

Leukotriene receptor antagonists: Montelukast and zafirlukast

Across the PrescQIPP membership (20.2 million patients, November 2013), annual spend for the leukotriene receptor antagonists montelukast and zafirlukast is almost £3million (ePACT November 2013). The majority of this spend (£2.8 million) is for montelukast of which over £700,000 is spent on the branded product Singulair®. QIPP projects in this area are aimed at ensuring prescribing is generic and also reviewing treatment to assess for continued need.

Recommendations

- Ensure all prescriptions for montelukast are prescribed generically so that maximum savings are realised.
- Ensure prescribing of leukotriene receptor antagonists is in line with the British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) Guideline on the Management of Asthma which suggests a limited role in therapy.
- Leukotriene receptor antagonist prescriptions should be started as acute prescriptions and only put on short term repeat if effective and a need to continue therapy is established.
- Review patients on long term montelukast for suitability to step down treatment in line with the BTS/SIGN asthma management guidelines.
- When initiating treatment, if a leukotriene receptor antagonist is appropriate, montelukast should be the treatment of choice as it is less costly than zafirlukast and is available in a wider range of products to treat both adults and children.

Clinical evidence

Montelukast is a leukotriene receptor antagonist which is licenced as an add-on therapy for mild to moderate persistent asthma inadequately controlled by inhaled corticosteroids (ICS) and short-acting β_2 -agonists. In those asthmatic patients in whom montelukast is indicated, it can also provide symptomatic relief of seasonal allergic rhinitis.¹ Montelukast is also indicated in the prophylaxis of asthma in which the predominant component is exercise induced bronchoconstriction.¹ There are several strengths and formulations of montelukast which are licensed to be used in different age groups.^{2,3}

The other agent in this class, zafirlukast, is only licensed for the treatment of asthma in adults.⁴

Montelukast has not been shown to be more effective than a standard dose of ICS but the two drugs seem to have an additive effect. The leukotriene receptor antagonists may be of benefit in exercise induced asthma and those with concomitant rhinitis but they are less effective in those with severe asthma who are receiving high doses of other drugs.³

In May 2012, a Cochrane Review on leukotriene receptor antagonist therapy in adults and children concluded that as monotherapy, inhaled corticosteroids (ICS) display superior efficacy to the leukotriene receptor antagonists in adults and children with persistent asthma; the superiority is particularly marked

in patients with moderate airway obstruction. On the basis of efficacy, the results from the review support the current BTS/SIGN guideline recommendation that ICS remain the preferred first line choice for addition to a short acting beta agonist at step 2 of the treatment pathway.⁵

There is limited evidence to support the use of leukotriene receptor antagonists over the use of inhaled corticosteroids as a preventative treatment for exacerbations in asthma.

In a systematic review of montelukast as an add-on therapy to ICS in adults and adolescents with asthma published in 2009, the authors concluded that adding montelukast to ICS was found to improve control of mild to moderate asthma. The analysis also showed that salmeterol was at least as effective as montelukast as an add-on therapy, but that montelukast may be safer long term. The authors suggested that the conclusions may require some caution in interpretation due to the scarcity of good quality data and heterogeneity between the studies used in the analysis.⁶

In contrast, in October 2013, a Cochrane Review found inconclusive evidence to support adding a leukotriene receptor antagonist to an ICS at step 3 for children and adolescents aged 6-18 years with mild to moderate asthma. The addition of leukotriene receptor antagonists to ICS was not associated with a statistically significant reduction in the need for rescue oral corticosteroids or hospital admission compared to the same or an increased dose of ICS in children and adolescents with mild to moderate asthma.⁷

A NICE Medicines Evidence Commentary suggested that until studies are published that show leukotriene receptor antagonists improve patient-oriented outcomes such as exacerbations requiring oral corticosteroids, prescribers should continue to follow the NICE-accredited BTS/SIGN guideline on the management of asthma, which recommends a limited role for leukotriene receptor antagonists in children and adolescents aged 5 years and above.⁸

National guidance

The BTS/SIGN Guideline on the Management of Asthma suggests a stepwise approach for treatment. The guideline is broken down into recommendations for adults and children over 12 years, children aged between 5 and 12 years and children under 5 years. As evidence for treatment in children under 2 years is less robust, the BTS/SIGN guideline suggests considering seeking a specialist opinion in children under 2 at an earlier stage of the treatment pathway (step 3- see below).⁹

The aim of therapy is to achieve early control and step up treatment as necessary, then step down treatment when control is good. It is important that when add-on therapies are started they are done so on an acute prescription and effectiveness is assessed before continuing therapy. When a patient is controlled, therapy should be stepped down in line with the BTS/SIGN guideline. Regular review of patients is also important including deciding when to step down treatment. When deciding which drug to step down first and at what rate, the severity of asthma, the side effects of the treatment, time on current dose, the beneficial effect achieved, and the patient's preference should all be taken into account.

The suggested place in the treatment pathway for the leukotriene receptor antagonists montelukast and zafirlukast is shown below.

Step 1

For all ages, evidence supports the use of an inhaled short acting β_2 agonist as short term reliever therapy.

Step 2

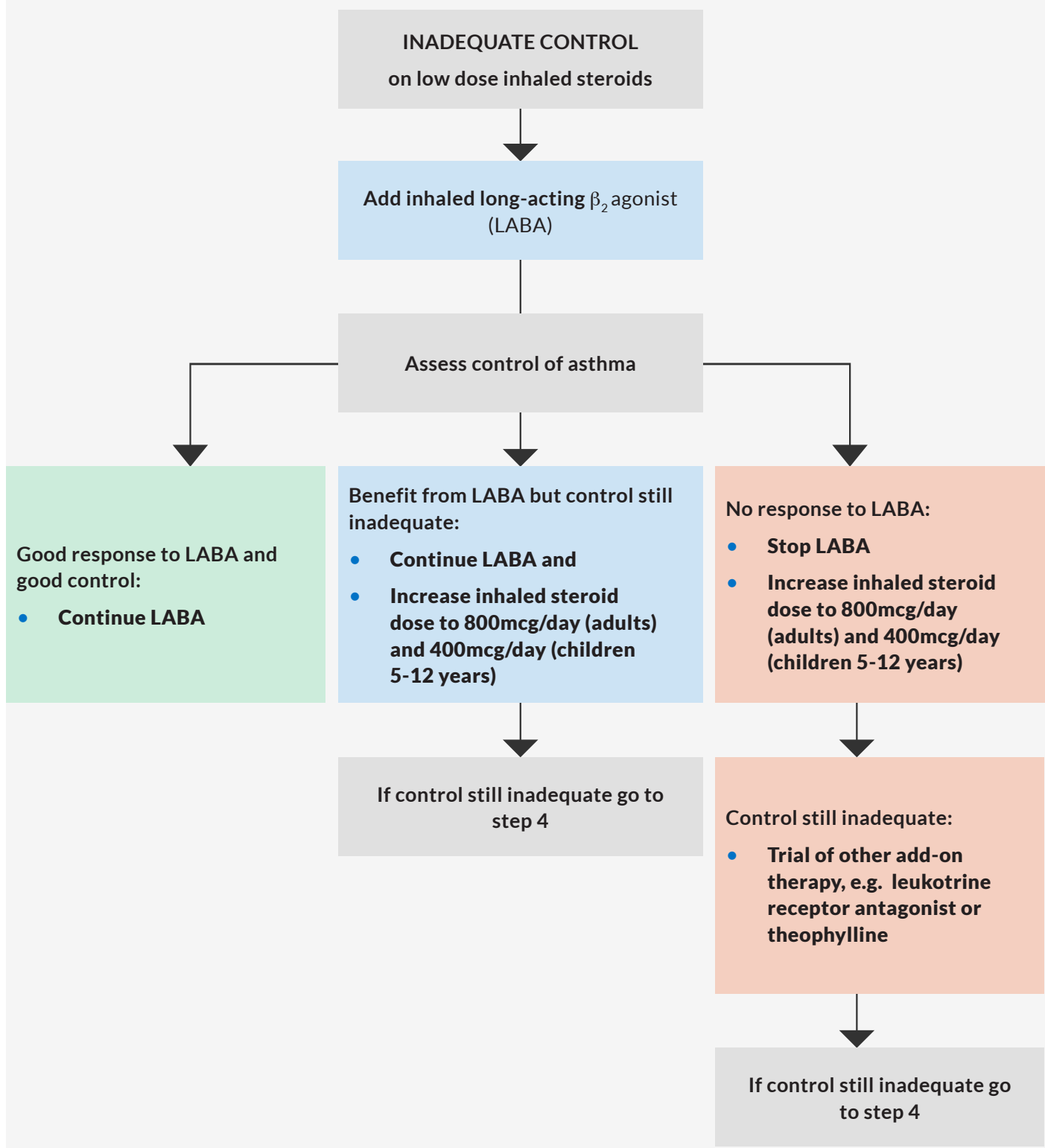
ICS are the preferred first line preventer treatment for asthma for all ages. There is increasing evidence that at appropriate doses ICS are safe and appropriate in children under 5 years with asthma. Alternative therapies are less effective than ICS.⁹

The BTS/SIGN guideline recommends leukotriene receptor antagonists as an alternative first line preventer in children under 5 years who are unable to take an ICS. This recommendation is a best practice recommendation based on the clinical experience of the guideline development group and not supported by a robust evidence base.⁹

Step 3

The first choice add-on therapy for adults and children over 5 years who are already taking an ICS but are uncontrolled, is a long acting beta agonist (LABA). This should be considered before increasing the dose of the ICS. The options at step 3 after addition of the LABA are shown below in figure 1.

Figure 1: Summary of step 3 of the BTS/SIGN guidelines in adults and children over 5 years - add-on therapy⁹



Leukotriene receptor antagonists are therefore an option for treatment at step 3 of the pathway for adults and children over 5 years where a LABA has been tried but is ineffective. Evidence suggests they may provide improvement in lung function, a decrease in exacerbations, and an improvement in symptoms.

In children under 5 years already taking an ICS, the first choice add-on therapy is a leukotriene receptor antagonist. A referral to a specialist should be considered at step 3 in children under 2 years.

Step 4

There are very few clinical trials in this specific patient group to guide management. The recommendations in the BTS/SIGN guideline are largely based on extrapolation from trials of add-on therapy to ICS alone. If a trial of an add-on treatment is ineffective, the drug should be stopped or in the case of increased dose of ICS, the dose reduced to the original dose.

The options for adults and children over 12 years are:

- Increasing ICS to 2000mcg beclometasone dipropionate/day (using spacer if dose is delivered through a metered dose inhaler (MDI)).
- Leukotriene receptor antagonists.
- Theophyllines.
- Slow release β_2 agonist tablets, though caution needs to be used in patients already on LABA.

There is no strong evidence available to indicate which of these is the best option, although the potential for side effects is greater with theophyllines and β_2 agonist tablets.

The options for children aged 5 to 12 years are:

- Increasing ICS to 800mcg beclometasone dipropionate/day (children 5-12 years) using a spacer if dose is delivered through an MDI.

For children under 5 years, step 4 is a referral to a specialist.

Step 5

In adults and children over 5 years the use of oral corticosteroids at the lowest dose that provides adequate control is recommended. A referral to a specialist should be considered.

In June 2007 the Scottish Medicines Consortium advised that Singulair® chewable tablets and granules were restricted for use as an alternative to low dose ICS in children 2-14 years with mild persistent asthma who have not recently had severe asthma attacks that required oral corticosteroids and who are not capable of using ICS. Singulair® chewable tablets and granules should be initiated by a specialist in paediatric asthma.¹⁰

Safety

Several formulations and doses of montelukast are available and care should be taken to ensure that the correct dose is prescribed according to the age of the patient to minimise side effects and potential problems. Doses are as follows:

- Child aged 6 months–6 years, 4 mg once daily in the evening.
- Child aged 6–15 years, 5 mg once daily in the evening.
- Child aged 15 years–adult, 10 mg once daily in the evening.

Churg-Strauss syndrome has occurred very rarely in association with the use of leukotriene receptor antagonists; in many of the reported cases the reaction followed the reduction or withdrawal of oral corticosteroid therapy.

Prescribers should be alert to the development of eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications or peripheral neuropathy.

Other very rare but serious side effects include hepatic disorders, hallucinations, suicidal thoughts and behaviour and disorientation.

Costs

Table 1: 28 day costs of leukotriene receptor antagonists^{2,11}

Product and dose	Age range	28 day cost
Montelukast (generic) 4mg chewable tablets (one daily)	Children aged 2 to 5 years	£2.21
Montelukast (generic) 5mg chewable tablets (one daily)	Children aged 6 to 14 years	£2.37
Montelukast (generic) 10mg tablets (one daily)	Adults and children over 15 years	£2.52
Montelukast (generic) 4mg paediatric granules (one sachet daily)	Children ages 6 months to 5 years	£4.02
Zafirlukast (Accolate®) 20mg tablets (one twice daily)	Adults only	£17.75
Montelukast (Singulair®) 4mg chewable tablets (one daily)	Children aged 2 to 5 years	£25.69
Montelukast (Singulair®) 5mg chewable tablets (one daily)	Children aged 6 to 14 years	£25.69
Montelukast (Singulair®) 4mg paediatric granules (one sachet daily)	Children ages 6 months to 5 years	£25.69
Montelukast (Singulair®) 10mg tablets (one daily)	Adults and children over 15 years	£26.97

Savings available

The patent for Singulair® expired in early 2013 and the price of generic montelukast has dropped significantly since then. **Switching all Singulair® prescribing to generic will save over £611,000 across the PrescQIPP membership (20.2 million patients). This is equivalent to £3,018 per 100,000 patients.**

Switching patients who are on zafirlukast to montelukast will save £188,000 across the PrescQIPP membership which is equivalent to £930 per 100,000 patients

If montelukast is no longer needed and is discontinued as part of a step down on the asthma treatment pathway, **a 50% reduction in prescribing would save £1.4 million across the PrescQIPP membership which is equivalent to £6,883 per 100,000 patients.**

Summary

- Montelukast is a leukotriene receptor antagonist which can be added to treatment used in steps 3 and 4 of the BTS management of chronic asthma guidelines [3, 9] for adults and children over 5 years and in steps 2 or 3 in children under 5 years. The addition of leukotriene receptor antagonists to ICS in asthma treatment has not been shown to reduce the need for rescue oral corticosteroids or hospital admission compared to the same or an increased dose of ICS in children and adolescents with mild to moderate asthma.
- When stepping down asthma treatment, clinicians should consider also stepping down and discontinuing montelukast therapy if patient is on a step where montelukast is not used (steps 1 and 2 in adults and children over 5 years and step 1 in children under 5 years).
- Montelukast should always be prescribed generically and initially on an acute prescription only. Effectiveness should be reviewed and treatment discontinued if ineffective.

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Additional resources



Briefing



Data pack



Implementation resources

Available for download here: <http://www.prescqipp.info/montelukast/viewcategory/179>

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