Healthcare professional group/clinical specialist statement

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 names:

[redacted]

On behalf of:

British Society for Allergy & 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? YES
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? YES

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

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

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.

The clinical need for omalizumab in the treatment of asthma

5.2 million children, teenagers and adults in the UK have asthma. In the British Thoracic Society and Scottish Intercollegiate Guidelines network (BTS/SIGN) guidelines on asthma management (www.sign.ac.uk/guidelines), widely used throughout the UK, asthma severity is defined in terms of the amount of treatment needed to control symptoms. For example in one study (Hoskins G et al. Thorax 2000;55:19-24), 2.4% of patients receive treatment at step 5 (the highest) according to these guidelines: by definition these patients (a minimum of 125,000) have constant symptoms and frequent exacerbations despite taking all established anti-asthma treatments, including systemic steroids. They have a very poor quality of life (Juniper EF et al. Eur Respir J 2004;23:287-291). Most of the £889 million annual direct costs to the NHS of treating asthma (2001 figures) arise from inadequately controlled, severe disease (Barnes P et al. Eur Respir J 1996;9:636-42; Blainey D et al. Health Trends 1990/91:22:151-153). New approaches to treatment of these severe patients are required. Omalizumab (OZ) is one such treatment applicable to a small subset of this category of patients because it reduces the incidence of severe disease exacerbations which are most injurious to duration and quality of life and which have a large impact on the use of health care resources by these patients. OZ therapy has now been incorporated into the BTS/SIGN guidelines as an add-on therapy for patients (from 6 years of age) at step 4/5 of “conventional” treatment, mirroring other national and international guidelines. Although other biologicals have been assessed for asthma therapy, none other than OZ has yet achieved a clear place in current treatment guidelines.

Uptake and geographical variation

NICE has performed two technology assessments for omalizumab, one in November 2007 (Reference TA133) which essentially deemed omalizumab therapy cost effective for adults with severe asthma as long as additional eligibility criteria over and above those stated in the manufacturer’s SPC were applied, and a second (Reference TA201) in October 2010 in which it was found that the treatment was not cost effective for severe asthmatic children between the ages of 6 and 11. This age dichotomy arose from the fact that the original study which formed the basis of FDA/EMA licensing and the manufacturer’s SPC (the INNOVATE study, Humbert et al. Allergy 2005; 60:309-316) happened (the precise reason is obscure) to include patients aged 12 years and above. This has created a dichotomy in eligibility for therapy in children according to age which patients, parents, physicians and patient organisations find uniformly undesirable. The cost effectiveness of any treatment is judged by NICE according to the cost per quality of life year gained (QaLY) which is an estimation of the improvement in quality of life gained by treatment standardised back to a figure between 0 (death) and 1 (normal quality of life). In the previous assessments, the cost of omalizumab per QaLY gained was considered acceptable

in adults because the treatment was saving adult patients from hospital admissions as well as improving symptoms and, to a lesser degree, systemic corticosteroid exposure. A big contributor to quality of life gained is prevention of death, since obviously if a treatment prevents premature death this produces years of prolongation of quality of life which looks good in the NICE calculations. One of the biggest problems with the TA201 assessment for children was that few if any children die (mercifully) of severe asthma, and so the cost per QaLY is not as impressive as with adults. Additionally the published paediatric studies are not directly comparable to how OZ is used by UK paediatricians. They have enrolled both moderate and severe patients were as the UK guidelines restrict it to severe disease where OZ will be more effective. This means that published studies have underestimated the effect size of OZ in a UK context.

Only a minority of patients with asthma fall into the severe SIGN/BTS step 4/5 groups. Nationwide uptake of OZ therapy has been difficult to assess because of uncertainty about the numbers of patients potentially eligible. It is the impression of many physicians and paediatricians (and certainly the manufacturers) that current uptake is considerably less than would be predicted by the number of patients with severe asthma. This may reflect ignorance of the availability of the treatment by patients and their carers, reluctance of some patients to undergo the treatment, distance from administration centres or a mixture of these. The additional eligibility criteria imposed by NICE compared with the manufacturer's SPC have also restricted uptake. Finally it is also possible that estimates of the numbers of eligible patients, based on indirect evidence from prescription records, is excessive. Some patients are excluded because they lie outside the dosage range included in the manufacturer's SPC (i.e. their total serum IgE concentration and/or their weight exceeds the maximum suggested dosage). Some of these patients have 2-20 hospital admissions per year for asthma but are denied access to omalizumab. It would be sensible for them to undergo a therapeutic trial of 16 weeks OZ to assess efficacy as this could provide a profound financial advantage to the NHS. Although the SPC has been altered to expand this table since the fist NICE assessment, this regimen is still not all inclusive. The "therapeutic" dosage of omalizumab was established, somewhat paradoxically, from studies in seasonal allergic rhinitis (Casale TB et al. J Allergy Clin Immunol 1997; 100:110-121; Am J Respir Crit Care Med 2001; 164(suppl.):818-821), the symptoms of which are far more clearly related to acute, IgE-mediated mast cell degranulation than is the case in asthma. Maximal clinical efficacy (for hay fever) was observed when serum total free IgE concentrations were reduced to <90% of the "normal" threshold (which is 100 IU/ml or 240 ng/ml). This required a dosage of omalizumab of 0.016 mg/kg per IU/ml of baseline serum total IgE. The effect is observed within 1 hour with intravenous infusion, and within 4 weeks with subcutaneous injection. It is still not clear whether or not total binding of all circulating IgE is necessary for OZ to exert its therapeutic effect in chronic asthma: if lower dosages were also effective the treatment would be cheaper and potentially inclusive of all eligible patients.

Predicting response

Assessment of OZ responsiveness remains based on physicians' global assessments of changes in symptom scores, lung function, disease control and exacerbations. The precise criteria for a "response" remain ill defined but physicians do see patients who appear clearly to be doing well and others who do not improve at all. Open, observational studies published since INNOVATE (Bousquet J et al. Allergy 2011; 66:671-678; Schumann C et al. Clin Respir J 2012 in press; Brusselle et al. Respir Med 2009; 103:1633-1642) suggest that responsiveness, although not tightly defined, after 16 weeks of treatment largely predicts responsiveness at later time points, somewhat justifying an initial 16 week trial of therapy before it is

continued or abandoned. Analysis of data gathered from key trials attempting to determine the "ideal" patient for omalizumab therapy (Bousquet J et al. Chest 2004; 125:1378-1386) suggested that the greatest response would be expected in patients with poor lung function (FEV_1 < 60% predicted) despite taking at least 800 µg inhaled beclometasone or equivalent daily, and having had at least one emergency treatment for asthma (A&E visit or hospital admission) in the previous year. In a recent paediatric study (Busse WW et al. NEJM 2011; 364: 2557-8), markers of allergy (e.g. cockroach and HDM sensitisation, elevated IgE, eosinophilia and raised exhaled nitric oxide) were associated with the best response to therapy. While these criteria are somewhat helpful in predicting responders to therapy, there are as yet no known criteria whereby those approximately 30% of treated patients who will not show a useful response to omalizumab therapy can be identified *a priori*.

Setting of therapy

For the present it remains the opinion of the BSACI that the decisions to initiate and continue treatment should be initiated by an experienced allergist chest physician or paediatrician in a secondary or tertiary asthma centre. The recent (and long awaited) availability of OZ in pre-filled syringes will make its administration more convenient and perhaps opens the way to its being administered in the longer term in the community provided the possible risks are considered acceptable (see below).

The advantages and disadvantages of the technology

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?

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.

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?

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 attraction of the technology is that it is a completely novel approach to the treatment of severe asthma which may help some patients who do not respond to available therapy. Since OZ therapy is time consuming and expensive there must be close scrutiny of its benefits. Arguably the key benefits of the therapy from the point of view of the suffering patients could be listed as:

(1) Reduction of exacerbations: Stabilisation of uncontrollable asthma, resulting in fewer A&E and hospital inpatient episodes, is clearly an extremely valuable benefit for the suffering patient as well as the NHS in terms of costs. Several (albeit open, unblinded) studies published since INNOVATE (Bousquet J et al. Allergy 2001; 66:671-678; Schumann C et al. Clin Respir J 2012 in press; Brusselle et al. Respir Med 2009; 103:1633-1642) have in general confirmed the findings of that study that OZ therapy reduces exacerbations and improves quality of life, reporting reductions of exacerbation rates between 70-85% in responders (albeit in uncontrolled trials of "non-Cochrane" quality). Indeed these figures are even more optimistic than earlier pooled analysis of 7 controlled trials of OZ (Bousquet J et al. Allergy 2005;302-308) with 4,308 participants aged 12-79 years and of duration 24-52 weeks which suggested a reduction in the annualised incidence of hospital admissions by 52% and A&E visits by 61% in the active compared with the placebo treated groups.

A study since the first NICE appraisal specifically addressing 419 inner city children (Busse WW et al. N Engl J Med 2011; 364:1005-1015) showed that treatment with OZ as compared with placebo for 60 weeks reduced the number of days with symptoms from 1.96 to 1.48 per fortnight, a 24.5% reduction. Similarly, 30.3% of patients treated with OZ as compared with 48.8% of those treated with placebo experienced one or more exacerbations. A similar reduction in exacerbations was seen in a RCT trial with 6-12 year olds with moderate to severe asthma (Lanier B et al. JACI 2009; 124: 1201-6).

Members of the BSACI who have had "hands on" experience with OZ in clinical practice uniformly agree that, in carefully selected patients with allergic asthma requiring BTS/SIGN step 4/5 therapy, the effects of OZ therapy can be dramatic and potentially life saving. Members have cases on file where patients' lives have been transformed from chaos (multiple admissions, frequent and extended periods away from work) to relative tranquillity. On the other hand there is a clear incidence of patients who fail to show any significant response meaning that they stop therapy after their 16 week trial.

(2) Reduction of oral corticosteroid therapy: No asthmatic patient wishes to be taking oral corticosteroid therapy for protracted periods of time. The potential perils of taking oral corticosteroids are easy to list but very difficult to quantify. Although a Cochrane analysis (Walker S et al. Cochrane Database Syst Rev 2006; Apr 19(2):CD003559) performed just prior to the first NICE assessment failed to show a significant oral corticosteroid sparing effect of OZ therapy in severe asthma, it is the opinion of the BSACI that this was most likely because none of the studies, including INNOVATE, on which the analysis was based was sufficiently powered to address this question. There have been several studies since addressing the oral corticosteroid sparing effort of OZ therapy but some of these must be viewed with caution given that they were not blinded and placebo controlled. One study (Siergiejko Z et al. Curr Med Res Opin 2011; 27:2223-2228) comparing patients with "optimised" asthma therapy to which OZ therapy had or had not been added in an open fashion noted a 45% reduction in the mean oral corticosteroid dosage in the OZ treated group over 32 weeks as compared with an 18% increase in the OZ untreated group. Other open studies have reported similar findings: mean oral prednisolone dosage was reduced from 22.6 to 2.9 mg/day in 16 severe asthmatic patients treated with OZ in addition to "maximal" inhaled therapy for 40 weeks (Pelaia G et al. Int J Clin Pharmacol Ther 2011; 49:713-721); mean oral prednisolone dosage was reduced by 7.5 mg/day after >16 weeks of OZ therapy in adult patients with severe asthma in a Franco-German study (Molimard et al. Respir Med 2010; 104:1381-1385). In a meta-analysis of placebo controlled studies involving 3,429 chronic severe asthmatic adults and children, the odds ratio of complete oral corticosteroid withdrawal was 1.80 (95% CI

1.42-2.28, p=0.00001) with OZ compared to placebo therapy (Rodrigo GJ et al. Chest 2011; 139:28-35); a similar analysis performed in the US involving 1,071 patients (Karpel J et al. Ann Allergy Asthma Immunol 2010; 105:465-470) reached similar conclusions (odds of receiving oral steroid bursts with OZ therapy 56% less than placebo treated controls). Most of these reductions were achieved despite improvements in overall disease stability as reflected by the numbers of exacerbations.

Despite all these studies, few are blinded and of "Cochrane" quality. Furthermore, in addressing slightly different aspects of the oral corticosteroid sparing effects of OZ therapy (changes in mean daily dosage over an arbitrary time period, odds of reducing or discontinuing oral corticosteroids) they have not allowed, in the opinion of the BSACI, a thorough analysis of long term changes in total oral corticosteroid exposure in chronic severe asthmatics as a result of OZ therapy. Furthermore, there are very few objective data about the risks of long-term oral corticosteroid therapy in populations and how such therapy affects quality of life and health service usage. The BSACI is of the opinion that attempts should be made to address the rather daunting task of factoring in costs per QaLY of therapies such as OZ which reduce long term exposure to oral corticosteroids.

(3) Reduction in inhaled corticosteroid therapy: The original Cochrane review showed that the odds ratios for reducing (by 50%) or withdrawing inhaled steroids were statistically significant in patients treated with OZ as compared with placebo, although the overall daily reduction in inhaled steroid dose was modest in relation to baseline steroid dose (e.g. mean 118 μg/day beclometasone equivalent in the INNOVATE study). It remains the view of the BSACI that, given the vastly superior safety of inhaled, as compared to systemic corticosteroid therapy for asthma, it is questionable whether reduction in inhaled corticosteroid therapy is a valid, or at least a critical outcome measure of the efficacy of OZ in the particular patients in whom it is likely to be effective.

(4) Death: approximately 1,000 asthmatics die every year in the UK. Although this figure has been reduced in the past decade it still represents nearly 3 deaths every single day. Prevention of death has the most profound effect of all on cost per QaLY calculations. In the view of the BSACI it would be salutary eventually to determine how many patients dying of asthma each year in the UK might have been eligible for OZ therapy with a view eventually to considering prevention of death as an outcome when evaluating OZ therapy. As an initial approach to this the BSACI suggests examining whether outcomes with OZ therapy in asthma can be linked to subsequent mortality.

Safety

OZ has proven remarkably safe in millions of injections administered worldwide in the face of surveillance by the FDA, the MHRA, the EMA and other bodies. In addition the American Academy of Asthma, Allergy and Immunology has set up a joint task force on omalizumab associated effects, in particular "anaphylactic" episodes which have been reported to occur in association with OZ therapy although not always in a fashion clearly temporally related to the numbers of injections or consistent with Type I hypersensitivity. In its latest report (Cox L et al. J Allergy Clin Immunol 2011; 128:210-212) this task force identified 77 out of 127 episodes reported to the FDA in a 2 year period (2006-2008) "likely or probably" related to OZ injections. 77% of these occurred within the recommended "wait period" after the injections recommended by the task force (2 hours after the first 3 doses, negotiated down with the patient according to the physician's clinical judgement, and 30 minutes after every subsequent dose), while 23% occurred later. The task force acknowledged that

many of these reports were vague and might not have reflected anaphylaxis (for example, some regarded reports of mild wheeze and flushing after the injection as significant). Serum tryptase was measured in only 6 of these cases and was not raised in any case. As a result of these findings some UK physicians provide adrenaline injector pens to their OZ patients while others do not. Anecdotal reports from BSACI members administering OZ in their own clinics suggest that the incidence of such reactions is extremely low.

Aside from these reactions the manufacturer has initiated a number of world wide post-marketing surveillance studies addressing the incidence of helminthic infections, Churg-Strauss syndrome, malignancy and other clinical safety issues (EXCELS study), foetal outcomes of OZ therapy in pregnancy and breast feeding (EXPECT) and an EU registry study of patient safety (eXpeRience). None of these has, to the knowledge of the BSACI, raised any other safety issues with OZ to date. Genentech has also initiated the TENOR series of studies (Slavin RG et al. Ann Allergy Asthma Immunol 2006; 96:406-141) partly to address safety vigilance with OZ therapy.

Summary

It is the view of the BSACI that OZ therapy continues to show great promise for the management of carefully selected, unstable atopic asthmatics, and that its potential and safety have been ratified by ongoing clinical experience. The BSACI finds it disappointing and surprising that there have been very few additional, high quality, placebo controlled data to add to those that were available at the time of the previous NICE assessment which would impact on cost per QaLY assessments. These particularly include possible influences of reduction of long term systemic corticosteroid exposure and mortality in both adults and children on cost per QaLY.

The BSACI considers it desirable that the current age dichotomy for OZ eligibility is removed as it is irksome and difficult to understand for patients, especially parents of severe asthmatic children. At the same time it would be disastrous if, as a result of an age unlimited analysis the cost per QaLY of OZ therapy was judged generally untenable. It is the view of the BSACI that such a move would cause a nationwide uproar.

The BSACI also considers it desirable for the requirement for patients to have had a certain number of severe disease exacerbations in the year prior to becoming eligible for OZ therapy be removed. Although it is recognised that reduction of unplanned hospital attendance and admission forms the backbone of the cost per QaLY equation for OZ, clinicians have different threshold for admitting patients and this admission requirement might well encourage patients to exacerbate deliberately in order to become eligible, which is clearly dangerous for patients, counterproductive and potentially costly in itself.

Finally, the BSACI urges NICE to consider the effects of OZ therapy separately in severe asthmatic patients taking and not taking systemic corticosteroids. While the BSACI endorses the view that any patient requiring continuous or frequent oral corticosteroid therapy for asthma should be deemed eligible for OZ therapy this would give a better appreciation of the QaLYs gained.

Many issues in addition to those mentioned above remain to be addressed, for example:

(1) The necessity for patients to have a positive skin prick test to one or more arbitrary aeroallergens in order to be eligible for treatment: there is currently no scientific or clinical basis for insisting on this requirement.

(2) The necessity for lifelong, as opposed to intermittent or lower dosage therapy. This is being preliminarily addressed in manufacturer initiated studies such as X-PORT but clearly expansion of clinical data in this regard is imperative. One single analysis of the INNOVATE study suggests that symptoms re-emerge on withdrawal of therapy (Slavin RG et al. J Allergy Clin Immunol 2009; 123:107-113) and also that continued therapy with the initial dose of OZ is necessary to maintain clinical efficacy).
(3) Understanding how to predict responsiveness to OZ therapy.

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.

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.

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)?

Since treatment is potentially life long there were initial concerns that treatment would create an increasingly large cohort of patients requiring continuous treatment that would exert an ever increasing strain on hospital services. So far this situation has not materialised, with fewer patients than anticipated currently under treatment. This partly reflects the stringency of the current NICE criteria as mentioned above.

Introduction of pre-filled syringes will further facilitate OZ administration in hospital clinics and perhaps ultimately also in the community, and also reduce wastage (for example if patients fail to attend booked appointments for injections). Staff should be conversant with the management of asthma and anaphylaxis, how to perform routine spirometry and examine quality of life and peak flow charts but need little other specific training.