Scottish Medicines Consortium

montelukast 10mg tablets (Singulair Ò) No. (185/05)

Merck, Sharp & Dohme Ltd (MSD)

***New indication**: for asthmatic patients in whom montelukast is indicated in asthma, montelukast can also provide symptomatic relief of seasonal allergic rhinitis.*

10 June 2005

The Scottish Medicines Consortium (SMC) 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 (Singulair®) 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.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Montelukast 10mg tablets (Singulair®)

Licensed indication under review

In those asthmatic adults in whom montelukast is indicated in asthma, montelukast can also provide symptomatic relief of seasonal allergic rhinitis (SAR).

Previously licensed for:

- add-on therapy in patients with mild to moderate persistent asthma inadequately controlled on inhaled corticosteroids and in whom "as needed" short-acting β-agonists (SABA) provide inadequate clinical control.
- prophylaxis of asthma which is predominantly due to exercise induced bronchoconstriction.

Dosing information under review

For adults over 15 years, 10mg daily in the evening.

UK launch date

February 2005

Comparator medications

No other agent is licensed specifically for both indications. The main comparator medications for SAR are oral or nasal antihistamines, or nasal corticosteroids or cromoglicate.

Cost per treatment period and relevant comparators

Costs from MIMS March 2005 except where stated otherwise.

Approved name	Proprietary name	Dose	Cost (28 days)
Montelukast tablets* **	**Singulair®**	**10mg daily**	**£26.97**
Cetirizine tablets	Generic	10mg daily	£3.80*
Loratadine tablets	Generic	10mg daily	£4.17*
Beclometasone dipropionate nasal spray	Generic	4-8 sprays daily	£1.89-£3.79*
Azelastine nasal spray	Rhinolast®	4 sprays daily	£8.28
Levocabastine nasal spray	Livostin®	8-16 sprays daily	£9.74**
Beclometasone dipropionate nasal spray	Beconase®	4-8 sprays daily	£2.09-£4.18
Budesonide nasal spray	Rhinocort Aqua®	2-4 sprays daily	£2.10-£4.19
Fluticasone nasal spray	Flixonase®	2-8 sprays daily	£4.36-£17.46
Sodium cromoglicate 4% nasal spray	Rynacrom®	4-8 sprays daily	£18.09/22ml

* drug tariff March 2005

** based on one spray unit of Livostin® which must be discarded one month after opening.

*** indicated for treatment of asthma and SAR

Summary of evidence on comparative efficacy

Montelukast is a leukotriene receptor antagonist that blocks the effects of cysteinyl leukotrienes in the airways. Leukotrienes are mediators of asthma and allergic rhinitis.

The key efficacy data for montelukast in patients with both SAR and asthma come from the results of one multi-centre, double-blind study conducted in Europe and the United States during the spring and autumn seasons. Eligible patients had ≥ 1 year history of active asthma and ≥ 2 year history of SAR which was of mild to moderate severity during a 3-5 day placebo run-in period. Patients were randomised to receive montelukast 10mg (n=415) or placebo (n=416) daily at bedtime for two weeks. Patients completed daily diaries scoring symptoms on a 4-point scale (0=none, 1=mild, 2=moderate and 3=severe).

The primary endpoint of the study was the Daily Rhinitis Symptoms Score defined as the mean of two components: Daytime Nasal Symptoms Score (average of nasal congestion, rhinorrhoea, sneezing, itching) and Night-time Symptoms Score (average of nasal congestion on awakening, difficulty going to sleep, night-time awakenings). After two weeks, the mean reduction from baseline in the Daily Rhinitis Symptoms score was -0.35 (±0.48) in the montelukast group compared to -0.24 (±0.46) in the placebo group: treatment difference -0.12 [95% CI: -0.18, -0.06, $p \leq 0.001$]. Similar improvements were seen in the two components of this score: treatment differences in Daytime Nasal Symptoms (-0.14 [-0.21, -0.07; $p \leq 0.001$]) and Night-time Symptoms (-0.10 [-0.16,-0.04; $p \leq 0.001$]).

Significant improvements compared to placebo were also reported in other endpoints including the daytime eye symptom score and global evaluations of allergic rhinitis and asthma as assessed by patient and physician ($p<0.05$). The secondary endpoint of the Rhinoconjunctivitis Quality-of-life Questionnaire score, a 6-point scale on 7 domains (nasal symptoms, eye symptoms, non-nose-eye symptoms, activity, sleep, emotions and practical problems) was completed by patients and also showed significant improvement (treatment difference –0.22, $p<0.01$). However, the clinical significance of this is unclear as it is less than the suggested minimum significant difference (0.57).

The effect of montelukast on rhinitis symptoms was also examined when patients were categorised according to their baseline level of asthma. The treatment difference between montelukast and placebo in the more severe asthma subgroups was numerically but not statistically larger than that for the whole study population. Montelukast also reduced the number of puffs/day of short-acting β_2-agonist (SABA) use in the whole study population, in those who used "as needed" SABA during the run-in period and in those with FEV_1 reversibility ≥12%.

The IMPACT and COMPACT studies assessed the efficacy of montelukast as add-on therapy for asthma. Post hoc analysis of these studies have provided supportive data for the use of montelukast in subgroups of patients with asthma and allergic rhinitis. However, neither study was designed or powered to look at this.

A recent meta-analysis assessed the effectiveness of leukotriene receptor antagonists compared to antihistamines and nasal corticosteroids in patients with SAR. This included 11 studies but was performed before the key study above was published and did not consider whether patients had concomitant asthma. Leukotriene antagonists (montelukast in all but one of the 11 studies) reduced mean daily rhinitis symptom scores 5% [95% CI: 3%, 7%] more than placebo, but antihistamines improved the score 2% [95% CI: 0%, 4%] more and

nasal corticosteroids improved the score 12% [95% CI: 5%, 18%] more than leukotriene receptor antagonists respectively.

Summary of evidence on comparative safety

During the key study, montelukast was well tolerated with rash (1.2%) and headache (1%) the most commonly reported adverse events. No new safety issues were raised in this patient population. Churg-Strauss syndrome has been associated with leukotriene receptor antagonists and cases have usually, but not always, followed the reduction or withdrawal of oral corticosteroids. The Committee on Safety of Medicines has advised that prescribers be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications or peripheral neuropathy.

Summary of clinical effectiveness issues

A significant proportion of patients with asthma also have rhinitis and while there are overlaps in the pathology of the conditions and their treatments, there are also differences. In some, but not all, studies treating rhinitis has led to improved asthma control.

The results of the key study demonstrate that montelukast reduced the symptoms associated with SAR. However, as in many rhinitis studies, the endpoints were subjectively measured by patients and were associated with a large placebo effect. The study is also limited by a very short duration of only two weeks and the lack of an active comparator. Although there are data for post hoc analysis of two asthma studies which looked at effects in patients with both asthma and SAR, these are of limited value since they were not designed or powered to do so.

The patients enrolled in the study had mild to moderate asthma and 41% were using inhaled corticosteroids (ICS) at baseline. This is a slightly different population from that recommended in the montelukast licence for asthma (as add-on therapy for patients inadequately controlled on inhaled corticosteroids and as required short-acting β_2-agonists) and the British Thoracic Society and Scottish Intercollegiate Guidelines Network (SIGN) guideline.

The licence extension for montelukast covers SAR and not rhinitis in general.therefore, the benefits gained in patients with these co-morbidities may be limited to the four months of the hayfever season.

Summary of comparative health economic evidence

A cost minimisation analysis was provided which used Scottish prescribing data to compare the costs of three strategies

a) Short acting β-agonist (SABA) + inhaled corticosteriods (ICS) + long-acting β_2-agonist (LABA) + use of prescription allergic rhinitis medications (ARMs),
b) SABA + fixed dose ICS/LABA combination products + use of ARMs,
c) SABA + ICS + montelukast (fixed dose 10mg) + lower use of ARMs (assumed to be 50% lower than in the comparator strategies).

The analysis assumed one year of treatment with each strategy, so that patients with co-morbid seasonal allergic rhinitis switched to the montelukast strategy would receive

montelukast treatment for the whole year and not just the allergy season. On this basis, the strategies cost £509, £508 and £472 respectively.

One way and two way sensitivity analysis was used to test assumptions regarding daily drug cost (based on dose variations), duration of allergy season and reduction in ARMs use in the montelukast strategy. This latter assumption still resulted in a lower cost compared to the comparator strategies. It was estimated that an 11% reduction in costs of LABA alone and 8% reduction in costs of combination ICS/LABA would be required to remove any cost savings for the montelukast strategy.

The data used suffer from some of the same limitations discussed in more detail in the clinical appraisal. There are limited data to support the claim of clinical equivalence. The manufacturer also claimed the economic evaluation may be conservative because co-morbid SAR has a detrimental effect on asthma, leading to higher doses of drugs being used. However, the evidence to support this is weak. In summary, the main problem with the economic case is the lack of good quality clinical data.

Budget impact

For the purposes of assessing budget impact the manufacturer estimated that there are an annual 164,000 adults with mild/moderate asthma and concomitant SAR in Scotland. Of these the prescribing data estimates just over 47,000 will be using the comparator strategies considered in the economic evaluation and 20,629 (43%) will be receiving prescription ARMs and hence eligible for using montelukast instead. It was assumed that switch rate from alternative inhaled corticosteroids (ICS)+Long acting β_2-agonists (LABA) or ICS/LABA combination strategies would be 15%, representing 3,094 patients, andproducing estimated budgetary cost savings of £113,000 per year. Cost savings ranged from £38,000 to £190,000 depending on alternative switch rate assumptions of 5% and 25%.

Guidelines and protocols

The British Thoracic Society and Scottish Intercollegiate Guidelines Network (SIGN) guideline on management of asthma places leukotriene receptor antagonists (e.g. montelukast) within step 3 and 4 as add-on therapy. The guideline states that, “If control is still inadequate after a trial of long-acting β_2-agonist and after increasing the dose of inhaled steroid, consider a sequential trial of add-on therapy, i.e. leukotriene receptor antagonists, theophyllines, slow release β_2-agonist tablets (this in adults only)”.

The guideline also briefly mentions rhinitis under specific management problems, stating that, “Patients with asthma often have rhinitis. The most effective therapy is intranasal steroids. Treatment of allergic rhinitis has not been shown to improve asthma control.”

Additional information

Montelukast was first licensed in the UK in 1998 for adults and children over 6 years. In 2001, the licence was extended to include children aged 2-5 years and in 2004 to include children aged 6 months – 2 years with a granule formulation. SMC issued “accepted for use” advice in August 2004 following an abbreviated submission for the new paediatric granule formulation.

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 ***13 May 2005.***

Drug prices are those available at the time the papers were issued to SMC for consideration.

The reference numbers in this document refer to the under-noted references. Those shaded grey are additional to those supplied with the submission.

Philip G, Nayak AS, Berger WE et al. The effect of montelukast on rhinitis symptoms in patients with asthma and seasonal allergic rhinitis. Curr Med Res Opin 2004; 20: 1549-58.

Bjermer L, Bisgaard H, Bousquet J et al. Montelukast and fluticasone compared with salmeterol and fluticasone in protecting against asthma exacerbation in adults: one year, double-blind, randomised, comparative trial. BMJ 2003; 327: 891-96.

Price DB, Hernandez D, Magyar P et al. COMPACT International Study Group. Randomised controlled trial of montelukast plus inhaled budesonide versus double dose inhaled budesonide in adult patients with asthma. Thorax 2003; 58: 211-16.

Wilson AM, O'Byrne PM, Parameswaran K. Leukotriene receptor antagonists for allergic rhinitis: a systematic review and meta-analysis. Am J Med 2004; 116: 338-344.

British Thoracic Society and Scottish Intercollegiate Guidelines Network (SIGN) British Guideline on the management of asthma (SIGN Guideline No.63). April 2004.