Comments on NICE technology Appraisal Committee's preliminary recommendations – omalizumab for chronic spontaneous urticaria

British Association of Dermatologists (BAD)

[redacted] and members of the BAD's Therapy & Guidelines sub-committee

[redacted]

[†]Chair, Therapy & Guidelines sub-committee

Omalizumab offers a remarkable advance in the management of chronic spontaneous urticaria (CSU). Clinical trials and worldwide use to date have shown that it is very effective and safe with no requirement for screening investigations or safety monitoring. Not only does it offer an alternative to existing off-licence therapies that carry important risk profiles, including immunosuppressants and oral corticosteroids, but it is also often effective for patients who have not responded to them or in whom they are contraindicated. In short, it is a breakthrough therapy for patients unresponsive to H1 antihistamines and, in particular, for patients who do not respond adequately to other treatments currently available.

The first technology appraisal does not appear to have taken sufficient account of the following areas in its preliminary recommendation:

1. **Impact of CSU on quality of life impairment**: like other persistent skin diseases, such as psoriasis, CSU ranges in severity between patients and, to a lesser extent, within patients during the course of their illness. Like psoriasis, CSU may cause substantial problems with functioning, as well as work, home, social and personal life. The degree of impairment in quality of life can be assessed by the dermatology life quality index (DLQI), a well-characterized patient-related outcome measure. A score of 10 is used as a threshold value for defining the need for treating psoriasis patients with biologics when conventional therapies have failed. A comparable threshold score should be used to assess the need of patients with CSU who have failed to respond to second-generation H1 antihistamines at above licensed doses. The mean (SD) overall DLQI score of patients recruited into the GLACIAL phase III study[1] was 13.1 (6.9) showing comparable life quality impairment with other inflammatory disorders affecting skin for which biological drugs have been approved by NICE.

2. **The need for better treatments of antihistamine-refractory CSU**: whilst H1 antihistamines will control urticaria symptoms adequately in around 50% of patients and limited trial evidence indicates that up-dosing to fourfold may control up to 75% of patients,[2] the remaining 25% require third-line drugs, including immunosuppressants (e.g. ciclosporin, methotrexate) or anti-inflammatories (e.g. dapsone, short or long courses of oral corticosteroids) and respond with varying success. These drugs require patient attendance for regular hospital and GP

monitoring and there is a significant risk of adverse effects. A very small number of these patients attending specialist urticaria clinics, respond very poorly or not all to all available treatments with consequent huge impairment in their quality of life (DLQI scores in excess of 20/30 despite best available treatment) and deserve better treatment outcomes.

Omalizumab has been compared to "no pharmacological treatment" which in real clinic scenario is not really an option for an extremely symptomatic condition such as CSU. In practice, the real choice is between omalizumab and immunosuppressants, and hence the comparison should be between these. Even though there is inadequate published data on the use of immunosuppressants in CSU, there is enough data on their side effects.

3. **Positioning of omalizumab in treatment pathways**: there is currently no trial data to position omalizumab beyond H1 antihistamines (with or without H2 antihistamine, antileukotrienes or both). Because it has not been compared to single therapies, such as ciclosporin, or a combination of therapies beyond H1 antihistamines, omalizumab is recommended as a third-line therapeutic option for patients who have not responded to up-dosed H1 antihistamines in the latest international guidelines on urticaria.[3] The committee's view that omalizumab be considered in the same place as immunosuppressants in the treatment pathway (section 4.3) in the population of CSU patients included in the GLACIAL study is appropriate but it should be positioned as a third-line rather than a fourth-line option. Specialists need the flexibility to choose therapy for their patients on the basis of clinical appropriateness.

4. **Effectiveness of omalizumab on retreatment**: (section 4.16) clinical experience at St John's Institute of Dermatology, London supports omalizumab having the same magnitude of effect during subsequent courses.

5. **High proportion of complete responders to omalizumab**: the experience of specialists in the tertiary urticaria clinic at St John's Institute of Dermatology, London has been to see a high proportion of treatment-refractory CSU patients showing a complete response to omalizumab. This is in line with a recent publication of real-life experience of treating CSU patients and other subtypes of chronic urticaria with omalizumab,[4] which described a complete response in 83% of CSU patients and only a 7% failure rate. This is better than expected from analysis of the GLACIAL study data and may indicate higher cost-effectiveness.

   The cost-effectiveness model by the Southampton Health Technology Assessments Centre does not appear to adequately encompass the costs of the very considerable disease burden caused by steroids and ciclosporin – diabetes, weight gain resulting in osteoarthritis, osteoporotic fracture, hypertension, cardiovascular disease, renal impairment, hyperlipidaemia, etc. If these iatrogenic diseases were included it could change the balance of the calculation.

6. **Clinical meaning of weekly urticarial activity scores:** the mean baseline UAS7 score of 30 in GLACIAL corresponds to the highest severity health state

(moderate-to-intense itch daily with multiple weals (hives) every day) reflecting the severity of CSU in patients treated in that study. In real world practice, limiting eligibility for omalizumab to severe or moderate health states is pragmatic in view of the need for providing suitable facilities for monthly administration in health care centres and the drug cost.

7. **Comparison of response rates in different phase III study populations**: the slightly lower frequency of response of patients recruited into the GLACIAL study (33.7% complete response, 52.4% almost complete response (UAS7, 1-6) than patients with similar baseline characteristics recruited into the ASTERIA I and II studies (40% and 58.8% responses respectively, pooled data) probably reflects a harder-to-treat study population. A more favourable cost-effectiveness analysis of omalizumab in the ASTERIA I and II population (refractory to the licensed dose of a second generation H1 antihistamine) seems likely at the possible expense of a larger eligible population.

8. **Current limits and restrictions on eligibility for omalizumab**: UK specialists were only able to seek funding approval for omalizumab from Primary Care Trusts up to 2011 by using Individual Funding Requests for the most severely affected chronic urticaria patients who remained highly symptomatic despite ongoing treatment with a basket of third-line therapies, including immunosuppressive drugs. A change in commissioning arrangements for omalizumab from individual PCTs to NHS England has seen a freeze in new commissioning decisions to date. The needs of the most severely affected treatment-refractory CSU patients have been recognized in a new commissioning policy that is due for final approval very shortly.

9. **Summary**: omalizumab is a new class of treatment for CSU that has no direct comparators. 'Treat the urticaria until it has gone,' is the objective of the 2014 guidelines.[3] No other treatment attains this objective in such a high proportion of CSU patients unresponsive to currently available options.

   In practice, dermatologists are likely to use omalizumab in patients who are not suitable for or have significant side-effects from other immunosuppressants and would be happy with a barrier to qualification higher than the licence suggests.

   Denying omalizumab for patients with a condition which impacts so significantly on their quality of life seems completely illogical.

References

1. Kaplan A *et al.* Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. *J Allergy Clin Immunol* 2013; **132:**101-9.
2. Staevska M *et al.* The effectiveness of levocetirizine and desloratadine in 4-times conventional doses in difficult to treat chronic urticaria. *J Allergy Clin Immunol* 2010; **125:**676-82.
3. Zuberbier *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.
4. Metz M *et al.* Omalizumab is an effective and rapidly acting therapy in difficult-to-treat chronic urticaria: a retrospective analysis. *J Dermatol Sci* 2014; **73:**57-62.