COMMENTS ON

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCEORGANISATION

HEALTH TECHNOLOGY APPRAISAL: CORTICOSTEROIDS FOR THE TREATMENT OF CHRONIC ASTHMA (IN ADULTS) - INVITATION TO MAKE A SUBMISSION

The Royal College of Physicians of Edinburgh is pleased to respond to the National Institute for Health and Clinical Excellence's invitation to make a submission on the above Appraisal.

The College is concerned that there are errors in the text. We have given specific comments below, including comments on the Plain English summary and on potential flaws in comparing clinical trials patients with "real world" asthma patients.

The College has concerns as to:

1. Outcomes – emphasis on mortality (where the UK does very well, with very low mortality) rather than morbidity, where the UK does very badly (about the worst in the world). So outcomes such as "asthma free days/weeks", "symptom-free days/weeks", "rescue-free days/weeks", or guideline defined levels of asthma control (as per GINA or BTS/SIGN), should receive equal value to standard measures such as FEV_1 / PEF, or Quality of Life.

2. Assessment of quality of meta-analyses (see specific comments below).

3. The application of "clinical trials patients" to "real world patients" (see below).

Comments on the Plain English Summary:

4.1 para 1 line 9: increasing age is NOT seen as a risk factor for developing asthma (NB. The reference used here [3] is a review article in a low impact journal, probably not refereed).

4.1 para 2: undue emphasis placed on mortality (which is very low in the UK) and none on morbidity (which is almost the highest in the world (GINA report, Global Burden of Asthma 2004),

4.2 para 1 last line: "rescue" medication is a term used for use of short acting β_2-agonists, not oral steroids.

4.2 para 3: Step 4 would not usually involve adding oral β_2-agonists, especially if the patient is already taking a long acting β_2-agonist. The usual add on drugs would be leukotriene receptor antagonist, theophylline, and anticholinergic.

4.2.1 para 1: BTS/SIGN Guidelines suggest add ICS if short acting β_2-agonists are being used more than twice per week.

4.2.1 para 1 last line: the word "should" should really be "must".

4.2.1 para 2: products: 3M no longer marketing in UK, IVAX is selling their products. Trinity Chiesi is now selling (or about to sell) their version of Formoterol.

4.2.1 para 4: "standard daily recommended doses" do NOT reflect the relative potencies of the drugs.

4.2.2 para 1: formoterol is now available from Trinity Chiesi.

4.2.2 para 2: Budesonide. It is important to recognise the complexities of the doses quoted (this will vary from study to study depending on the origin of the research work). The dose can be expressed as dose delivered or as dose actuated. Thus:

80/4.5 is the same as 100/6
160/4.5 is the same as 200/6
320/9 is the same as 400/12

The standard terminology in the UK is as per the second column.

4.2.2 para 2: Budesonide. 80/4.5 (100/6 in UK terms) is NOT the standard UK starting dose for adults, which is 200/6.

5.1 and 5.2.3: There are potential problems when incorporating a range of meta-analyses and RCTs. There is a significant risk of "double counting", either if two or more meta-analyses incorporate a number of the same primary trials or even a meta-analysis and a primary RCT. This may be less important if the meta-analyses were only used as a source of primary trials, but the wording of section 5.2.3 implies that this is not the intention, but that the conclusion/data of meta-analyses would be handled as if they were primary data sources. Depending on how the meta-analyses are handled one primary trial source may be re-used on numerous occasions.

The other main concern reflects how the quality of a meta-analysis is assessed. Simply checking that the methodology for selection of studies is appropriate does not mean that the meta-analysis is not flawed. (An excellent example in the field of asthma is a recent meta-analysis of safety of long acting β_2-agonists by Salpeter et al in Ann Intern Med 2006. Although the methodological approach to selection of papers, as written, appears sound, in reality the authors omit many studies that would appear to address the topic and fulfil their selection criteria. Further, their outcome assessment on risk of asthma death is based on one

paper, which contributes also to 80% weight of their outcome of risk of a severe asthma attack. The primary paper is highly flawed in design and patient recruitment, and yet is now twice counted by virtue of a flawed meta-analysis).

We do not think appendix 9.5 gives valuable reassurance that the criticisms implied above would necessarily be avoided.

5.2: assessment of "cost effectiveness", in a clinical trial of separate inhalers for ICS and LABA, ignores any potential "clinical effectiveness" of increased patient concordance with treatment if a combination inhaler is used.

5.2: omitting studies taking different doses of the same agent may limit the assessment of clinical effectiveness.

5.2.4: does combining asthma with COPD not confound the appraisal?

5.4 (and 4.2.1): The assumption that pMDI HFA and CFC equivalences are different is doubtful in accuracy. Only the 3M product (now from IVAX), namely QVAR makes that claim (and this is based on a combination of HFA effect and improved inhaler efficiency). Supporting studies for this are modest and the outcomes may reflect study design as much as scientific reality. Other manufacturers have attempted to achieve dose equivalence (HFA vs CFC) so as to avoid dosing problems for the prescriber. Further, the HFA vs CFC issue is pertinent only to beclometasone (not other ICS). In the HFA beclometasone goes into solution, rather than remaining in suspension, thereby reducing the inhaled particle mass median diameter, which may affect lung deposition.

6.5 (b) para 5: costs of the same product vary, depending on which device and which strength is being used (eg Seretide).

Comments on potential flaws in conclusions from RCTs and Meta-analyses

1. Asthma RTCs, and thus meta-analyses, are heavily biased in patient selection, primarily to fit with requirements of the FDA and EMEA to avoid patient inclusion whereby the patient may not have asthma! Thus, the vast majority of trials will select, for example, non-smokers (or ex-smokers with <10 pack years) with reversibility of > 12% FEV_1 to inhaled salbutamol, etc. The real world asthmatic is very different and responses to ICS in smoking asthmatics (probably c.25% of most asthma clinics) are different to the standard non-smoking clinical trial patient – requiring substantially higher doses of ICs for the same clinical benefit. A paper by Herland K et al (Respir Med 2005; 99: 11-19) suggests that as few as 5.4% "real life" asthmatics meet the "standard" study entry criteria. Example papers on the influence of smoking and ICS responses are: Tomlinson JE et al. Thorax 2005; 60: 282-7. and Livingstone E et al. Drugs 2005; 65: 1521-36.

2. Similar arguments apply to patients' abilities to use different inhaler devices efficiently. In clinical trials patients have to be able to use a particular inhaler device efficiently in order to be eligible for the study. In "real life" many patients do not, in fact, use all devices efficiently. The one most likely to be used most poorly is the pMDI, which because of pricing strategies in the UK may be cheaper than breath actuated or dry powder devices. Clinical trials will therefore overestimate the clinical effectiveness of such inhalers.

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18 July 2006