

## NEW MEDICINES ON THE MARKET

### Evaluated information for the NHS

## MONTELUKAST USE IN CHILDREN AGED 2 TO 5

### Summary

- Montelukast is an oral leukotriene receptor antagonist. It has had a UK licence since 1998 as add-on therapy for the treatment of patients, 6 years or older, with mild to moderate asthma inadequately controlled on 'as required' short-acting  $\beta$ -agonists and inhaled corticosteroids. It is also licensed for prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction. The licence has recently been extended to include the 2 to 5 year age group
- In children aged 2 to 5 years, abstract details of only one short-term study are available which appear to show statistically significant improvements in a range of asthma-related outcomes compared with placebo. There are no comparative studies with other agents.
- Montelukast is currently recommended for use at stage 3 of the British Thoracic Society guidelines. In the 2 to 4 year age group for whom long acting  $\beta$ -agonists such as salmeterol are unlicensed, montelukast may offer an alternative to theophylline as add-on therapy in asthma poorly controlled by short acting  $\beta$ -agonists and inhaled corticosteroids alone. However until further fully published, longer-term data is available, montelukast should be reserved until established alternatives have been tried.
- Montelukast should not be used to treat acute asthma attacks nor be substituted for inhaled or oral corticosteroids. There is no data to suggest that the dose of oral steroids can be reduced when montelukast is used.
- Thirst was the only adverse experience commonly reported as drug related in trials involving 2 to 5 year olds. Cough was reported as frequently (>1/10) occurring in trials regardless of causality.

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## MONTELUKAST

<b>Approved Name:</b>	Montelukast
<b>Brand Name (Manufacturer):</b>	Singulair® Paediatric 4mg Chewable Tablet (Merck Sharpe & Dohme Ltd)
<b>Presentation:</b>	Chewable tablets containing 4.2mg montelukast sodium equivalent to 4mg montelukast
<b>BNF Therapeutic Class:</b>	Leukotriene receptor antagonists. BNF 3.3.2
<b>Licensed Indication:</b>	Add-on therapy in those patients with mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom 'when required' short-acting $\beta$ -agonists provide inadequate clinical control. For the prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction
<b>Dosage and Administration:</b>	The dosage for paediatric patients 2 to 5 years of age is one chewable 4mg tablet daily at bedtime. No dose adjustment is necessary within this age group. If taken in conjunction with food, montelukast should be taken one hour before or two hours after food.
<b>Sector of Use:</b>	Hospital [Y] Primary Care [Y]

<b>Therapeutic Comment:</b>	Leukotriene receptor antagonists block the effects of cysteinyl leukotrienes in the airways. The license for montelukast has recently been extended to cover children aged 2 to 5 years. In older children and adults the leukotriene receptor antagonists have provided another option for the management of inadequately controlled asthma, although their exact place in therapy has yet to be determined
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<b>Cost and Course Details:</b>	The cost per 28 days treatment at 4mg daily is £25.69
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<b>Treatment Alternatives:</b>	Cost of 28 days treatment at usual maintenance dose for children under 6 years of age (Prices taken from Drug Tariff / MIMS April 2001)	<b>Cost</b>
Salmeterol inhaler (Serevent®) 50mcg bd (over 4 years only)		£26.69
Theophylline mr (Slo-Phyllin®) 60-120mg bd		£1.92-£3.84
Aminophylline (Phyllocontin®) 12mg/kg bd (assume 5yr old weighing approx 18kg)		£4.04

## INTRODUCTION

Montelukast was first licensed in January 1998 for use in children over 6 years of age and adults. In January 2001 the licence was extended to include children aged 2 to 5 years.

This review concentrates on the use of montelukast in children between 2 and 5 years of age. The use of montelukast in older children and adults has been covered in an earlier monograph [1]. However evidence for the use of montelukast in older children is also briefly discussed here as no fully published data were available in 1998.

Recent estimates have stated that 1 in 7 children aged 2 to 15 years in the UK have asthma symptoms requiring treatment; this is equivalent to over 1.5 million children [2]. The 1996 Health Survey for England revealed that among children who had experienced wheezing in the last 12 months, 23% had their sleep disturbed once or more a week and 66% said that their asthma interfered with their daily activities [2]. It is generally accepted that nocturnal symptoms can be a sign of poorly controlled asthma suggesting optimal asthma control is not being achieved in these symptomatic children. As the ability to comply with inhaled therapy is generally lower in the under 5's due to poor co-ordination skills, effective simple oral therapy may improve overall asthma control and reduce associated morbidity.

Montelukast is currently recommended for use at stage 3 of the British Thoracic Society guidelines for the management of chronic asthma.

## PHARMACOLOGY

Leukotriene receptor antagonists block the effects of cysteinyl leukotrienes in the airways. This results in a reduction in bronchoconstriction, mucous secretion, vascular permeability and eosinophil recruitment. It also inhibits both early- and late-

stage bronchoconstriction, implying both an anti-inflammatory and bronchodilatory action [3].

## PHARMACOKINETICS

Montelukast is rapidly absorbed following oral dosing. The mean peak plasma concentration is achieved 2 hours after fasted administration of the 4mg chewable tablet to 2 to 5 year olds [4]. Maximal therapeutic response is achieved after the first dose. Half-life is reported as being between 2.7 to 7 hours [5].

Montelukast is more than 99% bound to plasma proteins with a steady state volume of distribution of 8-11 litres (age not specified) [4].

Extensive hepatic metabolism takes place and both montelukast and its metabolites are excreted almost exclusively via the bile. No dosage adjustment is necessary in mild to moderate hepatic insufficiency. No data exists for patients with renal insufficiency or for those with severe hepatic insufficiency to guide dosage adjustment [4].

## EFFICACY

Information on the use of montelukast in children aged 2 to 5 years is available from a single short-term trial which is only reported in abstract form, and as data on file [6,7]. Information is therefore of a very limited nature and the methods used and results obtained have not been closely examined.

Six hundred and eighty-nine children aged 2 to 5 years were entered into a randomised, double-blind placebo-controlled multi-centre trial investigating the tolerability of montelukast by means of clinical and laboratory adverse-experience monitoring [6]. Efficacy outcomes were secondary to the tolerability outcome. Patients had been 'physician-diagnosed' with asthma and had experienced at least 3 episodes within 1 year of recruitment. Patients had also to

be symptomatic in the 2-week run-in placebo period to continue the trial [7]. After two weeks, randomisation took place and patients received either placebo (n=228) or montelukast 4mg (n=461) at bedtime for a further 12 weeks. Baseline characteristics were reported to be similar between the groups. Inhaled corticosteroids and cromoglycate were allowed at constant doses (27% of patients received concomitant corticosteroids and 13% received concomitant cromoglycate). Inhaled  $\beta$ -agonists were allowed when necessary. Effectiveness was measured against a total of eleven outcomes which included number of days with symptoms, daytime asthma symptom scores, days with  $\beta$ -agonist use, days without asthma, and number of corticosteroid rescues.

All outcomes were reported as showing statistically significant improvements ( $p < 0.05$ ) from baseline for montelukast compared with placebo except for asthma attacks, caregiver global evaluations and quality of life, although these results showed trends in favour of montelukast.

Five hundred and eighteen children went on to enter an open-label longer-term tolerability extension study. Data available for 6 to 12 months treatment in 290 participants does not show any clinically important clinical or laboratory adverse experiences as having been identified [7].

Older children aged 6 to 14 years (n=336) were recruited for a randomised placebo-controlled, double-blind trial of montelukast 5mg daily [8]. Entry to the trial required a forced expiratory volume in 1 second (FEV<sub>1</sub>) between 50 to 85% of predicted value, at least 15% reversibility after inhaled  $\beta$ -agonists, a minimal predefined level of daytime asthma symptoms and daily  $\beta$ -agonist use. Concomitant inhaled corticosteroids at

constant daily doses were allowed as were 'when required'  $\beta$ -agonists. The primary outcome measure was the percentage change from baseline in the morning FEV<sub>1</sub>.

At 8 weeks, the FEV<sub>1</sub> for the intervention group had increased from baseline by 8.23% (95% CI, 6.33% to 10.13%,  $p < 0.001$ ). In the control group the FEV<sub>1</sub> had increased by 3.58% (95% CI, 1.29% to 5.87%,  $p = \text{not significant}$ ). Other statistically significant improvements ( $p < 0.05$ ) were noted in some secondary endpoints including total daily  $\beta$ -agonist use, percentage of days with asthma exacerbation, and percentage of patients with asthma exacerbations. The most commonly reported adverse reactions were headache, asthma and upper respiratory tract infections, however none were significantly different in frequency between the groups.

### PROMOTIONAL DATA

Singular<sup>®</sup> Paediatric is marketed using the slogan 'Effective asthma control by adding a simple once-daily tablet'. In children aged 2 to 5 years, abstract details of only one short-term study are available which appear to show statistically significant improvements in a range of asthma-related outcomes compared with placebo. In the 2 to 4 year age group for whom long acting  $\beta$ -agonists such as salmeterol are unlicensed, montelukast may offer an alternative to theophylline as add-on therapy in asthma poorly controlled by short acting  $\beta$ -agonists and inhaled corticosteroids alone, however there are no comparative studies at present. Therefore until further fully published long-term data is available, montelukast should be reserved until all established alternatives have been tried. A recent Cochrane Review has also concluded that reliable conclusions regarding the efficacy of the leukotriene receptor antagonists in

any age group cannot be made due to the lack of fully published evidence [9].

## ADVERSE EFFECTS

In an interim analysis of the only study carried out in the 2 to 5 year age group the adverse experience profile was generally comparable to placebo [10]. Data on file reporting on this trial records the most frequently reported adverse effects regardless of causality as being worsening asthma, fever and upper respiratory tract infections [7].

The SPC reports that thirst was the only adverse experience commonly reported as drug related in 2 to 5 year olds. Cough was also reported as frequently (>1/10) occurring in trials regardless of causality [4].

In older children (6 to 14 years), headache was the most commonly reported drug-related adverse-effect [4]. Long term experience of dosing in these age groups is extremely limited.

## CONTRAINDICATIONS/ PRECAUTIONS (See SPC)

Montelukast should not be used to treat acute asthma attacks nor be substituted for inhaled or oral corticosteroids. There is no data to support a reduction in the dose of oral steroids when montelukast is used.

Montelukast 4mg tablets contain aspartame, a source of phenylalanine. Patients with phenylketonuria need to take this into account (See SPC for further details) [4].

Montelukast is metabolised extensively by CYP 3A4, therefore caution should be exercised especially in children when it is administered with inducers of CYP3A4 such as phenytoin, phenobarbital and rifampicin [4].

Safety and efficacy have not been established in children below 2 years of age.

Reduction of systemic corticosteroid doses in patients taking leukotriene antagonists (including montelukast) has been associated with Churg-Strauss syndrome. A causal relationship has not been identified between the reaction and leukotriene antagonists, but careful monitoring is recommended when steroid doses are reduced in patients taking montelukast [4].

## REFERENCES

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## TABLE OF MAJOR CLINICAL TRIALS FOR MONTELUKAST IN CHILDREN

RC=randomised controlled trial, DB=double blind, MC=multicentre, PC=placebo-controlled, FEV<sub>1</sub>=Forced expiratory volume in 1 second, URTI=upper respiratory tract infection

Reference	Trial Design	Regimen	Patient Numbers	Study length	Inclusion criteria	Primary & secondary outcome measures	Results	Adverse Events
Knorr BA et al 2000 [6]	RC,DB, MC,PC	Montelukast 4mg daily, constant daily doses of inhaled corticosteroids and inhaled sodium cromoglycate allowed. When-required β-agonists allowed	461	12 weeks	Children aged 2 to 5 years. History of physician-diagnosed asthma (at least 3 episodes within 1 year of study start). Symptomatic in 2 weeks before randomisation.	Primary endpoint- evaluation of tolerability using clinical and laboratory adverse-event monitoring. Secondary endpoints: days with symptoms, daytime asthma score, days with β-agonist use, days without asthma, corticosteroid rescues, physicians global evaluation, peripheral blood eosinophils, asthma attacks, caregiver global evaluations, quality of life	For the intervention group compared with placebo, all outcome measures achieved significance (p<0.05) except for asthma attacks, caregiver global evaluations and quality of life measures	Most frequently reported regardless of causality: worsening asthma, fever, URTI [10]
		Placebo plus additional therapy as detailed above	228				No results given for placebo group	
Knorr BA et al 1998 [8]	RC,DB, MC,PC	Montelukast 5mg daily, constant daily doses of corticosteroids allowed plus 1 course of 'rescue' oral corticosteroids if needed. When required β-agonists allowed	201	8 weeks	Children aged 6 to 14 years. History of intermittent or persistent asthma symptoms. Demonstrated reversible airway constriction in 2 weeks prior to randomisation	Primary endpoint = percentage change from baseline for morning FEV <sub>1</sub> Secondary endpoints included daytime asthma symptoms, nocturnal awakenings, am & pm peak expiratory flow rates, use of β-agonists	Change from baseline in morning FEV <sub>1</sub> = 8.23% ± 13.52% (p<0.001). Significant (p<0.05) changes also noted in some secondary endpoints	Headache (21.5% vs 18.9% placebo), asthma (22.2% vs 16.4% placebo) and URTI (29.6% vs 23.9% placebo) most commonly reported.
		Placebo plus additional therapy as detailed above	135				Change from baseline in morning FEV <sub>1</sub> = 3.58% ± 13.33% p=ns	