

montelukast 4mg and 5mg chewable tablets and 4mg granules (Singulair Paediatric[®]) **No. (383/07)**

Merck, Sharp & Dohme Ltd

8 June 2007

The Scottish Medicines Consortium has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

montelukast chewable tablet and granules (Singulair Paediatric[®]) is accepted for restricted use within NHS Scotland as an alternative treatment option to low-dose inhaled corticosteroids for patients, [children 2 to 14 years of age] with mild persistent asthma who do not have a recent history of serious asthma attacks that required oral corticosteroid use, and who have demonstrated that they are not capable of using inhaled corticosteroids.

It should be restricted to initiation by specialists in paediatric asthma care.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

An alternative treatment option to low-dose inhaled corticosteroids for patients (children 2 to 14 years of age) with mild persistent asthma who do not have a recent history of serious asthma attacks that required oral corticosteroid use, and who have demonstrated that they are not capable of using inhaled corticosteroids.

Dosing information

For children aged 2-5 years, 4mg chewable tablet or granules in the evening.

For children aged 6-14 years, 5mg chewable tablet in the evening.

Chewable tablets should be taken one hour before or two hours after food. The granules can be administered without regard to the timing of food ingestion either directly in the mouth, or mixed with a spoonful of cold or room temperature soft food. After opening the sachet, the full dose must be administered within 15 minutes.

Product availability date

21st April 2006

Summary of evidence on comparative efficacy

Montelukast is a leukotriene-receptor antagonist which blocks the action of cysteinyl leukotrienes (pro-inflammatory mediators produced by eosinophils and mast cells), which cause bronchoconstriction, mucous secretion, vascular permeability, and eosinophil migration.

A double-blind study recruited 994 patients aged 5-15 years with mild persistent asthma with forced expiratory volume in first second (FEV₁) at least 80% of predicted and an increase in FEV₁ of at least 12% in response to inhaled β -agonist and who were required to use a β -agonist on ≥ 2 but ≤ 6 days on 2 weeks of a 4-week single-blind placebo run-in baseline period where patients discontinued any asthma controller medication. Patients were equally randomised to receive either montelukast oral tablet once daily (5 mg to patients ≤ 14 years of age or 10 mg to those who turned 15 years of age during the study) or inhaled fluticasone 100 μ g twice daily for 12 months. Patients were allowed to use a salbutamol inhaler as required, systemic corticosteroids for rescue and, if asthma symptoms were not controlled adequately, any other controller medication at the investigator's discretion. Patients could continue immunotherapy at a stable dose if it had been initiated 3 months before the study. The primary efficacy end point was the percentage of asthma rescue-free days (RFDs) during 1 year of treatment, measured as a change from baseline period. An RFD was defined as a day on which no rescue medication was used (i.e. β -agonist, systemic corticosteroid or other rescue medications) and no asthma-related unscheduled visits to the general practitioner or hospital. This was assessed in all randomised patients who had been treated for ≥ 1 day. The trial was completed by 925 patients. Montelukast was demonstrated to be non-inferior to fluticasone in the change from baseline in percentage of asthma RFDs over a 12 month treatment period: 22% (95% confidence interval (CI): 21% to 24%) and 25% (24% to 27%) in the respective groups, with the difference in least-squares means between the groups of -2.8% (95%CI: -4.7% to -0.9%), which was above the pre-specified non-inferiority limit of -7%. In a per-protocol analysis, the estimated difference between treatments in least-squares means was -3.2% (95%CI: -5.2% to -1.3%).

The mean percentage of asthma RFDs over 12 months was 84% and 87% in the montelukast and fluticasone groups, respectively. Fluticasone was significantly superior to montelukast for mean change over 12 months from baseline in predicted FEV₁: 2.7% vs. 0.6%, with a least-square mean difference (95%CI) of -2.2 (-3.6 to -0.7) and decrease in days with β -agonist use: 25% vs. 23%, with a least-square difference of 2.7% (0.9% to 4.5%). The proportion of patients who used additional asthma rescue medication, excluding short-acting β -agonists, was also lower in the fluticasone group: 14% vs. 21%, with a relative risk of 1.56 (95%CI: 1.17 to 2.06), with the majority of these being systemic corticosteroids: 10% and 18% of patients in the respective groups. The proportion of patients with an asthma attack was also lower in the fluticasone group: 26% vs. 32%, with a relative risk of 1.26 (95%CI: 1.04 to 1.52). Both montelukast and fluticasone significantly improved the quality of life, assessed via a disease-specific questionnaire in a subgroup of patients aged 9 to 14 at selected centres, during the 12 month period compared to baseline: 0.92 and 1.05, respectively, with the difference (95% CI) between the groups of 0.13 (0.01 to 0.25) of borderline significance (p=0.036). Fluticasone was associated with significantly greater improvement from baseline over 12 months on the asthma control domain of the Paediatric Asthma Therapy Assessment Questionnaire: 1.3 vs. 1.1., with a difference (95%CI) of 0.2 (0.1 to 0.4). In the fluticasone and montelukast groups, the proportion of patients with ≥ 1 day lost from school during the 4 weeks preceding the month 12 visit were 6.2% and 8.8%, respectively, and the percentages of patients with >3 lost school days were 2.1% and 1.9%, respectively.

A double-blind study recruited 689 patients aged 2-5 years with persistent asthma, who had at least 3 episodes during the previous year and who used a β -agonist on at least 8 days during a 2-week single-blind placebo baseline period. Patients were randomised in a 2:1 ratio to receive montelukast 4mg chewable tablet or placebo at bedtime for 12 weeks. Concomitant permitted medication included immunotherapy at a constant dosage and oral inhaled or nebulised β -agonists as needed. Up to 50% of patients were permitted inhaled (or nebulised) corticosteroids or cromolyn at a constant dosage, beginning at least 1 month before and throughout the study. Oral corticosteroid rescue for worsening asthma was permitted according to a predefined plan. The primary objective was to determine the safety and pre-defined efficacy assessments were exploratory. These were assessed in all patients with a baseline and at least 1 post-baseline measurement. Montelukast, compared to placebo, was associated with a greater percentage of days without asthma and significant improvements in an overall daytime asthma symptom score, individual symptom scores for cough, wheeze, trouble breathing, limitation of activity and night-time symptom scores. It was also associated with a significantly fewer patients requiring rescue oral corticosteroids and fewer days when a β -agonist was used.

Summary of evidence on comparative safety

In the active-comparator study there were no significant differences in terms of clinical or laboratory adverse events between the montelukast and fluticasone groups and adverse event rates were low. The most common adverse events were headache (2.2% (n=11/495) and 1.0% (n=5/499) in the respective groups) and asthma (0.6% (n=3/495) and 0.4% (n=2/499) in the respective groups). The average rate of growth over the 12-month period in the fluticasone and montelukast groups were, 5.81 and 6.18 cm/year, with a difference between treatments of 0.41cm/year (95% CI: 0.07 to 0.75cm/year) that was significant (p=0.018).

Summary of clinical effectiveness issues

Although montelukast has been shown to be non-inferior to fluticasone with regard to the percentage of asthma-free days, fluticasone appeared to be superior to montelukast for a number of secondary outcomes.

Some Scottish clinicians advise that a very small percentage of Scottish asthmatic children with severe behavioural or neuro-developmental problems cannot use an inhaler alone or via a face-mask and spacer device even with the correct training.

Xanthines are alternatives to leukotriene receptor antagonist in children over 5 years, but according to Scottish experts are not routinely used in Scotland for mild persistent asthma.

Summary of comparative health economic evidence

The manufacturer provided a simple cost analysis to compare montelukast treatment to no treatment in children aged 2 to 14. The no treatment comparator was justified given the limited treatment options available to patients who are not able to take inhaled treatments. The results of the analysis indicated that treatment with montelukast was associated with a cost of £273 per patient. This figure was derived by taking into account the drug acquisition cost of montelukast of £335 per year and also savings of approximately £60 per year given lower rates of asthma attacks requiring treatment.

Summary of patient and public involvement

Patient Interest group Submission: Asthma UK Scotland.

Additional information: guidelines and protocols

British Thoracic Society and Scottish Intercollegiate Guidelines Network (SIGN): British Guideline on the Management of Asthma - A National Clinical Guideline, SIGN publication number 63; revised edition November 2005 recommends that if an inhaled steroid cannot be used a leukotriene receptor antagonists can be used as regular preventer therapy in children less than 5 years. In children aged 5-12 years who cannot use an inhaled corticosteroid the guidelines recommend non-specifically using another preventer drug.

The National Institute for Health and Clinical Excellence (NICE) Health is producing a health technology appraisal titled: Corticosteroids for the treatment of chronic asthma in children under the age of 12 years that is expected to be issued is November 2007. The NICE recommend a leukotriene receptor antagonist in children who cannot take an inhaled corticosteroid as regular preventer therapy.

Additional information: previous SMC advice

In August 2004 following an abbreviated submission the Scottish Medicines Consortium (SMC) issued advice that montelukast paediatric 4 mg granules (Singulair®) are accepted for use in NHS in Scotland for the treatment of asthma as add-on therapy in those patients with mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom 'as needed' short-acting beta-agonists provided inadequate clinical control of asthma. It is also accepted for the prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction. This formulation is suitable for the treatment of children aged 6 months to 5 years, and the licence for montelukast has been extended to include children aged 6 months to 2 years, though the Summary of Product Characteristics adds that experience in those aged 6 to 12 months is limited. Its introduction is expected to have minimal resource implications in Scotland.

In June 2005 following a full submission, the SMC issued advice that montelukast is accepted for restricted use within NHS Scotland for the symptomatic relief of seasonal allergic rhinitis (SAR) in adult patients in whom montelukast is indicated in asthma, as add-on oral therapy at steps 3 and 4 of the BTS/SIGN asthma guidelines. Other more effective and cost effective treatments for SAR are available for patients in whom montelukast is not required for the treatment of asthma.

Additional information: comparators

No other medicines are licensed for use as alternative treatment options to low-dose inhaled corticosteroids in children with mild persistent asthma who have demonstrated that they are not capable of using inhaled corticosteroid.

Zafirlukast is another leukotriene antagonist, but it is not licensed for this indication.

Costs of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Montelukast	4mg oral granules once daily	334
Montelukast	4mg or 5mg chewable tablet once daily	334
Zafirlukast*	20mg tablet twice daily	367

Doses are for general comparison and do not imply therapeutic equivalence;

* Zafirlukast is only licensed for use in children over 12 years.

Additional information: budget impact

The gross budget impact of using montelukast was estimated by the manufacturer as being £29k in year one rising to £86k in year five. This included the cost of montelukast and also the cost of any asthma attacks that require treatment when the children are on montelukast. The net costs (taking account of the additional savings associated with treating asthma attacks compared to if these children were on no active treatment) were £13k in year one rising to £132k in year five. These figures assumed 48 patients in year one rising to 145 by year five, representing 20% and 60% of the eligible patient populations in each year respectively.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 11 May 2007.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission.

Garcia Garcia ML, Wahn U, Gilles L et al. Montelukast, compared with fluticasone, for control of asthma among 6- to 14-year-old patients with mild asthma: The MOSAIC study. *Pediatrics* 2005;116:360-369.

Knorr B, Matz J, Bernstein JA et al. Montelukast for chronic asthma in 6- to 14- year old children: A randomized double-blind trial. *JAMA* 1998;279:1181-1186.

Knorr B, Franchi LM, Bisgaard H et al. Montelukast, a leukotriene receptor antagonist, for the treatment of persistent asthma in children aged 2 to 5 years. *Pediatrics*, 2001;108:1-10.