

## Drugs Altering Leukotrienes for Asthma

**Introduction:** Asthma continues to be a national health problem in the United States, affecting an estimated 14 to 15 million Americans and linked to 5,000 deaths annually. Children account for approximately one-third of the diagnosed cases, and asthma is the second most common cause of school absenteeism, after the common cold. A large economic impact is associated with the care of asthmatics with a total direct and indirect costs estimated at \$5.8 billion annually. Asthma is a chronic inflammatory disease of the airways that is complicated by episodes of acute inflammation. Even patients with mild disease show airway inflammation, including infiltration of the mucosa and epithelium with activated T cells, mast cells, and eosinophils. T cells and mast cells release cytokines that promote eosinophil growth and maturation and the production of IgE antibodies, and these, in turn, increase microvascular permeability, disrupt the epithelium, and stimulate neural reflexes and mucus-secreting glands. The result is airway hyperreactivity, bronchoconstriction, and hypersecretion, manifested by wheezing, coughing, and dyspnea. Since asthma is a chronic condition, the goal of treatment is management and improvement of quality of life, rather than cure. The specific goals of asthma maintenance are to: (1) minimize symptoms that impair normal activity including exercise; (2) minimize sleep interference or missed school/work days; (3) minimize the need for emergency room visits or hospitalization; (4) achieve normal percentage predicted values for forced expiratory volume in one second (FEV<sub>1</sub>)/peak expiratory flow; and (5) maintain near-normal lung function; and (6) reduce mortality.

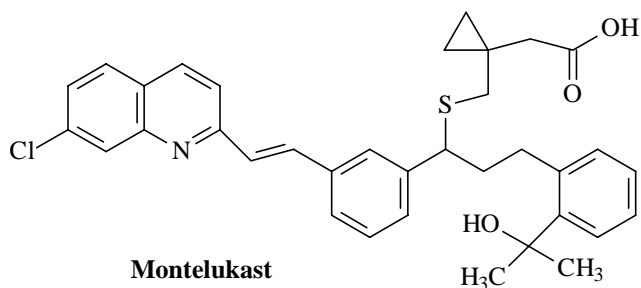
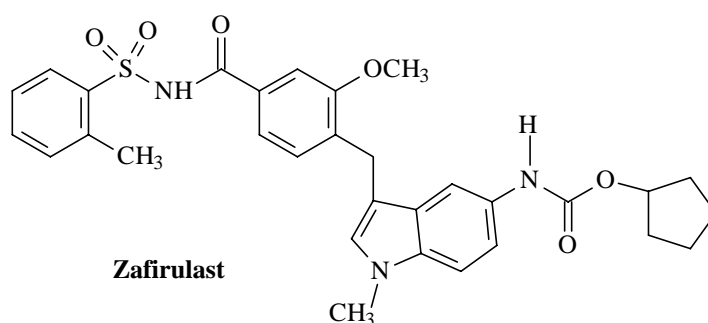
The National Institutes of Health (NIH) Guidelines for the Diagnosis and Management of Asthma have established a classification scheme for asthma and asthma treatment based on severity and frequency of symptoms (Table 1). Quick-relief medications, usually inhaled beta<sub>2</sub>-agonist (Ventolin®, Apo-Salvent®, Novo Salmol®, Berotec®, Bricanyl®, Maxair®) are indicated for all subtypes of asthma. These agents directly relax bronchial smooth muscle and thus promote prompt reversal of acute airflow obstruction and relief of the accompanying symptoms. However, the quick-relief medications do nothing for the underlying inflammation of asthma. Thus long-term control medications are indicated for all asthma subtypes other than the mild-intermittent form to attenuate airway inflammation. The most effective long-term controllers are the inhaled corticosteroids, but mast cell stabilizers (cromolyn or nedocromil), theophylline (TheoDur® and others) or the leukotriene modifying drugs (Accolate®, Singulair®) may be used as alternatives. Long-acting inhaled beta<sub>2</sub>-agonists are considered to be the drug of choice if it is necessary to add a medication to the inhaled corticosteroids to achieve long-term control. Salmeterol is the prototype long-acting inhaled beta<sub>2</sub>-agonist with high affinity and selectivity for β<sub>2</sub>-receptors and a prolonged duration of action (>12 hours). Salmeterol has demonstrated efficacy in the treatment of chronic asthma, including nocturnal asthma and exercise-induced asthma. Formoterol is the newest long-acting beta<sub>2</sub>-agonist to be approved for the maintenance treatment of various forms of asthma in adults and children (five years and older).

**Pharmacology:** The cysteinyl leukotrienes (LTC<sub>4</sub>, LTD<sub>4</sub>, LTE<sub>4</sub>) are products of arachidonic acid metabolism and are released from various cells, including mast cells and eosinophils. Leukotrienes are substances that induce numerous biological effects including augmentation of neutrophil and eosinophil migration, neutrophil and monocyte aggregation, leukocyte adhesion, increased capillary permeability and smooth muscle contraction. Cysteinyl leukotriene production and receptor occupation have been correlated with the pathophysiology of asthma, including airway edema, smooth muscle constriction and altered cellular activity associated with the inflammatory process, which contribute to

the signs and symptoms of asthma. The leukotriene receptor antagonists are selective and competitive antagonists of cysteinyl leukotriene (CysLT1) receptor. Thus they antagonize the contractile actions of LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub> in airway smooth muscle. These drugs are selective for CysLT1 receptors and do not bind with significant affinity to prostanoid, cholinergic, or beta-adrenergic receptors found in respiratory tissues.

The leukotriene receptor antagonists inhibit bronchoconstriction and attenuate the early- and late-phase reaction caused by several kinds of inhalational challenges in asthma patients including sulfur dioxide, cold air antigens such as grass, cat dander, ragweed, and mixed antigens. They also attenuate the increase in bronchial hyperresponsiveness to inhaled histamine that followed inhaled allergen challenge. Based on their pharmacologic actions, these drugs have the following indications:

- ◆ Zafirlukast: Prophylaxis and chronic treatment of asthma in adults and children  $\geq 5$  years of age.
- ◆ Montelukast: Prophylaxis and chronic treatment of asthma in adults and pediatric patients  $\geq 2$  years of age.



### Pharmacokinetics:

- ◆ Absorption: Both drugs are rapidly absorbed (60-80%) following oral administration, giving peak plasma levels in 3-4 hours. Administration of zafirlukast with food reduced the mean bioavailability by  $\gg 40\%$ . The oral bioavailability and C<sub>max</sub> of montelukast are not significantly influenced by a standard meal.
- ◆ Distribution: Both drugs are highly ( $>99\%$ ) bound to plasma proteins (predominantly albumin). Zafirlukast has a substantially larger volume of distribution (70 L) than montelukast (8-11 L).

Studies in animals indicate minimal distribution of montelukast across the blood-brain barrier.

- ◆ **Metabolism:** Both drugs are extensively metabolized. The most common metabolic products of zafirlukast are hydroxylated metabolites, formed through the cytochrome P450 2C9 (CYP2C9) enzyme pathway. The metabolites of zafirlukast found in plasma are at least 90 times less potent as LTD4 receptor antagonists than zafirlukast in a standard in vitro test of activity. Zafirlukast inhibits the CYP3A4 and CYP2C9 isoenzymes at concentrations close to the clinically achieved plasma concentrations. Based on this clearance profile, the C<sub>max</sub> and AUC of these drugs are significantly increased in patients with moderate to severe hepatic impairment. Doses need not be adjusted in renal impairment.
- ◆ Cytochromes P450 3A4 and 2C9 are involved in the metabolism of montelukast. Forming a diacid, sulfoxide, multiple hydroxy metabolites (positions 21, 25 and 36) and the acyl glucuronide.
- ◆ **Excretion:** Both drugs and their metabolites are excreted almost completely in the bile (biliary excretion). The mean plasma half-life of zafirlukast is 8-16 hours. The mean plasma half-life of montelukast ranges from 2.7 to 5.5 hours

#### **Adverse Reactions and Warnings:**

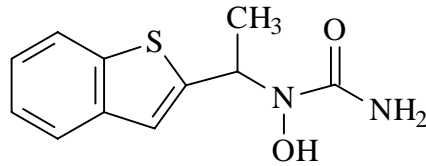
- ◆ **CNS:** Headache, dizziness
- ◆ **GI:** Nausea, diarrhea, abdominal pain, vomiting, dyspepsia
- ◆ **Infection:** An increased proportion of patients > 55 years of age receiving these drugs experience mild or moderate respiratory tract infections.
- ◆ Hypersensitivity reactions, including urticaria, angioedema, and rashes, with or without blistering have been reported in association with these drugs.
- ◆ Concomitant warfarin therapy with zafirlukast
- ◆ **Hepatic function impairment:** The clearance of these drugs is reduced in patients with cirrhosis.
- ◆ **Acute asthma attacks:** These drugs are not indicated for use in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus.
- ◆ **Churg-Strauss Syndrome,** a rare and sometimes fatal reaction, has been reported with zafirlukast, usually when patients are reducing their oral steroid dose.

#### **Drug Interactions:**

Because of zafirlukast's inhibition of cytochrome P450 2C9 and 3A4 isoenzymes, use caution with coadministration of drugs known to be metabolized by these isoenzymes.

Potent cytochrome P450 enzyme inducers, such as phenobarbital or rifampin, are coadministered with montelukast may reduce drug levels

## Zileuton



### Zileuton

**Pharmacology:** Zileuton is a specific inhibitor of 5-lipoxygenase and thus inhibits the formation of eukotrienes LTB<sub>1</sub>, LTC<sub>1</sub>, LTD<sub>1</sub> and LTE<sub>1</sub>. Both the R(+) and S(-) enantiomers of this drug are active as 5-lipoxygenase inhibitors. Zileuton also inhibits leukotriene-dependent smooth muscle contractions. Pretreatment with zileuton attenuates bronchoconstriction caused by a variety of stimuli in patients with asthma.

### Pharmacokinetics:

**Absorption:** Zileuton is rapidly absorbed upon oral administration with a time to peak plasma concentration (T<sub>max</sub>) of 1.7 hours and a mean peak level (C<sub>max</sub>) of 4.98 mcg/ml. The absolute bioavailability of zileuton is unknown. Administration of zileuton with food results in a small but statistically significant increase (27%) in zileuton C<sub>max</sub> without significant changes in the extent of absorption (AUC) or T<sub>max</sub>. Therefore, zileuton can be administered with or without food.

**Distribution:** The apparent volume of distribution of zileuton is about 1.2 L/kg and the drug is 93% bound to plasma proteins, primarily to albumin, with minor binding to alpha-acid glycoprotein.

**Metabolism:** Zileuton is converted to a number of metabolites including the diastereomeric O-glucuronide conjugates (major metabolites) and an N-dehydroxylated (reduced) metabolite of zileuton. The urinary excretion of the inactive N-dehydroxylated metabolite and unchanged zileuton each accounted for less than 0.5% of the dose. Zileuton and its N-dehydroxylated metabolite can be oxidatively metabolized by the cytochrome P450 isoenzymes including CYP1A2, CYP2C9 and CYP3A4. Based on this clearance profile zileuton is contraindicated in patients with active liver disease. Also, dose adjustment in renal dysfunction or hemodialysis is not necessary.

**Excretion:** Clearance of zileuton is mainly via metabolism with a terminal half-life of 2.5 hours.

### Adverse Reactions and Warnings:

- ◆ Hepatotoxicity: Elevations of one or more liver function tests
- ◆ Acute asthma attacks: Zileuton is not indicated for use in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus.
- ◆ Hematologic: Transient reductions in white blood cell count
- ◆ Hepatic function impairment: Caution!
- ◆ Common ADRs: GI and Headache

### Drug Interactions:

- ◆ Caution when using zileuton with other drugs that inhibit any of the P450 isoenzymes 1A2, 2C9 and 3A4.