Policy and Procedure	
PHARMACY STEP THERAPY POLICY AND CRITERIA ORPTCRES010.0625	**RESPIRATORY AGENTS** **ZYFLO® CR** (zileuton extended release tablet) **ZYFLO® Filmtab** (zileuton immediate release tablet)
Effective Date: 8/1/2025	**Review/Revised Date**: 04/09, 10/09, 02/10, 06/10, 04/11, 02/12, 06/13, 06/14, 06/15, 05/16, 05/17, 05/18, 05/19, 04/20, 05/21, 05/22, 04/23, 05/24, 04/25 (snm)
Original Effective Date: 02/08	**P&T Committee Meeting Date**: 02/08, 04/09, 10/09, 02/10, 06/10, 04/11, 02/12, 06/13, 06/14, 06/15, 06/16, 06/17, 06/18, 06/19, 06/20, 06/21, 06/22, 06/23, 06/24, 06/25
Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicaid

POLICY CRITERIA:

COVERED USES:
All medically accepted indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
Trial, intolerance, or contraindication to montelukast and zafirlukast

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS: N/A

COVERAGE DURATION:
Authorization will be approved until no longer eligible with the plan, subject to formulary or benefit changes

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Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale,

formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Zileuton is a leukotriene pathway inhibitor, which blocks 5-lipoxygenase, the enzyme that potentiates the formation of leukotrienes. Leukotrienes contribute to inflammation, edema, mucus secretion, and bronchoconstriction in the airways of asthmatic patients.

FDA APPROVED INDICATION:

Prophylaxis and chronic treatment of asthma in adults and children 12 years of age and older. Not indicated for use in the reversal of bronchospasm in acute asthma attacks; however, therapy can be continued during acute exacerbations of asthma.

POSITION STATEMENT:

Current treatment guidelines published by the National Asthma Education and Prevention Program (NAEPP) and the National Institutes of Health, (NIH) National, Heart, Lung, Blood Institute (NHLBI) emphasize the use of inhaled corticosteroids (ICS) as first-line therapy for long-term control of persistent asthma symptoms in both children and adults.[3] The Global Initiative for Asthma (GINA) guidelines, recommends that all adults and adolescents with asthma receive ICS-containing controller treatment to reduce their risk of serious exacerbations and to control symptoms. According to GINA 2024, leukotriene modifiers are less effective than ICS, particularly for exacerbations. Leukotriene modifiers may be appropriate for patients who are unable to use ICS, experience intolerable side effects from ICS, or patients with concomitant allergic rhinitis.[4]

Leukotriene modifiers include montelukast (Singulair®), zafirlukast (Accolate®) and zileuton (Zyflo® CR). Compared with montelukast and zafirlukast, zileuton is not a preferred choice because of limited efficacy data and the risk of liver toxicity. Zileuton use in children under the age of 12 is not recommended, as there is no data to support its efficacy and safety in this population.

Elevations of one or more hepatic function enzymes and bilirubin may occur during zileuton therapy. These laboratory abnormalities may progress to clinically

significant liver injury, remain unchanged, or resolve with continued treatment, usually within three weeks. The ALT (SGPT) test is considered the most sensitive indicator of liver injury for zileuton tablets. It is important to assess hepatic function enzymes prior to initiation of, and during therapy.

Neuropsychiatric events have also been reported in adult and adolescent patients taking zileuton. Post-marketing reports with zileuton include sleep disorders and behavior changes. Patients should be instructed to notify their prescriber if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment with zileuton if such events occur.

REFERENCE/RESOURCES:

1. Zileuton. In: DRUGDEX® System [Internet database]. Greenwood Village, Colorado: Thomson Reuters (Healthcare) Inc. Updated periodically, accessed April 24, 2025.
2. Zyflo Tablet Prescribing Information. Chiesi USA, Inc; Cary, NC. January 2022.
3. National Heart, Lung, and Blood Institute. 2020 Focused Updates to the Asthma Management Guidelines: Clinician's Guide. Last updated February 4, 2021. Available at: https://www.nhlbi.nih.gov/resources/clinician-guide-2020-focused-updates-asthma-management-guidelines. Accessed April 24, 2025.
4. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. Updated 2024. Available at: https://ginasthma.org/wp-content/uploads/2024/05/GINA-2024-Strategy-Report-24_05_22_WMS.pdf Accessed on: April 24, 2025.