NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Corticosteroids for the treatment of chronic asthma in children under the age of 12 years

Draft scope

Appraisal objective

To appraise the clinical and cost effectiveness of corticosteroids, including compound preparations, for the treatment of chronic asthma in children under the age of 12 years and to provide guidance to the NHS in England and Wales.[1]

Background

Asthma is characterised by symptoms such as dyspnoea, chest tightness, wheezing, sputum production and cough associated with variable airflow obstruction and airway hyperresponsiveness. Diagnosing asthma in children requires exclusion of other causes of recurrent respiratory symptoms and differentiation between asthma and non-asthmatic viral wheeze may be difficult. Persistent symptoms between acute attacks, personal or family history of atopic conditions such as eczema and hay fever are suggestive of asthma. In children old enough to perform peak flow measurements or spirometry the diagnosis may be confirmed by demonstrating reversible airway obstruction, preferably on several occasions.

Asthma attacks vary in frequency and severity. Some people who have asthma are symptom-free most of the time, with only occasional episodes of shortness of breath. Other people cough and wheeze most of the time and may have severe attacks after viral infections, exercise, or exposure to allergens or irritants, including cigarette smoke.

According to Asthma UK's criteria and independent analysis of large-scale surveys, there are 5.2 million people with asthma in the UK today (4.7 million in England and Wales). Of these 1.1 million are children (955,000 in England and Wales). Surveys have found an increase in the proportion of children diagnosed with asthma between the 1960s and the 1980s that is higher than can be explained by an increased readiness to diagnose asthma. This increase in the prevalence of childhood asthma from was accompanied by an increase in hospital admissions.

[1] The Department of Health and Welsh Assembly government remit to the Institute: To appraise the relative clinical and cost effectiveness of all licensed corticosteroids, including compound preparations, in the treatment of chronic asthma; and if the evidence allows, to advise on the groups of patients who are most likely to benefit from any particular corticosteroid.

The main mechanisms for the development and of asthma are considered to be related to inflammation and its resultant effects on airway structure and function. The role of corticosteroids in controlling inflammation is recognised as central to the pharmacological management of asthma in current guidelines.

Current British guidelines for the management of asthma recommend a stepwise approach to treatment in both adults and children.[2] Treatment is started at the step most appropriate to the initial severity of their asthma with the aim of achieving early control of symptoms and optimisation of peak flow rates. Control is maintained by stepping up treatment as necessary and stepping down when control is good.

Step 1 – Mild intermittent asthma

Occasional inhaled short acting $beta_2$ agonists used as required for symptomatic relief.

Step 2 – Introduction of regular preventer therapy

Inhaled corticosteroids are the recommended preventer drugs for achieving overall treatment goals. Other, less effective preventer therapies include chromomes (sodium cromoglycate, or nedocromil sodium), leukotriene receptor antagonists (montelukast and zafirlukast) and theophyllines (aminophylline and theophylline). In children who cannot take an inhaled corticosteroid, a leukotriene receptor antagonist should be used.

Step 3 – Add-on therapy

There is no precise threshold in terms of dose of inhaled corticosteroid for the introduction of a third drug. However, the guidelines recommend a trial of add-on therapy before increasing the daily dose of inhaled corticosteroid above 400 micrograms in children (5-12 years).[3] Options for add-on therapy in children taking doses of 400 micrograms are as follows.

- In children aged 5-12 years, the addition of an inhaled long-acting $beta_2$ agonist is the first choice. (Neither of the long-acting $beta_2$ agonists is licensed for use in children under the age of 4 years.)
- In children aged 2-5 years, a leukotriene receptor antagonist should be considered.
- In children aged under 2 years, referral to a respiratory paediatrician should be considered.

[2] British Guideline on the Management of Asthma: a national clinical guideline. The British Thoracic Society and Scottish Intercollegiate Guidelines Network. SIGN Guideline No. 63 Revised November 2005.

[3] Doses refer to beclometasone dipropionate given via a pressurised metered-dose inhaler. Adjustment is necessary for fluticasone and mometasone and some alternative delivery devices.

Step 4 – Poor control on moderate dose of inhaled steroid plus add-on therapy: addition of fourth drug (children aged 5-12 years).

For children aged under 5 years, step 4 is referral to a respiratory paediatrician.

In children aged 5-12 years, if control remains inadequate on inhaled corticosteroids at daily doses of 400 micrograms plus add-on therapy the following options should be considered:

- increasing the daily dose of inhaled corticosteroids to 800 micrograms
- leukotriene receptor antagonists
- theophyllines
- slow release beta$_2$ agonist tablets.

Step 5: (for children aged 5-12 years only) continuous or frequent use of oral corticosteroids. Before proceeding to this step, referral to specialist care should be considered.

The technologies

There are five inhaled corticosteroids licensed in the UK for the treatment of asthma. Of these, three are licensed for use in children under the age of 12 years. High dose inhalers are not licensed for use in children.

- Beclometasone dipropionate (AeroBec [3M], Asmabec Clickhaler [Celltech], Beclazone Easi-Breathe [IVAX], Beclometasone Cyclocaps [APS], Becodisks [Allen & Hanburys], Becotide [Allen & Hanburys], Filair [3M], Qvar [3M], Pulvinal Beclometasone Dipropionate [Trinity]).
- Budesonide (Budesonide Cyclocaps [APS], Novoliser [Viatris], Pulmicort [Astra-Zeneca])
- Fluticasone propionate (Flixotide [Allen & Hanburys])

All three drugs are available in both pressurised metered dose and dry powder formulations. They are also available in formulations for nebulisation.

Compound preparations are combinations of a corticosteroid and a long-acting beta$_2$ agonist in a single inhalation. There are two combinations available; budesonide with formoterol fumarate (Symbicort [AstraZeneca]) and fluticasone propionate with salmeterol xinafoate (Seretide [Allen & Hanburys]). The lowest dose Symbicort inhaler (budesonide 100 micrograms, formoterol fumarate 6 micrograms) is licensed for use in children aged 6 years and older. Symbicort is currently available as a dry powder inhaler only. The lowest strength Seretide inhalers are licensed for use in children aged 4 years and older. Seretide is available as a pressurised metered-dose inhaler and as a dry powder inhaler.

Intervention(s)	Corticosteroids for inhalation • beclometasone dipropionate • budesonide • fluticasone propionate Compound preparations containing a corticosteroid and a long-acting beta$_2$ agonist for inhalation • budesonide plus formoterol fumarate • fluticasone propionate plus salmeterol (as xinafoate)
Population(s)	Children younger than 12 years with asthma. The following subgroups should be considered • Children younger than 2 years • Children between the ages of 2 and 4 years • Children between the ages of 5 and 11 years
Standard comparators	For inhaled corticosteroids: • the agents will be compared with each other The compound preparations will be compared with each other and with: • inhaled corticosteroids and long-acting beta$_2$ agonists administered by separate inhalers • increased-dose inhaled corticosteroids alone • inhaled corticosteroids used in combination with other drugs such as cromones, theophyllines and leukotriene receptor antagonists
Outcomes	The outcome measures to be considered include: • objective measures of lung function (e.g. FEV1, PEF) • symptoms (e.g. wheeze, shortness of breath) • incidence of acute exacerbations • use of systemic corticosteroids • adverse effects of treatment • health-related quality of life.

Economic analysis	Ideally, the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	The drugs will be appraised in the context of the guidelines from the British Thoracic Society and Scottish Intercollegiate Guidelines Network. That is, it is assumed that the drugs will be used in the stepwise approach recommended by these guidelines. Variation in dose-equivalence between different drugs and formulations will be taken into account as far as the evidence allows. If the evidence allows, subgroups for whom any drug or formulation may be particularly effective should be identified. The role of the technologies in treating acute asthma will not be considered. The interventions will be appraised according to their licensed indications. Guidance will only be issued in accordance with the relevant marketing authorisations.
Related NICE recommendations	Related Technology Appraisals: National Institute for Clinical Excellence Guidance on the use of inhaler systems (devices) in children under the age of 5 years with chronic asthma Technology Appraisal Guidance No 10 London : NICE ; August 2000 National Institute for Clinical Excellence Guidance on the use of inhaler systems (devices) for the routine treatment of chronic asthma in older children (aged 5-15 years) Technology Appraisal Guidance No 38 London : NICE ; August 2000 Related Guidelines: None

Questions for consultation

Would it be feasible and useful to compare inhaled corticosteroids with other drugs such as leukotriene agonists and cromones? If so, should this comparison apply to all age groups?

For the compound preparations and inhaled corticosteroids used in combination with oral bronchodilators, would it be sufficient to compare them with increased doses of corticosteroids and/or inhaled corticosteroids and long-acting beta$_2$ agonists given separately?