Clinical Policy: Zileuton ER (Zyflo CR)
Reference Number: ERX.NPA.62
Effective Date: 02.27.18
Last Review Date: 05.18

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Zileuton extended-release (ER) (Zyflo CR®) is a leukotriene synthesis inhibitor.

FDA Approved Indication(s)
Zyflo CR is indicated for the prophylaxis and chronic treatment of asthma in adults and children 12 years of age and older.

Limitation(s) of use: Do not use Zyflo CR to treat an acute asthma attack.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Zyflo CR is medically necessary when the following criteria are met:

I. Initial Approval Criteria
   A. Asthma (must meet all):
      1. Diagnosis of asthma;
      2. Age ≥ 12 years;
      3. Failure of montelukast or zafirlukast, unless both are contraindicated or clinically significant adverse effects are experienced;
      4. Dose does not exceed 2400 mg/day (4 tablets/day).
   Approval duration: 12 months

   B. Other diagnoses/indications
      1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy
   A. Asthma (must meet all):
      1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
      2. Member is responding positively to therapy;
      3. If request is for a dose increase, new dose does not exceed 2400 mg/day (4 tablets/day).
   Approval duration: 12 months

   B. Other diagnoses/indications (must meet 1 or 2):
      1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
      Approval duration: Duration of request or 12 months (whichever is less); or
      2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:
   A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.
IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
- ER: extended-release
- FDA: Food and Drug Administration
- ICS: inhaled corticosteroid
- LABA: long-acting beta agonist
- LTRA: leukotriene receptor antagonist

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>montelukast (Singulair®)</td>
<td>Tablets: 10 mg PO QD</td>
<td>10 mg/day</td>
</tr>
<tr>
<td></td>
<td>Chewable tablets: 5 mg PO QD</td>
<td></td>
</tr>
<tr>
<td>zafirlukast (Accolate®)</td>
<td>20 mg PO BID</td>
<td>40 mg/day</td>
</tr>
</tbody>
</table>

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: General Information

• Per the National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3 (EPR-3) 2007 guidelines, the following stepwise approach is used for adults and adolescents ≥12 years of age:
  o Step 1:
    ▪ Preferred: short-acting bronchodilator as needed
  o Step 2:
    ▪ Preferred: low-dose ICS
    ▪ Alternatives: cromolyn, leukotriene receptor antagonists (LTRA), nedocromil, theophylline
  o Step 3:
    ▪ Preferred: low-dose ICS + LABA or medium-dose ICS
    ▪ Alternatives: low-dose ICS + LTRA, theophylline, or zileuton
• Leukotriene modifiers include LTRAs (e.g., montelukast and zafirlukast) and zileuton. Leukotriene modifiers are recommended as alternative, but not preferred, therapies. In addition, although LTRAs are recommended for those <12 years of age, zileuton is only recommended for those ≥12 years of age.

V. Dosage and Administration

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>Two 600 mg tablets PO BID within 1 hour after morning and evening meals</td>
<td>2400 mg/day</td>
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</table>

VI. Product Availability

Extended-release tablet: 600 mg

VII. References

Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th>Date</th>
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Important Reminder
This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.

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