PRIOR AUTHORIZATION CRITERIA

BRAND NAME*
(generic)

ZYFLO
(zileuton)

(zileuton extended-release)

Status: CVS Caremark Criteria
Type: Initial Prior Authorization ***Ref #4836-A***

**Drugs that are listed in the target drug box include both brand and generic and all dosage forms and strengths unless otherwise stated. OTC products are not included unless otherwise stated.*

FDA-APPROVED INDICATIONS

Zyflo
Zyflo is indicated for the prophylaxis and chronic treatment of asthma in adults and children 12 years of age and older.

Zileuton extended-release
Zileuton extended-release tablet is indicated for the prophylaxis and chronic treatment of asthma in adults and children 12 years of age and older.
Zileuton extended-release tablet is not indicated for use in the reversal of bronchospasm in acute asthma attacks.
Therapy with zileuton extended-release tablet can be continued during acute exacerbations of asthma.

COVERAGE CRITERIA

The requested drug will be covered with prior authorization when the following criteria are met:

- The requested drug is being prescribed for the prophylaxis or chronic treatment of asthma in a patient 12 years of age and older

AND

- The patient has experienced an inadequate treatment response to any of the following: A) An orally inhaled corticosteroid (ICS), B) A combination product containing an orally inhaled corticosteroid and long-acting beta agonist (ICS/LABA)
  [Note: The patient may continue to use an ICS containing product.]
  OR
- The patient has experienced an intolerance to any of the following: A) An orally inhaled corticosteroid (ICS), B) A combination product containing an orally inhaled corticosteroid and long-acting beta agonist (ICS/LABA)
  OR
- The patient has a contraindication that would prohibit a trial of any of the following: A) An orally inhaled corticosteroid (ICS), B) A combination product containing an orally inhaled corticosteroid and long-acting beta agonist (ICS/LABA)

RATIONALE

The intent of the criteria is to provide coverage consistent with product labeling, FDA guidance, standards of medical practice, evidence-based drug information, and/or published guidelines. Zileuton is indicated for the prophylaxis and chronic treatment of asthma in adults and children 12 years of age and older.[1]

Inhaled corticosteroids (ICS) alone or in combination with a long-acting beta-agonist are indicated for the daily treatment of asthma.[3,4]

The Global Initiative for Asthma (GINA) Strategy for Asthma Management and Prevention 2021 guideline recommends all adults and adolescents with asthma should receive inhaled corticosteroid (ICS)-containing controller treatment to reduce

their risk of serious exacerbations and to control symptoms. The 2021 GINA recommendations for adults and adolescents controller and reliever by preference for each Step are as follows:
Step 1 – Preferred: low dose combination ICS-formoterol taken as needed for relief of symptoms, and if needed before exercise. Alternative: low dose ICS taken whenever short-acting beta-agonist (SABA) is taken.
Step 2 – Preferred: low dose ICS-formoterol, taken as needed for relief of symptoms, and if needed before exercise. Alternative: daily low dose ICS plus as needed SABA. Other options: low dose ICS whenever SABA is taken, or leukotriene receptor antagonist (LTRA) (less effective than ICS, particularly for exacerbations).
Step 3 – Preferred: low dose ICS-formoterol maintenance and reliever. Alternative: low dose maintenance ICS/long-acting beta-agonist (LABA) plus as needed SABA. Other options: medium dose ICS, or (less efficacious) low dose ICS plus LTRA.
Step 4 – Preferred: medium dose ICS-formoterol maintenance and reliever therapy. Alternative: medium or high dose ICS/LABA with as needed SABA. Other options: long-acting muscarinic antagonist (LAMA) may be considered as add-on therapy, or (less efficacious than adding LABA) LTRA, or high dose ICS.
Step 5 – Preferred: refer for expert assessment, phenotyping, and add-on therapy. Add-on LAMA, consider combination high dose ICS/LABA, Other options: add-on azithromycin, add-on LTRA, add-on oral corticosteroids.[5]

The 2020 Focused Updates to the Asthma Management Guidelines recommendations for adults and adolescents preference for each Step are as follows:
Step 1 – Preferred: as needed SABA. Alternative: none
Step 2 – Preferred: daily low-dose ICS and as needed SABA, or as needed concomitant ICS and SABA. Alternative: daily LTRA and as needed SABA, or cromolyn, nedocromil, zileuton, or theophylline, and as needed SABA.
Step 3 – Preferred: daily and as needed combination low dose ICS-formoterol. Alternative: daily medium dose ICS and as needed SABA, or daily low dose ICS/LABA, daily low dose ICS + LAMA, or daily low dose ICS + LTRA, and as needed SABA, or daily low dose ICS + theophylline or zileuton, and as needed SABA.
Step 4 – Preferred: daily and as needed combination medium dose ICS-formoterol. Alternative: daily medium dose ICS/LABA or daily medium dose ICS + LAMA, and as needed SABA, or daily medium dose ICS + LTRA, daily medium dose ICS + theophylline, or daily medium dose ICS + zileuton, and as needed SABA.
Step 5 – Preferred: daily medium-high dose ICS/LABA + LAMA and as needed SABA. Alternative: daily medium-high dose ICS/LABA or daily high dose ICS + LTRA, and as needed SABA.
Step 6 – Preferred: daily high dose ICS/LABA + oral corticosteroids + as needed SABA. Alternative: none.[6]

The GINA guidelines refer to LTRAs as other options to preferred and alternative therapy at Steps 2, 3, 4, and 5. The GINA guidelines also state there is limited evidence to support a role for LTRAs in acute asthma.[5] The 2020 Focused Update refers to zileuton as an option in alternative therapy at Steps 2, 3, and 4. The 2020 Focused Update also states cromolyn, nedocromil, LTRAs including zileuton and montelukast, and theophylline were not considered for this update, and/or have limited availability for use in the United States, and/or have an increased risk of adverse consequences and need for monitoring that make their use less desirable.[6] The Expert Panel Report (EPR) 3 guideline recommended zileuton as alternative therapy as add-on to ICS at Steps 3 and 4. And state zileuton is a less desirable alternative due to limited studies as adjunctive therapy and the need to monitor liver function.[7] Therefore, a trial of a preferred therapy ICS or ICS combination product (ICS/LABA) will be required prior to approval of zileuton or zileuton ER (Zyflo, Zyflo ER).

REFERENCES

1. Zyflo [package insert]. Cary, NC: Chiesi USA, Inc.; January 2017.
2. Zileuton Extended-Release [package insert]. Baltimore, MD: Lupin Pharmaceuticals , Inc.; August 2020.
3. Lexicomp Online, AHFS DI (Adult and Pediatric) Online. Hudson, OH: UpToDate, Inc.; 2021; Accessed July 2021.
4. Micromedex (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com. Accessed July 2021.
5. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2021. Available at: http://www.ginasthma.org. Accessed June 2021.
6. 2020 Focused Updates to the Asthma Management Guidelines. A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. Available at: https://www.nhlbi.nih.gov/health-topics/asthma-management-guidelines-2020-updates. Accessed June 2021.
7. National Heart, Lung, and Blood Institute National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma Full Report 2007. Available at http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines. Accessed July 2021.

Written by: UM Development (TM)
Date Written: 06/2021
Revised:
Reviewed: Medical Affairs (CHART) 08/05/2021
External Review: 10/2021

CRITERIA FOR APPROVAL

1	Is the requested drug being prescribed for prophylaxis or chronic treatment of asthma in a patient 12 years of age or older? [If no, then no further questions.]	Yes	No
2	Has the patient experienced an inadequate treatment response to any of the following: A) An orally inhaled corticosteroid (ICS), B) A combination product containing an orally inhaled corticosteroid and long-acting beta agonist (ICS/LABA)? [Note: The patient may continue to use an ICS containing product.] [If yes, then no further questions.]	Yes	No
3	Has the patient experienced an intolerance to any of the following: A) An orally inhaled corticosteroid (ICS), B) A combination product containing an orally inhaled corticosteroid and long-acting beta agonist (ICS/LABA)? [If yes, then no further questions.]	Yes	No
4	Does the patient have a contraindication that would prohibit a trial of any of the following: A) An orally inhaled corticosteroid (ICS), B) A combination product containing an orally inhaled corticosteroid and long-acting beta agonist (ICS/LABA)?	Yes	No

Mapping Instructions			
	Yes	**No**	**DENIAL REASONS – DO NOT USE FOR MEDICARE PART D**
1.	Go to 2	Deny	You do not meet the requirements of your plan. Your plan covers this drug when you meet the following: - You are using it for prophylaxis or chronic treatment of asthma - You are 12 years of age or older Your request has been denied based on the information we have. [Short Description: No approvable diagnosis]
2.	Approve, 12 months	Go to 3	
3.	Approve, 12 months	Go to 4	
4.	Approve, 12 months	Deny	You do not meet the requirements of your plan. Your plan covers this drug when you have tried any of the following and it did not work for you or you cannot use it: - An orally inhaled corticosteroid (ICS) - A combination product containing an orally inhaled corticosteroid and long-acting beta agonist (ICS/LABA) [Short Description: No inadequate response, intolerance or contraindication to ICS, ICS/LABA]