Texas Vendor Drug Program

Drug Use Criteria: Leukotriene Receptor Antagonists

Publication History

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Notes: Information on indications for use or diagnosis is assumed to be unavailable. All criteria may be applied retrospectively; prospective application is indicated with an asterisk [*]. The information contained is for the convenience of the public. The Texas Health and Human Services Commission is not responsible for any errors in transmission or any errors or omissions in the document.

Medications listed in the tables and non-FDA approved indications included in these retrospective criteria are not indicative of Vendor Drug Program formulary coverage.

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1 Dosage

Leukotrienes are inflammatory molecules released by mast cells in response to inhaled allergens. Cysteinyl leukotrienes bind to receptors on airway smooth muscle and macrophages and activate a number of airway effects, ultimately resulting in bronchoconstriction and inflammation associated with asthma, as well as the pathophysiologic effects associated with allergic rhinitis. Leukotriene receptor antagonists (LTRAs) prevent binding of cysteinyl leukotrienes to active receptors. Currently available LTRAs include montelukast and zafirlukast, with montelukast FDA-approved for prevention and chronic management of asthma in adults and children 12 months of age and older, seasonal allergic rhinitis in adults and children 2 years of age and older, perennial allergic rhinitis in adults and children 6 months of age and older, and prevention of exercise-induced bronchoconstriction in adults and children 6 years of age and older. Zafirlukast is only FDA-approved for use in preventing and managing chronic asthma in adults and children 5 years of age and older.

The Expert Panel created by the National Heart, Lung and Blood Institute considers LTRAs to be alternative, not preferred, treatment options for mild to moderate persistent asthma, and alternative, not preferred, adjunctive therapy with inhaled corticosteroids for mild to moderate persistent asthma. The Global Initiatives for Asthma (GINA) guidelines consider LTRAs to be an option for children greater than 5 years of age, adolescents, and adults at all levels of severity, although clinical benefit is not as significant as that seen with low-dose inhaled corticosteroids. In adult patients, LTRAs may be used as an alternative therapy for mild persistent asthma; however, when used as monotherapy, LTRAs are less effective than low-dose inhaled corticosteroids and may contribute to loss of asthma control if substituted in patients already maintained on inhaled corticosteroid therapy. LTRAs may also be utilized as add-on treatment in patients not adequately controlled on low-dose inhaled corticosteroids and may contribute to inhaled corticosteroid dosage reductions in adults with moderate-to-severe asthma. However, most studies have shown that long-acting inhaled beta$_2$-agonists are more effective than LTRAs as add-on therapy. In pediatric asthma patients, GINA guidelines state that LTRAs provide partial protection against exercise-induced bronchoconstriction and provide moderate clinical improvement with reduced exacerbations when used as adjunctive therapy in patients inadequately controlled with low-dose inhaled corticosteroids. In moderate persistent asthma, however, increasing inhaled

corticosteroid doses is more effective than adding LTRAs to existing therapy, and in moderate-to-severe persistent asthma, the addition of montelukast has not been shown to decrease the use of inhaled corticosteroids.

1.1 Adults

Adult dosage recommendations for LTRAs are summarized in Table 1. Patient profiles containing dosages not conforming to these recommendations will be reviewed.

Table 1. LTRA Adult Dosage Recommendations

Treatment Indication	Drug Name	Dosage Form/ Strength	Maximum Recommended Dosage
Asthma	montelukast (Singulair®, generics)	10 mg tablets, 4 mg, 5 mg chewable tablets, 4 mg oral granule packets	10 mg once daily in the evening
Prophylaxis, exercise-induced bronchoconstriction			10 mg as a single dose, at least 2 hours before exercise; dose should not be repeated within 24 hours of previous dose
Perennial and/or seasonal allergic rhinitis			10 mg daily
Asthma	zafirlukast (Accolate®, generics)	10 mg, 20 mg tablets	20 mg twice daily

1.2 Pediatrics

Pediatric dosage recommendations for LTRAs are summarized in Table 2. Patient profiles containing dosages not conforming to these recommendations will be reviewed.

Table 2. LTRA Pediatric Dosage Recommendations

Treatment Indication	Drug Name	Dosage Form / Strength	Maximum Recommended Dosage
asthma	montelukast (Singulair®, generics)	10 mg tablets, 4 mg, 5 mg chewable tablets, 4 mg oral granule packets	adolescents greater than or equal to 15 years of age: 10 mg once daily in the evening (as tablet) children 6-14 years of age: 5 mg once daily in the evening (as chewable tablet) children 2-5 years of age: 4 mg once daily in the evening (as chewable tablet or oral granules) children 12–23 months of age: 4 mg once daily in the evening (as oral granules)
prophylaxis, exercise-induced bronchoconstriction			adolescents greater than or equal to 15 years of age: 10 mg as a single dose, at least 2 hours before exercise; dose should not be repeated within 24 hours of previous dose children 6 to 14 years of age: 5 mg (as chewable tablet) as a single dose, at least 2 hours before exercise; dose should not be repeated within 24 hours of previous dose
seasonal allergic rhinitis			adolescents greater than or equal to 15 years of age: 10 mg daily (as tablet) children 6-14 years of age: 5 mg daily (as chewable tablet) children 2-5 years of age: 4 mg daily (as chewable tablet or oral granules)

Treatment Indication	Drug Name	Dosage Form / Strength	Maximum Recommended Dosage
perennial allergic rhinitis			adolescents greater than or equal to 15 years of age: 10 mg daily (as tablet) children 6-14 years of age: 5 mg daily (as chewable tablet) children 2-5 years of age: 4 mg daily (as chewable tablet or oral granules) children 6-23 months of age: 4 mg daily (as oral granules)
asthma	zafirlukast (Accolate®, generics)	10 mg, 20 mg tablets	adolescents greater than or equal to 12 years of age: 20 mg twice daily children 5-11 years of age: 10 mg twice daily

2 Duration of Therapy

LTRAs are indicated for the management of chronic asthma and seasonal allergic rhinitis and may be continued indefinitely, as both allergic rhinitis and asthma are chronic, lifelong processes.

3 Duplicative Therapy

Zileuton (Zyflo®), a 5-lipoxygenase inhibitor, inhibits formation of cysteinyl leukotrienes. Concurrent administration of LTRAs with zileuton does not provide additional clinical benefit and may increase risk of developing adverse events. Concurrent administration of LTRAs with zileuton is not recommended and will be reviewed.

Adjunctive administration of montelukast and zafirlukast does not provide additional clinical benefit and may result in additive adverse effects. Combined administration of montelukast and zafirlukast is not recommended and will be reviewed.

4 Drug-Drug Interactions

Patient profiles will be assessed to identify those drug regimens which may result in clinically significant drug-drug interactions.

No dosage adjustments are necessary when montelukast is co-administered with theophylline, prednisone, prednisolone, oral contraceptives, digoxin, warfarin, thyroid hormones, sedative hypnotics, nonsteroidal anti-inflammatory agents, benzodiazepines, decongestants, and cytochrome P450 enzyme inducers. Continuous monitoring for montelukast efficacy is recommended when concurrently taking cytochrome P450 enzyme inducers.

Drug-drug interactions considered clinically relevant for zafirlukast are summarized in Table 3. Only those drug-drug interactions identified as clinical significance level 1 or those considered life-threatening which have not yet been classified will be reviewed.

Table 3. Zafirlukast Drug-Drug Interactions

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level#
Zafirlukast	pimozide	increased pimozide concentrations resulting in QTc prolongation and ventricular arrhythmias due to CYP3A4 inhibition by zafirlukast	contraindicated	1-severe (CP)
zafirlukast	other drugs metabolized by CYP3A4 (e.g., dofetilide, aripiprazole, cilostazol)	increased concentration of drugs metabolized by CYP3A4 due to CYP3A4 inhibition by zafirlukast	carefully monitor patient therapy for potentially enhanced pharmacologic effects and toxicity	2-major (CP) minor (DrugReax)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level#
zafirlukast	drugs metabolized by CYP2C9 (e.g., warfarin, phenytoin)	increased concentrations of drugs metabolized by CYP2C9 due to zafirlukast enzyme inhibition; prothrombin time increased by 35% with warfarin-zafirlukast combination	monitor for increased adverse events (e.g., regularly assess PT or INR with warfarin-zafirlukast combination, phenytoin levels)	2-major (CP) moderate (DrugReax)
Zafirlukast	other drugs metabolized by CYP3A4 (e.g., dofetilide, ergot alkaloids, aripiprazole, cilostazol)	increased theophylline concentration due to CYP 1A2 inhibition by zafirlukast and/or decreased zafirlukast serum levels	monitor for theophylline toxicity and/or reduced zafirlukast efficacy	3-moderate (CP) moderate (DrugReax)
zafirlukast	saquinavir (boosted with ritonavir)	saquinavir and zafirlukast are CYP3A4 inhibitors; combined use may increase saquinavir serum levels and potentially result in life-threatening arrhythmias (including torsades de pointes)	Contraindicated	1-severe (CP)
zafirlukast	erythromycin clarithromycin	decreased zafirlukast concentrations; mechanism unknown	monitor patient for lack of response to zafirlukast therapy; may consider azithromycin or montelukast as alternatives	3-moderate (CP) moderate (DrugReax)

- *CP = Clinical Pharmacology

5 References

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