Montelukast

Dose and Administration

- Asthma maintenance therapy
  - 12 months – 5 years: 4mg once daily
  - ≥6 years – <15 years: 5mg once daily
  - ≥15 years: 10mg once daily
- Prevention of exercise-induced bronchospasm
  - ≥6 years – <15 years: 5mg at least 2 hours prior to exercise
  - ≥15 years: 10mg at least 2 hours prior to exercise

Formulations

4mg granules (approved down to 1 year of age)

4mg chewable tablet (approved for children 2 – 6 years of age)

5mg chewable tablet

10mg tablet

Uses

Aspirin-exacerbated respiratory disease, exercise-induced asthma, monotherapy for mild persistent asthma, or add-on therapy for allergic asthma

Monitoring

Asthma symptoms, FEV_1, peak flow and/or other pulmonary function tests, mood or behavior changes, including suicidal thinking/behavior

Side Effects

Upper respiratory infection, fever, headache, sore throat, cough, stomach pain, diarrhea, earache or ear infection, flu, runny nose, and sinus infection

Boxed Warning

- The FDA recently added a boxed warning to montelukast. Concerns were demonstrated regarding potential behavioral and neuropsychiatric disturbances such as agitation, depression, sleep problems, and suicidal thoughts and actions with montelukast. The FDA advises health care providers to warn all patients about potential behavioral and mood-related changes and cautions against prescribing the drug for people with mild symptoms, including those with hay fever. The FDA recommended montelukast to be reserved for patients who have not responded adequately to other therapies or who cannot tolerate those therapies. Patients should be monitored for neuropsychiatric symptoms when taking montelukast.

Singulair® (montelukast) [package insert]. Whitehouse Station, NJ: Merck & Co., Inc., 1998.

Evidence Based Review based on Indication

Aspirin-Exacerbated Respiratory Disease

- The cysteinyl leukotrienes are the leading mediators of the airway reaction that occurs in patients with aspirin-sensitive asthma after exposure to aspirin. Studies have demonstrated that leukotriene receptor antagonists resulted in almost complete inhibition of aspirin-induced bronchoconstriction. For this reason, leukotriene receptor antagonists can prevent this reaction and are the treatment of choice for these patients.

O'Byrne PM, Israel E, Drazen JM, et al. Antileukotrienes in the treatment of asthma. *Ann Intern Med*. 1997;127(6):472-80.

Israel E, Fischer AR, Rosenberg MA, et al. The pivotal role of 5-lipoxygenase products in the reaction of aspirin-sensitive asthmatics to aspirin. *Am Rev Respir Dis*. 1993;148(6 Pt 1):1447-51.

Drazen JM, Israel E, O'Byrne PM. Treatment of asthma with drugs modifying the leukotriene pathway. *N Engl J Med*. 1999;340(3):197-206.

Wenzel SE. Antileukotriene drugs in the management of asthma. *JAMA*. 1998;280(24):2068-9.

Exercise-Induced Asthma

- During exercise, evaporation of water from the airway surface is the stimulus for release of inflammatory mediators such as histamine and cysteinyl leukotrienes. Leukotriene receptor antagonists are reported to decrease exhaled LTE4 in atopic children with asthma. Montelukast has been shown to be effective in controlling asthma symptoms after exercise in children. It is FDA-approved for the acute prevention of exercise-induced bronchospasm in patients ≥6 years of age. Leukotriene inhibitors can provide a useful alternative in preventing exercise-induced asthma, especially in young children for whom the use of an inhaler may be difficult, or for patients who receive incomplete protection for short-acting beta-2 agonists.

Scow DT, Luttermoser GK, Dickerson KS, et al. Leukotriene inhibitors in the treatment of allergy and asthma. *Am Fam Physician*. 2007;75(1):65-70.

Anderson SD. Single-dose agents in the prevention of exercise-induced asthma: a descriptive review. *Treat Respir Med*. 2004;3(6):365-79.

Edelman JM, Turpin JA, Bronsky EA, et al. Oral montelukast compared with inhaled salmeterol to prevent exercise-induced bronchoconstriction. A randomized, double-blind trial. *Ann Intern Med*. 2000;132(2):97-104.

Monotherapy for Mild Persistent Asthma

- While low-dose inhaled corticosteroid therapy is preferred for the management of mild persistent asthma, montelukast may be considered as an alternative. At doses equivalent to 500µg daily of beclomethasone, leukotriene receptor antagonists were less effective than inhaled corticosteroids on symptoms, pulmonary function and sputum eosinophils. However, in a recent study of 534 patients with mild asthma well controlled by low-dose inhaled corticosteroids, replacing inhaled corticosteroids with montelukast was associated with good asthma control in more than 75% of patients after 6 weeks, with an increase in compliance to treatment. Another consideration in the decision between inhaled corticosteroid and montelukast might be the concern for possible side effects in long-term treatment, particularly in children. Although many studies have confirmed the lack of a consistent effect of low-dose inhaled corticosteroid on the long-term growth in children (despite a mild delay in growth in the first year), treatment with montelukast might be used as first choice for avoiding this side effect, and changing to inhaled corticosteroid might be considered as an alternative.

McIvor RA, Kaplan A, Koch C, et al. Montelukast as an alternative to low-dose inhaled corticosteroids in the management of mild asthma (the SIMPLE trial): an open-label effectiveness trial. *Can Respir J*. 2009;16(Suppl A):11A-16A.

Busse W, Raphael GD, Galant S, et al. Low-dose fluticasone propionate compared with montelukast for first-line treatment of persistent asthma: a randomized clinical trial. *J Allergy Clin Immunol*. 2001;107(3):461-8.

Laviolette M, Malmstrom K, Lu S, et al. Montelukast added to inhaled beclomethasone in treatment of asthma. Montelukast/Beclomethasone Additivity Group. *Am J Respir Crit Care Med*. 1999;160(6):1862-8.

Jayaram L, Pizzichini E, Lemiere C, et al. Steroid naïve eosinophilic asthma: anti-inflammatory effects of fluticasone and montelukast. *Thorax.* 2005;60(2):100-5.

Doull IJ. The effect of asthma and its treatment on growth. *Arch Dis Child*. 2004;89(1):60-3.

Add-on Therapy for Allergic Asthma

- Montelukast provides relief from symptoms of seasonal allergic rhinitis, while also conferring a benefit for asthma, in patients with both allergic rhinitis and asthma.

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(10):1549-58.

Price DB, Swern A, Tozzi CA, et al. Effect of montelukast on long function in asthma patients with allergic rhinitis: analysis from the COMPACT trial. *Allergy*. 2006;61(6):737-42.

EPR3 Recommendations

- LTRAs are alternative, but not preferred, therapy for the treatment of mild persistent asthma (Step 2 care). LTRAs can also be used as adjunctive therapy with ICSs, but for youths ≥12 years of age and adults they are not the preferred adjunctive therapy compared to the addition of LABAs.
- Montelukast is indicated for long-term control and prevention of symptoms in mild persistent asthma for patients ≥1 year of age. May also be used with ICS as combination therapy in moderate persistent asthma.
- Children 0 – 4 years of age:
    - Step 2 care: Preferred treatment for step 2 care is daily ICS at a low dose. Alternative, but not preferred, treatments include cromolyn and montelukast.
    - Step 4 care: Medium-dose ICS AND either LABA or montelukast.
    - Step 5 care: High-dose ICS AND either LABA or montelukast is the preferred treatment.
    - Step 6 care: High-dose ICS AND either LABA or montelukast AND oral systemic corticosteroids may be given for step 6.
- Children 5 – 11 years of age:
    - Step 2 care: Daily low-dose ICS is the preferred step 2 treatment. Alternative treatments at this step include (listed in alphabetical order) cromolyn, LTRA, nedocromil, and theophylline.
    - Step 3 care: Low-dose ICS plus the addition of some form of adjunctive therapy or medium-dose ICS are equivalent options in step 3 care, based on extrapolation from studies in adults. Because of the lack of comparative data in this age group, however, the adjunctive therapies are listed in alphabetical order: LABA, LTRA, or, with appropriate monitoring, theophylline.
    - Step 4 care: Preferred therapy is medium-dose ICS + LABA. Alternative therapy is medium-dose ICS + either LTRA or theophylline.
    - Step 5 care: Preferred therapy is high-dose ICS + LABA. Alternative therapy is high-dose ICS + either LTRA or theophylline.
    - Step 6 care: Preferred therapy is high-dose ICS + LABA + oral systemic corticosteroid. Alternative therapy is high-dose ICS + either LTRA or theophylline + oral systemic corticosteroid.

EPR4 Recommendations

- A single small randomized controlled trial reported findings in participants ages 18 to 60 years after 6 months of treatment in a four-arm, parallel-group, unmasked, active-comparator trial (N=72 ICS plus LAMA, N=68 ICS plus LABA (used formoterol), N=81 montelukast plus ICS, and N=76 doxofylline plus ICS). These results were limited to 297 of 362 participants who completed the 6-month study. No critical outcomes designated by the Expert Panel were reported. Only one of the important outcomes was reported (rescue medication use, reported as difference at day 90 compared with baseline) - this did not differ between groups. With respect to harms, this study directly comparing the addition of montelukast versus LAMA as add-on therapy to ICS appears to show a similar rate of undesirable effects with either treatment.
    - Critical outcomes outlined in EPR4 include: asthma exacerbations, asthma control, asthma symptoms and Asthma-related Quality of Life
    - Important outcomes outlined in EPR4 include: rescue medication use, adverse events, and mortality

GINA Recommendations

- Personalized management for adults and adolescents 12+ years
    - Step 2: Preferred therapy is daily low dose ICS or as-needed low dose ICS-formoterol. Daily LTRA or low dose ICS taken whenever SABA is taken are listed as alternative controller options.
    - Step 3: Preferred therapy is low dose ICS-LABA. Medium dose ICS or low dose ICS+LTRA are listed as alternative controller options.
    - Step 4: Preferred therapy is medium dose ICS-LABA. High dose ICS, add-on tiotropium or add-on LTRA are listed as alternative controller options.
- Personalized management for children 6 – 11 years
    - Step 2: Preferred therapy is daily low dose ICS. Daily LTRA or low dose ICS taken whenever SABA is taken are listed as alternative controller options.
    - Step 3: Preferred therapy is low dose ICS-LABA or medium dose ICS. Low dose ICS + LTRA are listed as alternative controller options.
    - Step 4: Preferred therapy is medium dose ICS-LABA. High dose ICS-LABA, or add on tiotropium, or add-on LTRA are listed as alternative controller options.