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NICE Omalizumab for the treatment of severe persistent allergic asthma (MTA)
RCPCH submission on technology appraisal

With thanks to:
[redacted]

Expected place of the technology in current practice
Comments: This therapy is specifically effective in patients with severe asthma dependent on long term oral corticosteroids. There is no other therapy which has been shown to be of any consistent benefit in this group of patients. It should be reserved for use by Consultants in Respiratory Paediatrics working in specialist units. Until the most recent NICE guidance patients from 6 years of age upwards could be treated, but it is now recommended that this treatment be limited to those >12 years of age. We have accumulated significant clinical experience in the use of this agent in children both <12 and >12 and enclose a copy of a draft of this open label experience which is in the process of being submitted to Archives of Disease in Childhood. We would appreciate if this document could be treated in confidence although a previous draft has already been submitted directly to NICE. Our experience of the use of Omalizumab is that >90% of patients treated derive significant clinical benefit from the use of this agent, oral corticosteroids could be discontinued completely in a significant percentage of patients and the median reduction in oral steroid dose was 75%. The treatment was associated with significant improvements in both quality of life and asthma control score. There were no significant adverse effects. We were unable to detect any differences in response between those < and > 12 years of age. Technology could be used in secondary or primary care. Training by specialist nurses from secondary care would be essential for ongoing treatment of a patient in primary care. Cold chain supply is necessary to primary care from the hospital and a secondary care pharmacist's input would be very advantageous. The place for this technology has been universally agreed as being within tertiary respiratory paediatric centres. There is virtually no difference of opinion about its usage between specialist respiratory paediatricians. The current alternatives to the technology are regular oral corticosteroids such as prednisolone and poisonous, non-proven therapies such as methotrexate, cyclosporin and gold therapy. Even with the less hazardous oral steroid treatment, asthma control is inadequate and long-term toxicity is inevitable. There are therefore no suitable alternative therapies. Decisions on whether omalizumab should be considered should be entirely in the hands of paediatric respiratory specialist in UK tertiary centres. In children aged 6-12 years, although there is a UK marketing authorisation, omalizumab has not been approved for use by NICE. The technology is expensive and as usual in this situation, prescribing throughout the regions is very variable and at the discretion of local managers. The recent national guidelines for asthma management acknowledge there is a place for this technology. As usual there is much less evidence for its use in children than in adults because it will only be needed in a very small number of children with the most severe asthma symptoms. The lack of research studies using omalizumab in 6-12 year olds puts them at a significant disadvantage compared to teenagers and adults with severe asthma. We believe omalizumab has always been used within its licensed indications.
The advantages and disadvantages of the technology
Comments: This drug has been the only significant advance in the management of severe oral steroid dependent asthma in the last 30 years. Unfortunately most of the clinical trial data is derived form outside of the UK and largely reflects clinical practice in the USA, which is markedly different to that in Northern Europe. Most of the patients treated have been of moderate severity, and the number of truly

severe paediatric patients dependent on long term oral corticosteroids included in trials has been extremely small. The drug is very expensive and has to be administered by subcutaneous injection every 2 to 4 weeks. The main benefit of therapy is a reduction in the potential for well known serious adverse effects related to long term oral corticosteroid usage; these benefits are significant and greatly appreciated by patients, carers and clinicians. Although there will be significant economic benefits from these reductions in oral steroid usage they will only be realised over the long term and as such they are almost impossible to quantify in term of Health Economic analyses such as QALYs.

Note that the pharmaceutical presentation of omalizumab has changed to pre-filled pens of 75 and 150 mg dose size. There is potential for direct cost saving with this and also indirectly with a saving in nursing time.

Omalizumab is an expensive medication whose usage must be decided by tertiary respiratory paediatric experts but its efficacy and safety compare extremely well with its toxic and often non-clinically researched counterparts. The long-term side-effects of moderate or high dose oral steroids are well known. Numerous studies confirm their lack of adequate efficacy and their toxicity in relation to bone biochemistry, growth and immune suppression. There are no appropriate studies (except for anecdotal reports) for the use of the other comparable treatments – methotrexate, cyclosporin and gold therapy.

Studies undertaken using omalizumab show a good safety profile and proven efficacy. An important aspect of omalizumab use is its ability to reduce the dosage of regular oral steroid therapy. Respiratory paediatricians worldwide will acknowledge the lack of studies undertaken in children under 12 years of age but the collective clinical view is consensual and positive in relation to anecdotal management.

It is important to recognise that the pathology of asthma in young children aged 6-12 years is the same as that in teenagers and in adults. There is therefore no reason to believe that the technology is less effective in children. To my knowledge no additional adverse effects have come to light subsequent to previous clinical trials when omalizumab has been used in routine clinical practice.

It is imperative to recognise that omalizumab will only ever be used by a very small number of children with extremely severe asthma.

In relation to NICE outcome measures, we assume that there is a grammatical error in the 3rd bullet point of the table in appendix B. Surely, it should read ‘Use of oral corticosteroids’ (as part of outcome measures) and the next word ‘mortality’ should either be a separate bullet point or separated from ‘Use of oral corticosteroids’. These are important issues that will be alluded to in the next comments section.

Any additional sources of evidence

Comments: Please see attached.

Long-term oral corticosteroid use will inevitably lead to long-term side-effects despite producing inadequate asthma control. Mortality in the 6-12 year age group because of asthma is negligible and makes economic analysis in relation to cost per quality-adjusted life year a meaningless target. This issue was discussed at the RCPCH/NICE meeting held over one year ago and we really must not accept quality-adjusted life year assessment based on adult standards to be used to assess outcomes in children. If quality of life assessments are to be used in children they must include assessment of their educational progress, examination results and life-long outcomes as otherwise adult orientated economic quality assessments will lead to unacceptable moral and political discrimination against children. The principal reason for the development of the Medicines for Children Research Network and the change in European law on medicines for children was that in the past studies in children were inadequate in number and were wrongly based on methodological principles only applicable to adults. Should NICE not recognise that there needs to be a different economic analysis for children, they will fail to recognise that children are unique and require novel approaches to understand appropriate management for them. The study by Broder et al in *Allergy Asthma Proc* (2009 **30** pp148-157) has looked at these aspects of quality of life in children.

Implementation issues

Comments: There are numerous studies which show that well-controlled asthma is much cheaper to manage than when the disease is poorly controlled. Total evaluation of very severe asthma in a small number of children can be estimated by expert pharmaco-economists. Appropriate quality of life measures suitable for children have rarely been undertaken but it is vital that this concept is grasped by NICE if fairness is to be observed in all age groups. There are a small number of experts in this field within the UK who would be delighted to work with NICE on this issue.

Within the final scope, as documented in August 2011, under ‘other considerations’ it is suggested that ‘If the evidence allows, social factors affecting adherence to treatment will be considered’. Another way

of looking at this statement is that it is not a young child who doesn't comply with treatment, it is the parent who does not have the ability to ensure his or her child receives the medication. Where this occurs one should be even more willing to consider a technology such as omalizumab rather than denying it on the grounds of non-compliance. This is another issue pertinent to children. The child must not be punished because of parental shortcomings.

In relation to the long-term use of omalizumab, we do not know whether or not the treatment will be needed for many years but it is probable if efficacy has been shown after 16 weeks of treatment. The technology, however, will only be used in a very small number of children and will not be available 'on demand' by parents or by other healthcare professionals. We do not believe that the numbers requiring the technology will increase over the years as there is no evidence that the prevalence of very severe asthma in children is rising.

Given that NICE's appraisal relates to all ages, if the cost effectiveness analysis is expressed as incremental cost per quality-adjusted life year but includes assessment of children without accounting for long-term educational disruption etc., this will have a negative effect on the other age groups over 12 years of age by introducing bias against them.

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