



## 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.

**Available Therapeutic Alternatives:**

Preferred Formulary	Non-preferred Non-Formulary
montelukast (Singulair <sup>®</sup> ) [Merck]	zileuton (Zyflo <sup>®</sup> & Zyflo CR <sup>®</sup> ) [Critical Therapeutics]
zafirlukast (Accolate <sup>®</sup> ) [AstraZeneca]	

\* covered with prior authorization

**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 Zylfo 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.

### ***Consideration in subpopulations***

- **Pediatrics** - The safety and effectiveness of zileuton (Zyflo CR) in pediatric patients under 12 years of age have not been established.
- **Hepatic Disease** - Zileuton (Zyflo CR) is contraindicated in patients with active liver disease or persistent ALT elevations  $\geq 3 \times$  ULN (upper limits of normal).
- **Geriatrics** - Zileuton immediate release tablet data suggest that females  $\geq 65$  years of age appear to be at increased risk of ALT elevations.
- **Pregnancy** - Category C: There are no adequate and well-controlled studies in pregnant women. Zileuton (Zyflo CR) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### **Expert opinion**

Expert opinion was sought from 26 providers including primary care physicians and allergists. Comments included were:

- Leukotriene inhibitors are third line drugs for asthma
- Less effective than inhaled steroids for maintenance therapy

## Product Value

Zileuton (Zyflo CR) provides another treatment option for patients 12 years and older with asthma. The twice daily dosage form is more convenient than the original four-times a day option. There are preferred formulary alternatives that are more cost effective.

## Conclusion

- 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	Cost <sup>b</sup>
montelukast (Singulair <sup>®</sup> ) <sup>3</sup>	2/1998	08/2008	Allergic rhinitis	10mg PO QD ≥ 15 years	\$115
			Asthma	5mg PO QD 6-14 yrs	\$115
			Exercise-induced bronchoconstriction (EIB)	4mg PO QD 2-4 yrs	\$115
				4mg PO QD granules 6-23 months	\$115
zafirlukast (Accolate <sup>®</sup> ) <sup>2</sup>	9/1996	09/2010	Asthma	20mg PO BID ≥12 yrs	\$99
				10mg PO BID 5-11yrs	\$99
zileuton (Zyflo) (Zyflo CR <sup>®</sup> ) <sup>1</sup>	12/1996	12/2010	Asthma	600mg PO QID ≥ 12 years	\$305
	5/2007	06/2012		1200mg PO BID ≥ 12 years	\$305

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

<sup>b</sup> Cost estimate based on AWP (average wholesale price) listed in First Data Bank as of November 2007 for 1 month of therapy.

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

## References

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