



## Therapeutic Class Review<sup>SM</sup>

### Respiratory – zileuton (Zyflo CR<sup>®</sup>)

February 2008

**New Product for Review:**

zileuton (Zyflo CR<sup>®</sup>) [Critical Therapeutics]

**Dossier Provided by Manufacturer: Yes**

**Dossier Evaluation: 3**

- 1 - Dossier missing significant clinical trial(s).
- 2 - Mfg. provided all relevant trials; Missing pharmacoeconomic model.
- 3 - Mfg. provided all relevant trials and information.

#### Executive Summary

- Leukotriene modifiers interfere with the pathway of leukotriene mediators, which are released from mast cells, eosinophils, and basophils. These medications include leukotriene receptor antagonists (LTRAs) (montelukast and zafirlukast) and a 5-lipoxygenase inhibitor (zileuton).
- Zileuton is the only leukotriene formation inhibitor available.
- Zileuton (Zyflo CR) was FDA approved May 30, 2007 and launched in October 2007.
- Zileuton (Zyflo CR) is administered as two tablets twice daily, an improvement over zileuton (Zyflo), one tablet four times a day.
- Zileuton (Zyflo and Zyflo CR) is the most expensive leukotriene modifier treatment option.
- Modest effect size has been observed with zileuton (Zyflo CR). These results are in line with other leukotriene modifier agents.
  - The benefits of leukotriene modifier therapy with zileuton, montelukast or zafirlukast in children and adults with asthma are improved pulmonary function, decreased daytime and nocturnal symptoms, a reduced need for short-acting rescue  $\beta_2$  agonists, fewer exacerbations of asthma, and an increased quality of life.<sup>[17]</sup>
  - Leukotriene modifier agents have an additive benefit in patients whose disease is not adequately controlled by inhaled corticosteroids.<sup>[17]</sup>
  - Leukotriene modifier agents are inferior to long-acting  $\beta_2$  agonists as add-on therapy to inhaled corticosteroids (particularly with respect to improving lung function).<sup>[17]</sup>
- There is not evidence of comparative efficacy/safety zileuton (Zyflo CR) to the leukotriene receptor antagonists (LTRAs) montelukast and zafirlukast.
- There are no safety advantages of Zyflo CR over Zyflo:
  - Similar frequency of hepatotoxicity compared to Zyflo.

- Liver enzymes must be monitored during treatment with zileuton.
- The National Heart, Lung, and Blood Institute in the updated 2007 Asthma Guidelines<sup>[9]</sup> state that inhaled corticosteroids (ICS) are the most consistently effective long-term control medication at all steps of care for persistent asthma.
  - Combination with leukotriene modifiers is considered second line.
  - Because of limited add-on therapy efficacy data for zileuton, and its liver function test monitoring requirements, it is a less desirable alternative than LTRA for add-on therapy.

## Evidence

- There are two randomized controlled trials (RCTs) of uncertain validity. They are not useful for making healthcare decisions because:
  - Both used a primary efficacy endpoint of FEV<sub>1</sub>.
  - There were excessive drop-outs.
  - No intent-to-treat analysis was included.

## Decision

- Zileuton (Zyflo CR) is non-preferred/non-formulary because:
  - It has the same safety concerns with increased liver enzymes as with zileuton (Zyflo).
  - It provides no advantages over formulary alternatives in terms of safety or efficacy.
  - Administration is BID, as is zafirlukast (Accolate), and montelukast (Singulair) is administered once daily.
  - It is the most expensive leukotriene modifier treatment option.

## Products

Drug Products	FDA approval <sup>a</sup>	Patent expiration <sup>c</sup>	FDA approved indications	Usual Dose/Route
montelukast (Singulair <sup>®</sup> ) <sup>3</sup>	2/1998	08/2008	Allergic rhinitis Asthma Exercise-induced bronchoconstriction (EIB)	10mg PO QD ≥ 15 years 5mg PO QD 6-14 yrs 4mg PO QD 2-4 yrs 4mg PO QD granules 6-23 months
zafirlukast (Accolate <sup>®</sup> ) <sup>2</sup>	9/1996	09/2010	Asthma	20mg PO BID ≥12 yrs 10mg PO BID 5-11yrs
zileuton (Zyflo) (Zyflo CR <sup>®</sup> ) <sup>1</sup>	12/1996 5/2007	12/2010 06/2012	Asthma	600mg PO QID ≥ 12 years 1200mg PO BID ≥ 12 years

<sup>a</sup> Date applies to approval date for the original brand name medication where there are now generics available.

<sup>c</sup> Based on patents listed in the Orange Book as of November 2007.

## References

1. Zyflo CR<sup>®</sup> (zileuton) extended-release tablets. Prescribing Information. May 2007. Critical Therapeutics, Inc., Lexington, MA.
2. Accolate<sup>®</sup> (zafirlukast) tablets. Prescribing Information July 2004. AstraZeneca Pharmaceuticals LP, Wilmington, DE

3. Singulair<sup>®</sup> (montelukast sodium) Tablets, Chewable Tablets, And Oral Granules. April 2007. Prescribing Information. Merck & Co. Inc. Whitehouse Station, NJ
4. Ducharme FM, Di Salvo F. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. *Cochrane Database of Systematic Reviews* 2004, Issue 1. Art. No.: CD002314. DOI: 10.1002/14651858.CD002314.pub2.
5. Ducharme F, Schwartz Z, Kakuma R. Addition of anti-leukotriene agents to inhaled corticosteroids for chronic asthma. *Cochrane Database of Systematic Reviews* 2004, Issue 1. Art. No.: CD003133. DOI: 10.1002/14651858.CD003133.pub2.
6. Ducharme FM, Lasserson TJ, Cates CJ. Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma. *Cochrane Database of Systematic Reviews* 2006, Issue 4. Art. No.: CD003137. DOI: 10.1002/14651858.CD003137.pub3.
7. Nelson H, Kemp J, Berger W, Corren J, Casale T, Dube L, Walton-Bowen K, LaVallee N, Stepanians M. Efficacy of zileuton controlled-release tablets administered twice daily in the treatment of moderate persistent asthma: a 3-month randomized controlled study. *Ann Allergy Asthma Immunol.* 2007 Aug;99(2):178-84.
8. Wenzel S, Busse W, Calhoun W, Panettieri R Jr, Peters-Golden M, Dube L, Walton-Bowen K, Russell H, Harris J. The safety and efficacy of zileuton controlled-release tablets as adjunctive therapy to usual care in the treatment of moderate persistent asthma: a 6-month randomized controlled study. *J Asthma.* 2007 May;44(4):305-10.
9. National Heart, Lung, and Blood Institute (NHLBI); National Asthma Education and Prevention Program: Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma; 2007. Available at: <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm> accessed on 8/29/2007.
10. Ram FSF, Cates CJ, Ducharme FM. Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma (Review). *The Cochrane Database of Systematic Reviews* 2005, Issue 1. Art. No.: CD003137.pub2. DOI:10.1002/14651858.CD003137.pub2.
11. Global Initiative for Asthma (GINA) Report, Global Strategy for Asthma Management and Prevention Revised November 2006. <http://www.ginasthma.com/Guidelineitem.asp?i1=2&i2=1&intId=60> accessed 12/27/06.
12. Zflo<sup>®</sup> (zileuton) tablets. Prescribing Information. March 2005. Critical Therapeutics, Inc., Lexington, MA.
13. Beers MH, Berkow R, eds. The Merck Manual of Diagnosis and Therapeutics. 17th Edition. Merck, Inc. Available at: <http://www.merck.com/mrkshared/mmanual/section6/chapter64/64a.jsp>. Accessed on 2/01/2006.
14. The Cleveland Clinic Disease Management Project. Pulmonary function testing: basics of physiology and interpretation. Available at: <http://www.clevelandclinicmeded.com/diseasemanagement/pulmonary/pft/pft1.htm>. Accessed on 1/31/2006.
15. Dennis RF, Solarte I, FitzGerald JM. Respiratory disorders (chronic): Asthma (Search date October 2006). *BMJ Clin Evid* 2007;08:1501.
16. Ducharme FM, Di Salvo F. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. *Cochrane Database of Systematic Reviews* 2004, Issue 1. Art. No.: CD002314. DOI: 10.1002/14651858.CD002314.pub2.
17. Peters-Golden M, and Henderson WR. Mechanisms of Disease Leukotrienes. *N Engl J Med* 2007;357:1841-54.