribe immunosuppressives, for instance.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages? The current alternatives to omalizumab include up-dosed H1 antihistamines, H2 antihistamines, doxepin, leukotriene antagonists, dapsone, sulphasalazine or immunosuppressive drugs, including ciclosporin, methotrexate and mycophenolate mofetil

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Some chronic spontaneous urticaria patients are more severely affected than others with longer disease duration, greater severity, less responsiveness to H1 antihistamines and are more likely to have angioedema in addition to itchy weals. Although several indicators of disease severity have been recognized, including a weal response to intradermally injected autologous serum (the autologous serum skin test, ASST), increased blood D-dimer levels, reduced total cellular blood histamine and positive basophil histamine release assay (response of healthy donor basophils to incubation with patient sera, these investigations are not routinely available to clinicians and there is currently no information on their potential utility as biomarkers of response to omalizumab

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology? To date, no subgroups of CSU have been identified that have a better likelihood of response to omalizumab or a higher risk of causally related adverse effects

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In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Secondary care and tertiary clinics would be the main prescribers. It is recommended that patients should be monitored for 2 hours after the first injection with shorter intervals being appropriate for subsequent treatments in view of a very low incidence of post treatment anaphylaxis reported in patients with asthma treated with omalizumab. However, there is currently no trial evidence that anaphylaxis is a risk in patients with chronic spontaneous urticaria who may represent a different population in terms of risk of severe adverse effects

Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)? Omalizumab is given by subcutaneous injection and can therefore be administered by trained nurses in an appropriate healthcare setting with facilities for resuscitation being immediately available

If the technology is already available, is there variation in how it is being used in the NHS? Omalizumab has currently been restricted to specialist urticaria clinics for patients with the most disabling disease after successful IFR funding applications so the experience of using it for the CSU indication in the UK to date is very limited

Is it always used within its licensed indications? If not, under what circumstances does this occur? Experience has shown that some patients with CSU respond adequately to 150 mg/month off licence rather than 300 mg/month. Small case series of patients with inducible urticarias (such as cholinergic urticaria, delayed pressure urticaria, cold contact or solar urticaria) indicate that patients with these variants of chronic urticaria also respond to omalizumab

Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations. Omalizumab is recommended as a third line treatment for chronic urticaria in the European guidelines [1]. The level of evidence assessment used the SIGN criteria. The strength of recommendations used a modified GRADE methodology [2]. Omalizumab is placed as a 4th line treatment in the American Practice guidelines [3].

1 Zuberbier et al. The EAACI/GA 2LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. Allergy 2014; DOI: 10.1111/all.123131
2 Zuberbier et al. Methods report on the development of the 2013 revision and update of the EAACI/GA(2) LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria. Allergy. 2014 Jul;69(7):e1-e29.
3 Bernstein et al. The diagnosis and management of acute and chronic urticaria: 2014 update. J Allergy Clin Immunol. 2014 May;133(5):1270-7. doi: 0.1016/j.jaci.2014.02.036.

The advantages and disadvantages of the technology
About 50% of patients with CSU respond symptomatically to the licensed dose of a non-sedating H1 antihistamine. Up to 70% will respond to up-dosing to fourfold. Others are treated with a range of off-licence therapies, including short courses of oral corticosteroids as rescue therapy. Some respond well to immunosuppressive drugs, especially when there is evidence of functional autoantibodies. The most widely used and evidenced therapy is ciclosporin. Other treatments that may benefit severe chronic urticaria, when taken in conjunction with H1 antihistamines, include

leukotriene receptor antagonists, dapsone and H2 antihistamines. Immunosuppressive drugs require blood monitoring for myelosuppression, renal or liver dysfunction and are contraindicated by prior malignancy (except non-melanoma skin cancer) and chronic viral infection (including hepatitis and HIV). The main advantage of omalizumab over unlicensed therapies is the very high level of effectiveness seen in many patients (complete symptom relief in about 40% and good symptom control in about 60% of patients in the phase III licensing studies), its apparent safety and lack of requirement for routine blood monitoring. The main disadvantage is the need for post treatment monitoring for adverse reactions, including anaphylaxis, and the implication that the treatments would generally be given in secondary care.

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use? Omalizumab is given by subcutaneous injection so it can be administered by suitably trained healthcare professionals without requiring an infusion suite, provided facilities for ambulant monitoring and resuscitation are available. There are no directly comparable biological treatments available for the treatment of chronic spontaneous urticaria

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation. Patients who do not respond to a daily dose of a non-sedating H1 antihistamine with a high level of symptom relief should be offered H1 antihistamine updosing, with or without a leukotriene receptor antagonist and an H2 antihistamine before considering omalizumab or an immunosuppressive drug. The severity of urticaria for non-responders should be assessed with validated tools of disease activity (e.g. a daily urticarial activity score for itch and weal numbers, the UAS7) and a measure of life quality impairment, such as the Dermatology Life Quality Index (DLQI). This is a generic assessment tool that has been validated across a wide range of dermatological disorders, including psoriasis and eczema. Patients with a score of 28/42 or higher on the UAS7 despite other medication (equivalent to moderate itch and 20-50 weals every day) should be considered for omalizumab or a trial of ciclosporin provided their DLQI score is 10 or higher. This is the threshold for considering biological treatments for patients with psoriasis. Patients who do not respond to 3 injections of omalizumab with at least a 50% reduction in baseline UAS7, DLQI or both should have their treatment discontinued. Those who respond should discontinue treatment after 6 injections to assess whether they need to continue beyond this since it is known that about 50% of CSU patients will go into spontaneous disease remission over the first 6 months of their illness. The literature indicates that omalizumab controls symptoms for 6-8 weeks after the last injection and does not appear to have a disease modifying effect, although this may occur in subgroups that remain to be identified. Patients who relapse despite a daily dose of a nonsedating H1 antihistamine should be allowed to restart omalizumab if they meet

the start criteria again. Subsequent treatments would generally be given in 6 month cycles.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes? Yes. Although patients recruited into Asteria I and Asteria II were only taking the licensed dose of a non-sedating antihistamine (plus diphenhydramine as rescue treatment – a classical sedating antihistamine not in prescription use in the UK) the Dermatology Life Quality Impairment scores are in the region that would be expected for a difficult-to treat-chronic urticaria population (median 12-13/30), the proportion of patients with angioedema and prior use of oral corticosteroids is within expectations for a general population with this severity of illness. The weal count used in the licensing studies was an average of two readings over 24 hours and used a different scale to the more commonly used European UAS7 retrospective score of total weal numbers over the previous 24 hours. However, the semiquantitative assessment of itch (none, mild, moderate, severe) is the same for both scoring systems and the primary outcome measure adopted for the phase 3 studies was pruritus (itch) at 12 weeks. The parallel improvement in weal numbers to itch over the treatment and follow-up phases of the licensing studies supports a biologically credible assessment system of the two main consequences of mast cell degranulation in the skin: pruriitus and vasopermeability. The inclusion criteria for Glacial were more in line with standard practice in the UK since patients failing to respond to up to four-fold licensed doses of non sedating H1 antihistamines who were also on montelukast, H2 antihistamines or both, were included. The limited UK experience of omalizumab for severe chronic urticaria has been relatively skewed by the requirement to make IFR funding requests. Local guidelines agreed by Guys and St Thomas' NHS Foundation Trust in 2010 (before a product licence was granted for omalizumab in chronic spontaneous urticaria) required the prior use of at least two immunosuppressive drugs and a DLQI score of at least 20 before making a funding application. Even though patients meeting these criteria had necessarily had greater prior exposure to treatment and were more severely affected than those included in the phase III studies, the proportion achieving a successful outcome (no more symptoms, or well controlled symptoms) was similar to the phase III study data

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice? The adverse effect profile in the phase III studies and real life practice is reassuringly favourable. Importantly, no confirmed events of anaphylaxis were seen in the phase III studies for chronic spontaneous urticaria and I am not aware of any in a personal clinical experience of treating around 25 patients for up to 4 years.

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Any additional sources of evidence:
Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined. No

Implementation issues
The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance. If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction. Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.
No comment

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)? The main providers of omalizumab for chronic spontaneous urticaria will be Dermatologists, Allergists and Immunologists in secondary and tertiary care. Education in completing urticarial activity scores (UAS7) and Dermatology Life Quality Index (DLQI) scores to assess the pretreatment severity of CSU and monitor progress may be required across all three specialties but is easy to achieve and the documentation to create the score sheets is straightforward with no additional cost. Medical and nursing staff might need additional training in administration of subcutaneous injections and resuscitation skills. The latter are usually compulsory modules of mandatory training in secondary care and should not provide a burden on health care resource utilization.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:
- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; - could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

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Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. None required