Therapeutic Class Overview
Leukotriene Modifiers

INTRODUCTION

- The leukotriene modifiers can be divided into two pharmacologic categories: the leukotriene receptor antagonists, zafirlukast (ACCOLATE®) and montelukast (SINGULAIR®), and the 5-lipoxygenase inhibitors, zileuton (ZYFLO®) and zileuton extended-release (ZYFLO CR®). The leukotriene modifiers are all Food and Drug Administration (FDA)-approved for prophylaxis and chronic treatment of asthma. Montelukast carries additional indications for the relief of symptoms of seasonal and perennial allergic rhinitis and for the prevention of exercise-induced bronchoconstriction (Drugs@FDA, 2017).
- Currently, montelukast, zileuton extended-release (ER), and zafirlukast are available generically. Montelukast is available in tablets, chewable tablets, and oral granules. Zafirlukast is available in tablets. Zileuton is available as immediate-release and extended-release tablets (Drugs@FDA, 2017).
- Treatment guidelines generally position leukotriene modifiers not as first-line agents, but rather as alternatives or additive therapy to other classes of medications for the treatment of asthma, allergic rhinitis, and exercise-induced bronchospasm.
- For asthma, inhaled corticosteroids (ICSs) are first-line therapy for control of persistent asthma; leukotriene modifiers may be used as alternatives to ICSs or the addition of a leukotriene receptor antagonist may assist patients stepping down from low-dose ICS in mild asthma; it may also be used as additive therapy to ICSs in moderate to severe asthma (National Heart, Lung, and Blood Institute [NHLBI], 2007; Global Initiative for Asthma [GINA], 2017).
- For allergic rhinitis, intranasal corticosteroids are the most effective medication class, and antihistamines are also effective. Leukotriene modifiers may be used as alternatives or in combination with other agents, but are not as effective as intranasal corticosteroids (Wallace et al, 2008; Snellman et al, 2013).
- Although β_2-agonists are the most effective agents for the prophylaxis and relief of exercise-induced bronchoconstriction, daily use of β_2-agonists can lead to tolerance. Leukotriene modifiers can be considered as a daily therapy option as their use does not lead to tolerance. However, leukotriene modifiers do not provide complete protection against exercise-induced bronchoconstriction as they are not effective at reversing airway obstruction (Weiler et al, 2016). Leukotriene modifiers may be an option in patients with exercise-induced bronchoconstriction who have persistent symptoms despite using a short-acting β_2-agonist before exercise, or who require an inhaled short-acting β_2-agonist daily or more frequently (Parsons et al, 2013).
- Medispan class: Leukotriene Modifiers

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
SINGULAIR (montelukast)	Merck & Co., Inc.	02/20/1998*	✔
ACCOLATE (zafirlukast)	AstraZeneca Pharmaceuticals LP	09/26/1996	✔
ZYFLO (zileuton)	Chiesi USA Inc.	12/09/1996	-
ZYFLO CR (zileuton ER)	various	05/30/2007	✔

*07/26/2002 for the oral granule dosage form

(Drugs@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	SINGULAIR (montelukast)	ACCOLATE (zafirlukast)	ZYFLO, ZYFLO CR (zileuton)
Prophylaxis and chronic treatment of asthma	✔ (age ≥12 months)	✔ (age ≥5 years)	✔ (age ≥12 years)
Acute prevention of exercise-induced bronchoconstriction	✔ (age ≥6 years)		
Relief of symptoms of perennial allergic rhinitis	✔ (age ≥6 months)		
Relief of symptoms of seasonal allergic rhinitis	✔ (age ≥2 years)		

(Prescribing information: ACCOLATE, 2013; SINGULAIR, 2016; ZYFLO, 2014; ZYFLO CR, 2017)

Information on indications, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Clinical Trials

- There are numerous placebo-controlled trials examining the efficacy of the leukotriene modifiers for asthma. When compared to placebo, leukotriene modifiers demonstrated efficacy in most aspects of asthma control, including pulmonary function, asthma symptoms, β_2-agonist use, asthma exacerbations and nighttime symptom control (Virchow et al, 2010(a); Virchow et al, 2010(b); Knorr et al, 1998; Reiss et al, 1998; Visitsunthorn et al, 2011; Yildirim et al, 2004; Price et al, 2003; Bozek et al, 2012; Chen et al, 2014).
- There is also a large body of clinical data comparing the leukotriene modifiers to inhaled corticosteroids and long-acting β_2-agonists. When compared to these other long-term controller medications, the leukotriene modifiers have not demonstrated equivalence or significant advantages in clinical outcomes (Szefler et al, 2005; Zeiger et al, 2006; Garcia et al, 2005; Busse et al, 2001; Sorkness et al, 2007; Bjermer et al, 2003; Calhoun et al, 2001; Maspero et al, 2008; Lemanske et al, 2010; Fish et al, 2001; Wilson et al, 2010(a); Wilson et al, 2010(b); Ducharme et al, 2006; Suissa et al, 1997; Busse et al, 1999; Israel et al, 1996; Israel et al, 1993; Nelson et al, 2007; Wenzel et al, 2007).
- Leukotriene modifiers have not been adequately studied in comparison to one another. However, in one randomized, open-label, comparative multicenter clinical trial, results suggest that zileuton ER has better therapeutic efficacy for the treatment of asthma in comparison to montelukast as shown by changes in peak expiratory flow rate (PEFR) and mean overall symptom intensity score (Kubavat et al, 2013).
- According to a 2013 Cochrane review, there is no firm evidence to support that adding montelukast to an ICS is safe and effective to reduce the occurrence of moderate or severe asthma attacks in children taking a low-dose ICS and whose symptoms remain uncontrolled. After being on the market for more than 10 years, the limited number of available studies testing antileukotrienes in children, the absence of data on preschoolers, and the inconsistency of available trials in reporting of efficacy and safety clinical outcomes is disappointing and limit the conclusions (Chauhan et al, 2013).
- With regard to allergic rhinitis, montelukast has been shown to be more effective than placebo and has demonstrated comparable efficacy to second-generation antihistamines; however, it has not been shown to be as effective as intranasal corticosteroids (Cingi et al, 2010; Li et al, 2009; Esteitie et al, 2010; Baena-Cagnani et al, 2003; Meltzer et al, 2000; Saengpanich et al, 2003; Pullerits et al, 2002; Mucha et al, 2006; Wasfi et al, 2011; Wei, 2016).
- The Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review of pharmacological therapies for the treatment of seasonal allergic rhinitis. A total of 59 randomized controlled trials met inclusion criteria to compare agents of six classes for relative efficacy. Agents included oral and nasal antihistamines and decongestants, intranasal corticosteroids, leukotriene modifiers, cromolyn, ipratropium, and normal saline. Overall, there was insufficient evidence to draw a conclusion about relative efficacy among most of the agents used for the treatment of seasonal allergic rhinitis. For a few comparisons, sufficient evidence was available to draw a conclusion. Oral selective antihistamines and montelukast were equivalent for efficacy in reducing nasal and eye symptoms. Montelukast was superior to oral selective antihistamines for controlling asthma symptoms. Based on evidence, intranasal antihistamines and intranasal corticosteroids had equivalent efficacy for nasal and eye symptoms. Similarly, montelukast was comparable to intranasal corticosteroids for nasal symptoms. The combination

of intranasal antihistamines and intranasal corticosteroids demonstrated equivalent efficacy in nasal and eye symptom resolution compared to either monotherapy. No information was available about the use of these agents for the treatment of seasonal allergic rhinitis in pregnant women. For children, conclusions about relative efficacy were not determined due to insufficient evidence (Glacy et al, 2013).

- Montelukast has also been shown to be more effective than placebo in preserving pulmonary function in patients with exercise-induced bronchoconstriction (Wasfi et al, 2011).

Treatment Guidelines

- Treatment guidelines published by NHLBI recommend the use of ICSs as first-line therapy for long-term control of persistent asthma symptoms in children and adults. All three leukotriene modifiers can be used as alternative adjunctive agents to low- and medium-dose ICS; however, they are not recommended as preferred agents (NHLBI, 2007).
- The Global Initiative for Asthma (GINA) guidelines recommend that leukotriene receptor antagonists be used as alternative agents to low-dose ICSs. The leukotriene receptor antagonists are particularly appropriate in patients who are unable or unwilling to use ICSs, in those who experience intolerable adverse events on ICS therapy, or in patients with concomitant allergic rhinitis. The leukotriene receptor antagonists are also recommended as add-on treatment to ICS agents; however, the benefit reported with this treatment combination has been shown to be less than that of a combination of ICS and LABA. When good asthma control is established, leukotriene receptor antagonists may be used to allow tapering of low-dose ICSs in mild asthma. Completely stopping ICSs are not recommended, however, as it is associated with higher risk of exacerbations (GINA, 2017).
- The Joint Task Force on Practice Parameters for Allergy and Immunology recommends intranasal corticosteroids as the most effective medication class for controlling symptoms of allergic rhinitis, and all are considered equally efficacious. It is also suggested that intranasal antihistamines be considered as first-line treatment for both allergic and non-allergic rhinitis. The leukotriene receptor antagonists alone or in combination with antihistamines are effective in the treatment of allergic rhinitis (Wallace et al, 2008).
- The Institute for Clinical Systems Improvement (ICSI) guidelines notes that intranasal corticosteroids are the most effective single agents for controlling the spectrum of allergic rhinitis symptoms and should be considered as first-line therapy in patients with moderate to severe symptoms. Antihistamines and cromolyn can be considered as alternatives in patients who prefer not to use intranasal corticosteroids. Antihistamines are somewhat less effective than intranasal corticosteroids; however, oral antihistamines are effective alternatives in patients who cannot use or prefer not to use intranasal corticosteroids. Leukotriene modifiers are as effective as second-generation antihistamines for the treatment of allergic rhinitis; however, they are not as effective as intranasal corticosteroids (Snellman et al, 2013). According to a recent clinical practice guideline from the American Academy of Otolaryngology-Head and Neck Surgery, leukotriene modifiers should not be recommended as the first-line therapy for patients with allergic rhinitis because they are as effective or less effective than oral antihistamines and intranasal corticosteroids; however, they may be an appropriate primary therapy for certain patients who have asthma and allergic rhinitis (Seidman et al, 2015).
- An American Thoracic Society guideline states that for patients with exercise-induced bronchoconstriction, administration of a short-acting β_2-agonist before exercise is recommended. A controller agent is generally added when the short-acting β_2-agonist is used daily or more frequently. For patients with exercise-induced bronchoconstriction who continue to have symptoms despite use of a short-acting β_2-agonist before exercise, or who require a short-acting β_2-agonist daily or more frequently, options include adding daily use of an ICS, daily use of a leukotriene modifier, or the use of either a mast cell stabilizer or an inhaled anticholinergic agent before exercise (Parsons et al, 2013).
- The American Thoracic Society acknowledges leukotriene modifiers may provide benefit for the treatment of asthma in elderly patients. The management of asthma is based on the guidelines for younger patients, as there are not many studies that included older patients with asthma. ICS is the controller therapy of choice for asthma in elderly. From the few studies available, using leukotriene modifiers for asthma in elderly improved asthma indices, but it was not as pronounced as in younger patients. Also, the improvements seen with leukotriene modifiers were less than the improvements seen with ICSs for the elderly (Skloot et al, 2016).
- The Joint Task Force on Practice Parameters for Allergy and Immunology recommends β_2-agonists as the most effective agents for the prophylaxis and relief of exercise-induced bronchoconstriction; however, daily use of β_2-agonists may lead to tolerance. The use is therefore recommended only on an intermittent basis for the prevention of exercise-induced bronchoconstriction. Leukotriene receptor antagonists may be used daily or intermittently for the

prevention of exercise-induced bronchoconstriction without development of tolerance; however, these agents do not reverse airway obstruction when it occurs (Weiler et al, 2016).

SAFETY SUMMARY

- All leukotriene modifiers are contraindicated in patients with known hypersensitivity and/or allergic reaction to the medication or components of the product. In addition, both zafirlukast and zileuton have contraindications related to hepatic insufficiency. Zafirlukast is contraindicated in patients with hepatic impairment, including cirrhosis. Zileuton is contraindicated in patients with active liver disease or transaminase elevations greater than or equal to three times the upper limit of normal.
- Key warnings and precautions include:
    - Leukotriene modifiers are not indicated for reversal of acute asthma attacks.
    - All leukotriene modifiers may cause neuropsychiatric events.
    - Zileuton has several drug interactions; it may increase the plasma activity of propranolol, theophylline, and warfarin. Zafirlukast may increase the activity of warfarin.
    - Patients taking montelukast or zafirlukast should be monitored for signs and symptoms of systemic eosinophilia.
    - Hepatotoxicity may occur with zafirlukast or zileuton.
- The most common adverse reactions for montelukast (incidence ≥5% and greater than placebo) include upper respiratory infection, fever, headache, pharyngitis, cough, abdominal pain, diarrhea, otitis media, influenza, rhinorrhea, sinusitis, and otitis.
- The most common adverse reaction for zafirlukast for patients ≥12 years of age (incidence ≥5% and greater than placebo) is headache. For children aged five to 11 years, the most common adverse reactions (incidence ≥2% and higher than placebo) include headache and abdominal pain.
- The most common adverse reactions for zileuton (incidence ≥5% and greater than placebo) include headache, dyspepsia, unspecified pain, and nausea. For extended-release zileuton, the most common adverse reactions (≥5% and more than placebo) include sinusitis, nausea, and pharyngolaryngeal pain.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Generic Name	Dosage Form: Strength	Usual Adult Dose	Pediatric Dose	Administration Considerations
Montelukast	Chewable tablet: 4 mg 5 mg Oral granules: 4 mg Tablet: 10 mg	<u>Prophylaxis and chronic treatment of asthma:</u> Tablet: 10 mg once daily in the evening <u>Prevention of exercise-induced bronchoconstriction:</u> Tablet: 10 mg at least two hours before exercise; additional doses should not be administered within 24 hours <u>Relief of symptoms of perennial and seasonal allergic rhinitis:</u> Tablet: 10 mg daily at any time of day	<u>Prophylaxis and chronic treatment of asthma:</u> Chewable tablet: six to 14 years of age, 5 mg once daily in the evening; two to five years of age, 4 mg once daily in the evening Oral granules: 12 months to five years of age, 4 mg once daily in the evening Tablet: 15 years of age and older, 10 mg once daily in the evening <u>Prevention of exercise-induced bronchoconstriction:</u> Chewable tablet: six to 14 years of age: 5 mg at least two hours before exercise	May be taken with or without food. Oral granules may be given directly in the mouth or mixed with baby formula, breast milk, or soft foods (applesauce, carrots, rice, or ice cream). Contents of the packet must be administered within 15 minutes after opening the packet.

Generic Name	Dosage Form: Strength	Usual Adult Dose	Pediatric Dose	Administration Considerations
			Tablet: 15 years of age and older, 10 mg at least two hours before exercise <u>Relief of symptoms of perennial and seasonal allergic rhinitis:</u> Chewable tablet: two to five years of age, 4 mg once daily; six to 14 years of age, 5 mg once daily Oral granules: six months to five years of age (perennial) or two to five years of age (seasonal allergic rhinitis), 4 mg once daily Tablet: 15 years of age and older, 10 mg once daily	
Zafirlukast	Tablet: 10 mg 20 mg	<u>Prophylaxis and chronic treatment of asthma:</u> Tablet: 20 mg twice daily	<u>Prophylaxis and chronic treatment of asthma:</u> Tablet: five to 11 years of age, 10 mg twice daily; 12 years of age and older, 20 mg twice daily	Should be taken within one hour before or two hours after meals
Zileuton	Extended release tablet: 600 mg Tablet: 600 mg	<u>Prophylaxis and chronic treatment of asthma:</u> Extended release tablet: 1,200 mg twice daily Tablet: 600 mg four times a day	<u>Prophylaxis and chronic treatment of asthma:</u> Extended release tablet: 12 years of age and older, 1,200 mg twice daily Tablet: 12 years of age and older, 600 mg four times a day	Extended-release tablet: Should be taken within one hour after morning and evening meals. Tablet: Should be taken with meals and at bedtime.

SPECIAL POPULATIONS

Table 4. Special Populations

Generic Name	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
Montelukast	No dosage adjustment required in the elderly population.	Approved for use in children 12 months of age and older for asthma, six years of age and older for exercise induced bronchoconstric-tion, two years of age and older for seasonal allergic rhinitis, and six months of age	No dosage adjustment required.	No dosage adjustment is required in patients with mild-to-moderate hepatic insufficiency. Studies have not been conducted in patient with severe hepatic disease.	Pregnancy Category B Unknown whether excreted in breast milk; use caution.

Generic Name	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
		and older for perennial allergic rhinitis.			
Zafirlukast	No dosage adjustment required in the elderly population.	Approved for use in children five years of age and older.	No dosage adjustment required.	Contraindicated in patients with hepatic impairment, including cirrhosis.	Pregnancy Category B Excreted in breast milk; do not administer to nursing mothers.
Zileuton	No dosage adjustment required in the elderly population.	Safety and efficacy in pediatric patients under 12 years of age have not been established; use is not recommended.	No dosage adjustment required.	Contraindicated in patients with active liver disease and in patients with transaminase elevations greater than or equal to three times the upper limit of normal.	Pregnancy Category C Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug.

*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.
Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

CONCLUSION

- The leukotriene modifiers consist of two categories of agents: the leukotriene receptor antagonists (montelukast and zafirlukast) and the 5-lipoxygenase inhibitor (zileuton). All leukotriene modifiers are FDA-approved for the chronic treatment and prophylaxis of asthma. Montelukast is also indicated for prophylaxis of exercise-induced bronchoconstriction as well as for the treatment of symptoms of both seasonal and perennial allergic rhinitis.
- Current treatment guidelines recommend the use of leukotriene modifiers as a treatment alternative to low-dose ICSs in patients with mild persistent asthma. In mild asthma, adding a leukotriene receptor antagonist may allow an ICS dose to be stepped down, as well. These agents can also be considered as alternative adjunctive therapy in patients not achieving adequate symptom control with an ICS as monotherapy or in combination with a LABA. Either leukotriene receptor antagonist is preferred over zileuton due to the latter's limited efficacy data and the need for liver function monitoring (GINA, 2017; NHLBI, 2007). Guidelines position intranasal corticosteroids as first-line treatments for the management of allergic rhinitis, and note that the leukotriene modifiers can be considered as second-line agents along with antihistamines (Wallace et al, 2008; Brozek et al, 2010). A guideline for the treatment of exercise-induced bronchoconstriction recommends that β_2-agonists are the most effective therapy for the prophylaxis and relief of bronchoconstriction, while leukotriene receptor antagonists may also be used as prophylaxis but have no role on reversal of airway obstruction (Parsons et al, 2013; Weiler et al, 2016).
- In placebo-controlled trials, the leukotriene modifiers demonstrated efficacy in most aspects of asthma control. However, when compared to other long-term control medications, such as ICSs and LABAs, the leukotriene modifiers were unable to demonstrate equivalence or significant advantages in clinical outcomes. In patients with allergic rhinitis, montelukast has been shown to be more effective than placebo and has demonstrated comparable efficacy to the second-generation antihistamines; however, it was shown to be less effective than intranasal corticosteroids. Montelukast has also been shown to be more effective than placebo in preventing exercise-induced bronchoconstriction (Wasfi et al, 2011). Although one small, open-label trial suggests that extended-release zileuton has better therapeutic efficacy for the treatment of asthma in comparison to montelukast, comparative trial data is insufficient to draw any definitive conclusions (Kubavat et al, 2013).

- In regards to safety, postmarking data show that both zafirlukast and zileuton appear to have a higher risk of hepatotoxicity than montelukast. In addition, when compared to the other two agents, montelukast has the advantages of fewer drug interactions and more data supporting its use in children and infants as young as six months of age.

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