# Leukotriene Inhibitor Criteria for Use in Veteran Patients

VHA Pharmacy Benefits Management Strategic Healthcare Group
and the Medical Advisory Group

*The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient situation.*

The two leukotriene inhibitors that are available are montelukast (Singulair®) and zafirlukast (Accolate®). Montelukast is listed on the VA National Formulary.

## 1. Asthma

### *Mild Persistent Asthma*

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| **Recommendation** | • Orally inhaled corticosteroids (ICS), at low-moderate doses, remain the drug of choice.<br>• Leukotriene inhibitors are an option for patients unable to use a metered dose inhaler (MDI) with spacer or a dry powder inhaler (DPI) or are poorly compliant with inhalers. |
| **Evidence** | ICS and leukotriene inhibitors are both effective as monotherapy; however, current evidence shows that low dose ICS have a greater effect than leukotriene inhibitors.[1, 2] |

### *Moderate Persistent Asthma*

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| **Recommendation** | For patients uncontrolled on low-moderate doses of ICS there are several options<br>• Increase dose of ICS<br>• Add a regularly scheduled beta-agonist to the current ICS dose<br>• Add a leukotriene inhibitor to the current ICS dose<br>• Add a mast cell stabilizer to the current ICS dose |
| **Evidence** | Either increasing the dose of ICS or adding a long-acting beta-agonist (LABA) to the existing ICS dose improves asthma control. However, there is a large body of literature suggesting that adding a LABA to low dose ICS is superior to doubling or increasing the dose of ICS.[3-13]<br><br>There are insufficient data to show that either increasing the ICS dose or adding montelukast provides better asthma control (the only published study used zafirlukast at 4 times the recommended dose[14])<br><br>There are 3 studies comparing the addition of a LABA versus a leukotriene inhibitor to ICS. Adding either drug to ICS improved peak flow or $FEV_1$, symptom scores, as needed albuterol use. Improvement in pulmonary function was statistically, although probably not clinically, better with LABA. There was no difference is exacerbation rates over a 12 week period.[15-17] |

### *Severe Persistent Asthma*

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| **Recommendation** | There are insufficient data to recommend the addition of a leukotriene inhibitor to high dose ICS in this group of patients. |
| **Evidence** | One crossover study found no additional benefit in pulmonary function or symptoms when montelukast 10mg daily for 2 weeks was added to high dose ICS ± LABAs, theophylline, or oral steroids.[18]<br><br>In a 12-week study of patients requiring moderate-high dose ICS, addition of montelukast 10mg daily allowed a 47% reduction in the dose of ICS versus by 30% in those given placebo (p=0.046).[19] |

***Exercise-induced asthma***

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| **Recommendation** | • For patients with exercise-induced symptoms, a short-acting beta-agonist (SABA) should be used before exercise.<br>• For those patients who participate in prolonged exercise/activity where a SABA is not providing the needed control, a LABA can be used prior to exercise. Administer 15 and 30 minutes prior to exercise for formoterol and salmeterol respectively.<br>• Montelukast can be used for those patients who participate in prolonged exercise/activity where a SABA is not providing the needed control; however, it should be used in conjunction with asthma maintenance medications and not used as monotherapy. |
| **Evidence** | When given as single-doses prior to exercise, a crossover study in 10 patients found salmeterol 100mcg and montelukast 10mg to have similar protective effects.[20] Two 8-week and one 12-week trials comparing salmeterol and montelukast 10mg daily found a greater bronchoprotective effect with montelukast.[21-23] |

**2. Chronic Obstructive Lung Disease (COPD)**

The leukotriene believed to mediate inflammation in COPD is $LTB_4$ and in asthma is $LTD_4$. Montelukast and zafirlukast do not inhibit the $LTB_4$ receptor and are therefore not expected to improve pulmonary function and symptoms of COPD.[24] One single dose study of 16 patients (majority who had $\geq$12% increased in $FEV_1$ with albuterol 400mcg) with COPD found the following rank order improvement in $FEV_1$: salmeterol 50mcg + zafirlukast 40mg = salmeterol 50mcg > zafirlukast 40mg > placebo. However, there was a subgroup of 7 patients who had a better response with the combination than with salmeterol alone.[25, 26] **Larger and longer term studies are needed before these agents can be routinely recommended**

**3. Seasonal Allergic Rhinitis[27-35]**

Montelukast does not offer a clinical advantage over the other currently available drugs used to treat seasonal allergic rhinitis. Because nasally inhaled steroids and antihistamines are more cost-effective, they remain the drugs of choice both as first-line and second-line agents. The benefit of adding montelukast to a combination of nasal steroids and antihistamines has not been evaluated and thus cannot be recommended. Montelukast has not been evaluated in perennial rhinitis.

**4. Other uses**

There are preliminary data on the use of leukotriene inhibitors in atopic dermatitis[37,38] and chronic urticaria[39]. Until more is known, these conditions should be managed with established therapies.

**5. Safety**

Overall, the incidence of adverse events is low for both agents. Two issues that merit further discussion are the potentials for hepatotoxicity and Churg-Strauss syndrome.

***Hepatotoxicity***

Rarely, zafirlukast and montelukast can cause elevated hepatic enzymes. Seven cases of liver impairment have been reported in the literature with zafirlukast. If liver dysfunction is suspected based upon clinical signs or symptoms, the leukotriene inhibitor should be discontinued.[40-44]

***Churg-Strauss syndrome***

Churg-Strauss syndrome (allergic angiitis and granulomatosis) is an uncommon syndrome that generally occurs in patients with asthma and allergic rhinitis. The hallmark features are eosinophilia $\geq$ 10% of WBC, mono- or polyneuropathy, pulmonary infiltrates, and eosinophilic vasculitis. Several cases of Churg-Strauss have been reported with zafirlukast and montelukast use.[45-62] In most of these cases, the leukotriene inhibitor was started while steroids were being withdrawn or within a few months of stopping steroids. It is thought that the syndrome is the result of unmasking a previously existing condition due to systemic steroid withdrawal and not necessarily a direct effect of the leukotriene inhibitor. Nonetheless, clinicians need to monitor the patient for eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy.

## 6. Drug interactions [63-67]

Zafirlukast is an inhibitor of CYP450 isoenzymes 2C9 and 3A4; therefore, the metabolism of co-administered drugs that utilize 2C9 or 3A4 pathway may be inhibited. Montelukast does not inhibit or induce the CYP450 isoenzymes. Both zafirlukast and montelukast are metabolized via 2C9; co-administered drugs that either induce or inhibit this enzyme may potentially affect the disposition of the leukotriene inhibitor.

## 7. Dosage

| | Montelukast | Zafirlukast |
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| Adult dose | 10mg q evening | 20mg BID at least 1 hour ac or 2 hours pc |
| Adjustment in elderly | No | Cmax and AUC are nearly doubled; dosing suggestions for the elderly not provided |
| Adjustment for hepatic insufficiency | No adjustment for mild-moderate hepatic insufficiency; pts. with severe impairment or hepatitis have not been studied | Cmax and AUC are doubled in patients with stable EtOH cirrhosis; dosing recommendations not provided |
| Adjustment for renal insufficiency | No | No |
| Dosage form | 10mg film-coated tablet<br>4 mg and 5mg chew tablet | 10mg and 20mg coated tablet |

## 8. Patient Follow-up

Responses vary in different subsets of asthmatics, making it important to individualize therapy. Leukotriene inhibitor therapy should be continued only if pulmonary function, symptoms, or exercise tolerance improves.

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