**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration
Rockville, MD 20857

**TRANSMITTED BY FACSIMILE**

Paul D. Rubin, M.D.
President and Chief Executive Officer
Critical Therapeutics, Inc.
60 Westview Street
Lexington, MA 02421

**Re: NDA # 20-471**
**Zyflo® Filmtab® (zileuton tablets)**
**MACMIS ID # 13652**

# WARNING LETTER

Dear Dr. Rubin:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a mechanism of action sheet (MOA sheet) (MKTG-PRMATL-23-Rev01) for Zyflo® Filmtab® (zileuton tablets) (Zyflo) submitted by Critical Therapeutics, Inc. (Critical Therapeutics) under cover of Form FDA 2253. The MOA sheet is false or misleading in that it presents efficacy claims for Zyflo, but fails to communicate any risks associated with its use and fails to present the approved indication. Thus, the MOA sheet misbrands the drug in violation of Sections 502(a) and 201(n) of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. §§ 352(a) & 321(n). Your MOA sheet raises public health and safety concerns through its complete omission of risk information for Zyflo by suggesting that Zyflo is safer than has been demonstrated.

## Background

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

According to the Clinical Pharmacology (Mechanism of Action) section of the approved product labeling (PI), Zyflo is a specific inhibitor of 5-lipoxygenase and thus inhibits leukotriene ($LTB_4$, $LTC_4$, $LTD_4$, and $LTE_4$) formation. Leukotrienes are substances that induce numerous biological effects, including augmentation of neutrophil and eosinophil migration, neutrophil and monocyte aggregation, leukocyte adhesion, increased capillary permeability, and smooth muscle contraction. These effects contribute to inflammation, edema, mucus secretion, and bronchoconstriction in the airways of asthmatic patients.

Zyflo is contraindicated in patients with active liver disease or transaminase elevations greater than or equal to three times the upper limit of normal ($\geq$3xULN). The Warnings section of the PI states that Zyflo is not indicated for use in the reversal of bronchospasm in acute asthma attacks, including status

asthmaticus. In addition, the co-administration of Zyflo with theophylline, warfarin, and/or propanolol warrants close monitoring and dosage adjustments of the co-administered drug.

The Precautions (Hepatic) section of the PI states (in pertinent part):

> It is recommended that hepatic transaminases be evaluated at initiation of, and during therapy with, ZYFLO. Serum ALT should be monitored before treatment begins, once-a-month for the first 3 months, every two to three months for the remainder of the first year, and periodically thereafter for patients receiving long-term ZYFLO therapy. If clinical signs and/or symptoms of liver dysfunction (e.g., right upper quadrant pain, nausea, fatigue, lethargy, pruritus, jaundice, or "flu-like" symptoms) develop or transaminase elevations greater than 5 times the ULN occur, ZYFLO should be discontinued and transaminase levels followed until normal.

The Adverse Reactions section of the PI indicates that dyspepsia was the most common adverse reaction that occurred at a significantly greater frequency than placebo (8.2% in Zyflo-treated patients, 2.9% in placebo-treated patients, $p \leq 0.05$ vs placebo).

**Omission of Material Facts**

Promotional materials are false or misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. The MOA sheet presents efficacy claims for Zyflo but fails to present <u>any</u> risk information or the approved indication.

The MOA sheet makes efficacy claims by making representations of Zyflo's mechanism of action by depicting the effects of zileuton on 5-LO (5-lipoxygenase), the effects of 5-LO on leukotrienes, and the effects of leukotrienes on eosinophils, smooth muscle cells, mast cells, monocytes, and neutrophils (see Background section). In addition, the MOA sheet contains the efficacy claim, "Zileuton inhibits activity in eosinophils, smooth muscle cells, mast cells, monocytes and neutrophils." However, the MOA sheet entirely omits risk information, including the most serious and frequently occurring risks associated with the drug. In addition, the MOA sheet fails to present the approved indication for Zyflo. The statement, "Please see accompanying full prescribing information" in small type at the lower left-hand corner of the MOA sheet does not mitigate these misleading omissions.

**Conclusion and Requested Action**

For the reasons discussed above, the MOA sheet misbrands Zyflo in violation of the Act. 21 U.S.C. §§ 352(a) & 321(n).

DDMAC requests that Critical Therapeutics immediately cease the dissemination of violative promotional materials for Zyflo such as those described above. Please submit a written response to this letter on or before November 23, 2005, stating whether you intend to comply with this request, listing all violative promotional materials for Zyflo such as those described above, and explaining your

plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional material. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, facsimile at 301-796-9878. In all future correspondence regarding this matter, please refer to MACMIS ID # 13652 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Zyflo comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

*{See appended electronic signature page}*

Thomas Abrams, RPh, MBA
Division Director
Division of Drug Marketing, Advertising, and Communications

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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Thomas Abrams

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