CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-471/S007

Trade Name: Zyflo Filmtabs, 600 mg

Generic Name: (zileutin tablets)

Sponsor: Abbott Laboratories

Approval Date: September 4, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-471/S007

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-471/S007

APPROVAL LETTER

NDA 20-471/S-007

Abbott Laboratories
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, IL 60064-3500

Attention: James D. Steck
Director, Regulatory Affairs

Dear Mr. Steck:

Please refer to your supplemental new drug application dated March 31, 1998, received April 1, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyflo Filmtabs (zileuton tablets), 600 mg.

This supplemental new drug application provides for the addition of rash and urticaria to the PRECAUTIONS, "Post-Marketing Experience" subsection of the package insert.

We note that this supplement was submitted as a 'Special Supplement - Changes Being Effected' under 21 CFR 314.70(c).

We have completed the review of this supplemental application and it is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted March 31, 1998). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-471/S-007." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Mr. David Hilfiker, Project Manager, at (301) 827-1046.

Sincerely yours,

John K. Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-471/S007

LABELING

(1)

(No. 8036)
03-4854-R2-Rev. March, 1998
ZYFLO™ FILMTAB®
(zileuton tablets)
Tear at perforation to dispense patient information.

034854

SPECIMEN

JA
12-28-98

ZYFLO™ FILMTAB®
(zileuton tablets)
Patient Information

Medication Guide
Zyflo™ Filmtab® Tablets

Generic Name: zileuton

Please read this leaflet carefully before you start taking Zyflo™ Filmtab® tablets. Also, read it each time you get your Zyflo prescription refilled.

This leaflet provides important information about taking Zyflo. It is not meant to take the place of your doctor's specific instructions. Talk to your doctor if you have any questions about Zyflo. Your doctor or pharmacist can also provide you with additional information about Zyflo.

What is the most important information I should know about Zyflo?

The most important things to remember are to take all your doses of Zyflo every day and to make sure that you return to your doctor's office for scheduled liver enzyme tests.

You should also know that you should seek medical help immediately if you need more "puffs" of your bronchodilator inhaler than normal or if you use the maximum number of "puffs" prescribed for one 24-hour period. These could be a sign of worsening asthma which means that your asthma therapy may need to be changed.

What is Zyflo?

Zyflo, which contains the active ingredient zileuton, blocks the formation of certain chemicals (leukotrienes) that may contribute to your asthma symptoms.

Who should not take Zyflo?

You should not take Zyflo if you:

- have active liver disease or have liver enzymes that are elevated.
- have ever had an allergic reaction to this medicine.

Your doctor will determine if it is safe for you to take Zyflo.

What should I tell my doctor before I take the first dose of Zyflo?

You should tell your doctor if you:

- have ever had liver disease, hepatitis, jaundice (yellow eyes or skin), or dark urine.
- drink alcohol.
- are taking any prescription or nonprescription medicines. Your doctor may adjust the doses of some of your other medicines while you are taking Zyflo.
- if you are taking theophylline for your asthma, the blood-thinning medication warfarin, or the blood-pressure medication propranolol. Your doctor may need to change the doses of these drugs.
- are pregnant, planning to become pregnant, or are breast-feeding.

How should I take Zyflo?

- Zyflo is taken four times a day with or without food. It may be easier to remember to take Zyflo if you make it part of your daily routine such as with meals and at bedtime.
- For Zyflo to help control your asthma symptoms, it must be taken every day as prescribed by your doctor. Zyflo WILL NOT relieve an asthma attack that has already started. While taking Zyflo, it is important to keep taking your other asthma medicines as directed and to follow all of your doctor's instructions.

(2)

Medication Guide
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Generic Name: zileuton

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- For Zyflo to help control your asthma symptoms, it must be taken every day as prescribed by your doctor. Zyflo WILL NOT relieve an asthma attack that has already started. While taking Zyflo, it is important to keep taking your other asthma medicines as directed and to follow all of your doctor's instructions.
- Even if you have no asthma symptoms, do not decrease the dose of Zyflo or stop taking the medicine without talking to your doctor first. Feeling good is a sign that the medicine is working.
- When you take your dose of Zyflo, the tablets may be swallowed whole or split in half to make them easier to swallow.

What should I avoid while taking Zyflo?

- Because Zyflo may affect how other medications work, always talk to your doctor before you start or stop taking any medicines while taking Zyflo. This includes all prescription and nonprescription medicines.
- Never take a larger dose of Zyflo or take it more often than your doctor has prescribed.
- It is also important for you to know that it may take several days or a few weeks to get the full benefit from Zyflo and that you should not stop taking it if you do not feel better right away.

What are the possible side effects of Zyflo?

All medicines, including Zyflo, cause side effects in some people. Some of the most common side effects are abdominal pain, upset stomach, and nausea. You should tell your doctor if you experience any new or unusual symptoms while taking Zyflo.

One side effect that occurs in a small number of patients is an increased release of substances from the liver called "enzymes." Liver enzymes can be measured by a simple blood test. It is important that your doctor makes sure that your liver enzymes do not become too high and that it is safe for you to continue taking Zyflo. To insure your safety, your doctor will do this blood test before you first start taking Zyflo and repeat it on a regular basis while you are taking the medicine.

Usually, even if your liver enzymes are increased, you will not notice any symptoms. However, some symptoms of increased liver enzymes are feeling more tired than normal,

(3)

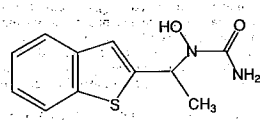
EAR AT PEP-GRATION

ZYFLO™ FILMTAB®

(zileuton tablets)

DESCRIPTION

Zileuton is an orally active inhibitor of 5-lipoxygenase, the enzyme that catalyzes the formation of leukotrienes from arachidonic acid. Zileuton has the chemical name (±)-1-(1-Benzo[b]thien-2-ylethyl)-1-hydroxyurea and the following chemical structure:



Zileuton has the molecular formula $C_{11}H_{12}N_2O_2S$ and a molecular weight of 236.29. It is a racemic mixture (50:50) of R(+) and S(-) enantiomers. Zileuton is a practically odorless, white, crystalline powder that is soluble in methanol and ethanol, slightly soluble in acetonitrile, and practically insoluble in water and hexane. The melting point ranges from 144.2°C to 145.2°C. ZYFLO tablets for oral administration is supplied in one dosage strength containing 600 mg of zileuton.

Inactive Ingredients: crospovidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, pregelatinized starch, propylene glycol, sodium starch glycolate, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action:

Zileuton is a specific inhibitor of 5-lipoxygenase and thus inhibits leukotriene (LTB_4, LTC_4, LTD_4, and LTE_4) formation. Both the R(+) and S(-) enantiomers are pharmacologically active as 5-lipoxygenase inhibitors in *in vitro* systems. 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. Sulfidopeptide leukotrienes (LTC_4, LTD_4, LTE_4, also known as the slow-releasing substances of anaphylaxis) and LTB_4, a chemoattractant for neutrophils and eosinophils, can be measured in a number of biological fluids including bronchoalveolar lavage fluid (BALF) from asthmatic patients.

Zileuton is an orally active inhibitor of *ex vivo* LTB_4 formation in several species, including dogs, monkeys, rats, sheep, and rabbits. Zileuton inhibits arachidonic acid-induced ear edema in mice, neutrophil migration in mice in response to polyacrylamide gel, and eosinophil migration into the lungs of antigen-challenged sheep.

Zileuton inhibits leukotriene-dependent smooth muscle contractions *in vitro* in guinea pig and human airways. The compound inhibits leukotriene-dependent bronchospasm in antigen and arachidonic acid-challenged guinea pigs. In antigen-challenged sheep, zileuton inhibits late-phase bronchoconstriction and airway hyperreactivity. In humans, pretreatment with zileuton attenuated bronchoconstriction caused by cold air challenge in patients with asthma.

PHARMACOKINETICS

Zileuton is rapidly absorbed upon oral administration with a mean time to peak plasma concentration (T_{max}) of 1.7 hours and a mean peak level (C_{max}) of 4.98 µg/mL. The absolute bioavailability of ZYFLO is unknown. Systemic exposure (mean AUC) following 600 mg ZYFLO administration is 19.2 µg.hr/mL. Plasma concentrations of zileuton are proportional to dose, and steady-state levels are predictable from single-dose pharmacokinetic data. Administration of ZYFLO with food resulted in a small but statistically significant increase (27%) in zileuton C_{max} without significant changes in the extent of absorption (AUC) or T_{max}. Therefore, ZYFLO can be administered with or without food (see **DOSAGE AND ADMINISTRATION**).

The apparent volume of distribution (V/F) of zileuton is approximately 1.2 L/kg. Zileuton is 93% bound to plasma proteins, primarily to albumin, with minor binding to α1-acid glycoprotein.

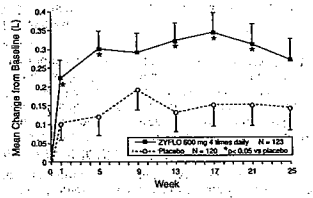
Elimination of zileuton is predominantly via metabolism with a mean terminal half-life of 2.5 hours. Apparent oral clearance of zileuton is 7.0 mL/min/kg. ZYFLO activity is primarily due to the parent drug. Studies with radiolabeled drug demonstrated that orally administered zileuton is well absorbed into the systemic circulation with 94.5% and 2.2% of the radiolabeled dose recovered in urine and feces, respectively. Several zileuton metabolites have been identified in human plasma and urine. These include two diastereomeric O-glucuronide conjugates

Table 1
MEAN CHANGE FROM BASELINE TO END OF STUDY
(Six-Month Study)

Efficacy Endpoint	ZYFLO 600 mg 4 times/day	Placebo
Trough FEV_1(L)	0.27	0.14
AM PEFR (L/min)	30.60*	5.04
PM PEFR (L/min)	24.59*	7.98
β-Agonist Use (puffs/day)	-1.77*	-0.22
Daily Symptom Score (0-3 Scale)	-0.49*	-0.28
Nocturnal Symptom Score (0-3 Scale)	-0.29*	-0.04

Figure 1 shows the mean effect of ZYFLO versus placebo for the primary efficacy variable, trough FEV_1, over the course of Study 1.

Figure 1
Mean Change From Baseline in Trough FEV_1 (L)



Of all the patients in Study 1 and Study 2, 7.0% of those administered ZYFLO 600 mg four times daily required systemic corticosteroid therapy for exacerbation of asthma, whereas 18.7% of the placebo group required corticosteroid treatment. This difference was statistically significant.

In these trials, there was a statistically significant improvement from baseline in FEV_1, which occurred 2 hours after initial administration of ZYFLO. This mean increase was approximately 0.10 L greater than that in placebo-treated patients.

These studies evaluated patients receiving as-needed inhaled beta-agonist as their only asthma therapy. In this patient population, post-hoc analyses suggested that individuals with lower FEV_1 values at baseline showed a greater improvement.

The role of ZYFLO in the management of patients with more severe asthma, patients receiving anti-asthma therapy other than as-needed, inhaled beta-agonists, or patients receiving it as an oral or inhaled corticosteroid-sparing agent remains to be fully characterized.

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

ZYFLO tablets are contraindicated in patients with:

- Active liver disease or transaminase elevations greater than or equal to three times the upper limit of normal (≥3xULN) (see **PRECAUTIONS, Hepatic**).
- Hypersensitivity to zileuton or any of its inactive ingredients.

WARNINGS

ZYFLO is not indicated for use in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus. Therapy with ZYFLO can be continued during acute exacerbations of asthma.

Co-administration of ZYFLO and theophylline results in, on average, an approximate doubling of serum theophylline concentrations. Theophylline dosage in these patients should be reduced and serum theophylline concentrations monitored closely (see **PRECAUTIONS, Drug Interactions**).

Co-administration of ZYFLO and warfarin results in a clinically significant increase in prothrombin time (PT). Patients on oral warfarin therapy and ZYFLO should have their prothrombin times monitored closely and anticoagulant dose adjusted accordingly (see **PRECAUTIONS, Drug Interactions**).

Co-administration of ZYFLO and propranolol results in doubling of propranolol AUC and consequent increased beta-blocker activity. Patients on ZYFLO and propranolol should be closely monitored and the dose of the propranolol reduced as necessary (see **PRECAUTIONS, Drug Interactions**).

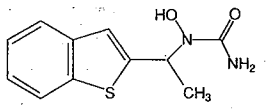
PRECAUTIONS

Hepatic: Elevations of one or more liver function tests may occur during ZYFLO therapy. These laboratory abnormalities may progress, remain unchanged, or resolve with continued therapy. In a few cases, initial transaminase elevations were first noted after discontinuing treatment, usually within 2 weeks. The ALT (SGPT) test is considered the most sensitive indicator of liver injury. In placebo-controlled clinical trials, the frequency of ALT elevations greater than or equal to three times the upper limit of normal (3xULN) was 1.9% for ZYFLO-treated patients, compared with 0.2% for placebo-treated patients.

In a long-term safety surveillance study, 2458 patients received

(47)

arachidonic acid. Zileuton has the chemical name (±)-1-(1-Benzo[b]thien-2-ylethyl)-1-hydroxyurea and the following chemical structure:



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Elimination of zileuton is predominantly via metabolism with a mean terminal half-life of 2.5 hours. Apparent oral clearance of zileuton is 7.0 mL/min/kg. ZYFLO activity is primarily due to the parent drug. Studies with radiolabeled drug demonstrated that orally administered zileuton is well absorbed into the systemic circulation with 94.5% and 2.2% of the radiolabeled dose recovered in urine and feces, respectively. Several zileuton metabolites have been identified in human plasma and urine. These include two diastereomeric O-glucuronide conjugates (major metabolites) and an N-dehydroxylated metabolite of zileuton. The urinary excretion of the inactive N-dehydroxylated metabolite and unchanged zileuton each accounted for less than 0.5% of the dose. *In vitro* studies utilizing human liver microsomes have shown that zileuton and its N-dehydroxylated metabolite can be oxidatively metabolized by the cytochrome P450 isoenzymes 1A2, 2C9 and 3A4 (CYP1A2, CYP2C9 and CYP3A4).

Special populations:

Effect of age: Zileuton pharmacokinetics were similar in healthy elderly subjects (>65 years) compared to healthy younger adults (18 to 40 years).

Effect of gender: Across several studies, no significant gender effects were observed on the pharmacokinetics of zileuton.

Renal insufficiency: The pharmacokinetics of zileuton were similar in healthy subjects and in subjects with mild, moderate, and severe renal insufficiency. In subjects with renal failure requiring hemodialysis, zileuton pharmacokinetics were not altered by hemodialysis and a very small percentage of the administered zileuton dose (<0.5%) was removed by hemodialysis. Hence, dosing adjustment in patients with renal dysfunction or undergoing hemodialysis is not necessary.

Hepatic insufficiency: ZYFLO is contraindicated in patients with active liver disease (see **CONTRAINDICATIONS** and **PRECAUTIONS, Hepatic**).

CLINICAL STUDIES

Two double-blind, parallel, placebo-controlled, multi-center studies have established the efficacy of ZYFLO in the treatment of asthma. Three hundred seventy-three (373) patients were enrolled in the 6-month, double-blind phase of Study 1, and 401 patients were enrolled in the 3-month double-blind phase of Study 2. In these studies, the patients were mild-to-moderate asthmatics who had a mean baseline FEV_1 of approximately 2.3 liters and who used inhaled beta-agonists as needed, the mean being approximately 6 puffs of albuterol per day from a metered-dose inhaler. In each study, patients were randomized to receive either ZYFLO 400 mg four times daily, ZYFLO 600 mg four times daily, or placebo. Only the ZYFLO 600 mg four times daily dosage regimen was shown to be efficacious by demonstrating statistically significant improvement across several parameters.

Efficacy endpoints measured in Study 1 are shown in Table 1 below as mean change from baseline to the end of the study (six months). Statistically significant differences from placebo at the $p<0.05$ level are indicated by an asterisk(*). Similar results were observed after three months in Study 2.

β-Agonist Use (puffs/day)	-1.77*	-0.22
Daily Symptom Score (0-3 Scale)	-0.49*	-0.28
Nocturnal Symptom Score (0-3 Scale)	-0.29*	-0.04

Figure 1 shows the mean effect of ZYFLO versus placebo for the primary efficacy variable, trough FEV_1, over the course of Study 1.

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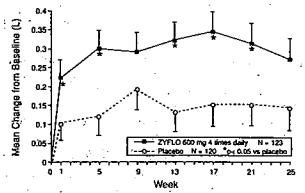

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In a long-term safety surveillance study, 2458 patients received ZYFLO in addition to their usual asthma care and 489 received their usual asthma care. In patients treated for up to 12 months with ZYFLO in addition to their usual asthma care, 4.6% developed an ALT of at least 3xULN, compared with 1.1% of patients receiving only their usual asthma care. Sixty-one percent of these elevations occurred during the first two months of ZYFLO therapy. After two months of treatment, the rate of new ALT elevations ≥ 3xULN stabilized at a mean of 0.30% per month for patients receiving ZYFLO-plus-usual-asthma care compared with 0.11% per month for patients receiving usual asthma care alone. Of the 61 ZYFLO-plus-usual-asthma-care patients with ALT elevations between 3 to 5xULN, 32 patients (52%) had ALT values decrease to below 2xULN while continuing ZYFLO therapy. Twenty-one of the 61 patients (34%) had further increases in ALT levels to ≥ 5xULN and were withdrawn from the study in accordance with the study protocol. In patients who discontinued ZYFLO, elevated ALT levels returned to < 2xULN in an average of 32 days (range 1-111 days).

In controlled and uncontrolled clinical trials involving more than 5000 patients treated with ZYFLO, the overall rate of ALT elevation ≥ 3xULN was 3.2%. In these trials, one patient developed symptomatic hepatitis with jaundice, which resolved upon discontinuation of therapy. An additional 3 patients with transaminase elevations developed mild hyperbilirubinemia that was less than three times the upper limit of normal. There was no evidence of hypersensitivity or other alternative etiologies for these findings. In subset analyses, females over the age of 65 appeared to be at an increased risk for ALT elevations. Patients with pre-existing transaminase elevations may also be at an increased risk for ALT elevations (see **CONTRAINDICATIONS**).

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.

Since treatment with ZYFLO may result in increased hepatic transaminases, ZYFLO should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease.

Information for Patients: Patients should be told that:

- ZYFLO is indicated for the chronic treatment of asthma and

(3)

should be taken regularly as prescribed, even during symptom-free periods.
- ZYFLO is not a bronchodilator and should not be used to treat acute episodes of asthma.
- When taking ZYFLO, they should not decrease the dose or stop taking any other antiasthma medications unless instructed by a physician.
- While using ZYFLO, medical attention should be sought if short-acting bronchodilators are needed more often than usual, or if more than the maximum number of inhalations of short-acting bronchodilator treatment prescribed for a 24-hour period are needed.
- The most serious side effect of ZYFLO is elevation of liver enzyme tests and that, while taking ZYFLO, they must return for liver enzyme test monitoring on a regular basis.
- If they experience signs and/or symptoms of liver dysfunction (e.g., right upper quadrant pain, nausea, fatigue, lethargy, pruritus, jaundice, or "flu-like" symptoms), they should contact their physician immediately.
- ZYFLO can interact with other drugs and that, while taking ZYFLO, they should consult their doctor before starting or stopping any prescription or non-prescription medicines.

A patient leaflet is included with the tablets.

Drug Interactions: In a drug-interaction study in 16 healthy volunteers, co-administration of multiple doses of zileuton (800 mg every 12 hours) and theophylline (200 mg every 6 hours) for 5 days resulted in a significant decrease (approximately 50%) in steady-state clearance of theophylline, an approximate doubling of theophylline AUC, and an increase in theophylline C_{max} (by 73%). The elimination half-life of theophylline was increased by 24%. Also, during co-administration, theophylline-related adverse events were observed more frequently than after theophylline alone. Upon initiation of ZYFLO in patients receiving theophylline, the theophylline dosage should be reduced by approximately one-half and plasma theophylline concentrations monitored. Similarly, when initiating therapy with theophylline in a patient receiving ZYFLO, the maintenance dose and/or dosing interval of theophylline should be adjusted accordingly and guided by serum theophylline determinations (see **WARNINGS**).

Concomitant administration of multiple doses of ZYFLO (600 mg every 6 hours) and warfarin (fixed daily dose obtained by titration in each subject) to 30 healthy male volunteers resulted in a 15% decrease in R-warfarin clearance and an increase in AUC of 22%. The pharmacokinetics of S-warfarin were not affected. These pharmacokinetic changes were accompanied by a clinically significant increase in prothrombin times. Monitoring of prothrombin time, or other suitable coagulation tests, with the appropriate dose titration of warfarin is recommended in patients receiving concomitant ZYFLO and warfarin therapy (see **WARNINGS**).

Co-administration of ZYFLO and propranolol results in a significant increase in propranolol concentrations. Administration of a single 80-mg dose of propranolol in 16 healthy male volunteers who received ZYFLO 600 mg every 6 hours for 5 days resulted in a 42% decrease in propranolol clearance. This resulted in an increase in propranolol C_{max}, AUC, and elimination half-life by 52%, 104%, and 25%, respectively. There was an increase in ß-blockade and decrease in heart rate associated with the co-administration of these drugs. Patients on ZYFLO and propranolol should be closely monitored and the dose of propranolol reduced as necessary (see **WARNINGS**). No formal drug-drug interaction studies between ZYFLO and other beta-adrenergic blocking agents (i.e., ß-blockers) have been conducted. It is reasonable to employ appropriate clinical monitoring when these drugs are co-administered with ZYFLO.

In a drug interaction study in 16 healthy volunteers, co-administration of multiple doses of terfenadine (60 mg every 12 hours) and ZYFLO (600 mg every 6 hours) for 7 days resulted in a decrease in clearance of terfenadine by 22% leading to a statistically significant increase in mean AUC and C_{max} of terfenadine of approximately 35%. This increase in terfenadine plasma concentration in the presence of ZYFLO was not associated with a significant prolongation of the QTc interval. Although there was no cardiac effect in this small number of healthy volunteers, given the high inter-individual pharmacokinetic variability of terfenadine, co-administration of ZYFLO and terfenadine is not recommended.

Drug-drug interaction studies conducted in healthy volunteers between ZYFLO and prednisone and ethinyl estradiol (oral contraceptive), drugs known to be metabolized by the P450 3A4 (CYP3A4) isoenzyme, have shown no significant interaction. However, no formal drug-drug interaction studies between ZYFLO and dihydropyridine, calcium channel blockers, cyclosporine, cisapride, and astemizole, also metabolized by CYP3A4, have been conducted. It is reasonable to employ appropriate clinical monitoring when these drugs are co-administered with ZYFLO.

Drug-drug interaction studies in healthy volunteers have been conducted with ZYFLO and digoxin, phenytoin, sulfasalazine, and naproxen. There was no significant interaction between ZYFLO and any of these drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In 2-year carcinogenicity studies, increases in the incidence of liver, kidney, and vascular tumors in female mice and a trend towards an increase in the incidence of liver tumors in male mice were observed at 450 mg/kg/day (providing approximately 4 times [females] or 7 times [males] the systemic exposure [AUC] achieved at the maximum recommended human daily oral dose). No increase in the incidence of tumors was observed at 150 mg/kg/day (providing approximately 2 times the systemic exposure [AUC] achieved at the maximum recommended human daily oral dose). In rats, an increase in the incidence of kidney tumors was observed in both sexes at 170 mg/kg/day (providing approximately 6 times [males] or 14 times [females] the systemic exposure [AUC] achieved at the maximum recommended human daily oral dose). No increased incidence of kidney tumors was seen at 80 mg/kg/day (providing approximately 4 times [males] or 6 times [females] the systemic exposure [AUC] achieved at the maximum recommended human daily oral dose). Although a dose-related increased incidence of benign Leydig cell tumors was observed, Leydig cell tumorigenesis was prevented by supplementing male rats with testosterone.

Zileuton was negative in genotoxicity studies including bacterial reverse mutation (Ames) using *S. typhimurium* and *E. coli*, chromosome aberration in human lymphocytes, *in vitro* unscheduled DNA synthesis (UDS), in rat hepatocytes with or without zileuton pretreatment and in mouse and rat kidney cells with zileuton pretreatment, and mouse micronucleus assays. However, a dose-related increase in DNA adduct formation was reported in kidneys and livers of female mice treated with zileuton. Although some evidence of DNA damage was observed in a UDS assay in hepatocytes isolated from Arocior-1254 treated rats, no such finding was noticed in hepatocytes isolated from monkeys, where the metabolic profile of zileuton is more similar to that of humans.

In reproductive performance/fertility studies, zileuton produced no effects on fertility in rats at oral doses up to 300 mg/kg/day (providing approximately 8 times [male rats] and 18 times [female rats] the systemic exposure [AUC] achieved at the maximum recommended human daily oral dose). Comparative systemic exposure (AUC) is based on measurements in male rats or nonpregnant female rats at similar dosages. However, reduction in fetal implants was observed at oral doses of 150 mg/kg/day and higher (providing approximately 9 times the indicated adverse effects (reduced body weight and increased skeletal variations) in rats at an oral dose of 300 mg/kg/day (providing approximately 18 times the systemic exposure [AUC] achieved at the maximum recommended human daily oral dose). Comparative systemic exposure [AUC] is based on measurements in nonpregnant female rats at a similar dosage. Zileuton and/or its metabolites cross the placental barrier of rats. Three of 118 (2.5%) rabbit fetuses had cleft palates at an oral dose of 150 mg/kg/day (equivalent to the maximum recommended human daily oral dose on a mg/m^2 basis). There are no adequate and well-controlled studies in pregnant women. ZYFLO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Zileuton and/or its metabolites are excreted in rat milk. It is not known if zileuton is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for tumorigenicity shown for ZYFLO in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and effectiveness of ZYFLO in pediatric patients under 12 years of age have not been established.

ADVERSE REACTIONS

Clinical Studies: A total of 5542 patients have been exposed to zileuton in clinical trials, 2252 of them for greater than 6 months and 742 for greater than 1 year.

Adverse events most frequently occurring (frequency ≥3%) in ZYFLO-treated patients and at a frequency greater than placebo-treated patients are summarized in Table 2.

TABLE 2
Proportion of Patients Experiencing Adverse Events in Placebo-Controlled Studies in Asthma

BODY SYSTEM/Event	ZYFLO 600 mg 4 times daily % Occurrence (N = 475)	Placebo % Occurrence (N = 491)
BODY AS A WHOLE		
Headache	24.6	24.0
Pain (unspecified)	7.8	5.3
Abdominal Pain	4.6	2.4
Asthenia	3.8	2.4
Accidental Injury	3.4	2.0
DIGESTIVE SYSTEM		
Dyspepsia	8.2*	2.9
Nausea	5.5	3.7
MUSCULOSKELETAL		
Myalgia	3.2	2.9

* $p \leq 0.05$ vs placebo

Less common adverse events occurring at a frequency of greater than 1% and more commonly in ZYFLO-treated patients included: arthralgia, chest pain, conjunctivitis, constipation, dizziness, fever, flatulence, hypertonia, insomnia, lymphadenopathy, malaise, neck pain/rigidity, nervousness, pruritus, somnolence, urinary tract infection, vaginitis, and vomiting.

The frequency of discontinuation from the asthma clinical studies due to any adverse event was comparable between ZYFLO (9.7%) and placebo-treated (8.4%) groups.

In placebo-controlled clinical trials, the frequency of ALT elevations ≥3xULN was 1.9% for ZYFLO-treated patients, compared with 0.2% for placebo-treated patients. In controlled and uncontrolled trials, one patient developed symptomatic hepatitis with jaundice, which resolved upon discontinuation of therapy. An additional 3 patients with transaminase elevations developed mild hyperbilirubinemia that was less than three times the upper limit of normal. There was no evidence of hypersensitivity or other alternative etiologies for these findings. ZYFLO is contraindicated in patients with active liver disease or transaminase elevations greater than or equal to 3xULN (see **CONTRAINDICATIONS**). It is recommended that hepatic transaminases be evaluated at initiation of and during therapy with ZYFLO (see **PRECAUTIONS, Hepatic**).

Occurrences of low white blood cell count ($\leq 2.8 \times 10^9$/L) were observed in 1.0% of 1,678 patients taking ZYFLO and 0.6% of 1,056 patients taking placebo in placebo-controlled studies. These findings were transient and the majority of cases returned toward normal or baseline with continued ZYFLO dosing. All remaining cases returned toward normal or baseline after discontinuation of ZYFLO. Similar findings were also noted in a long-term safety surveillance study of 2458 patients treated with ZYFLO plus usual asthma care versus 489 patients treated only with usual asthma care for up to one year. The clinical significance of these observations is not known.

In the long-term safety surveillance trial of ZYFLO plus usual asthma care versus usual asthma care alone, a similar adverse event profile was seen as in other clinical trials.

Post-Marketing Experience: Rash and urticaria have been reported with ZYFLO.

OVERDOSAGE

Human experience of acute overdose with zileuton is limited. A patient in a clinical trial took between 6.6 and 9.0 grams of zileuton in a single dose. Vomiting was induced and the patient recovered without sequelae. Zileuton is not removed by dialysis. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted as required. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. A Certified Poison Control Center should be consulted for up-to-date information on management of overdose with ZYFLO.

The oral minimum lethal doses in mice and rats were 500-4000 and 300-1000 mg/kg in various preparations, respectively (providing greater than 3 and 9 times the systemic exposure [AUC] achieved at the maximum recommended human daily oral dose, respectively). No deaths occurred, but nephritis was reported in dogs at an oral dose of 1000 mg/kg (providing in excess of 12 times the systemic exposure [AUC] achieved at the maximum recommended human daily oral dose).

DOSAGE AND ADMINISTRATION

The recommended dosage of ZYFLO for the symptomatic treatment of patients with asthma is one 600-mg tablet four times a day for a total daily dose of 2400 mg. For ease of administration, ZYFLO may be taken with meals and at bedtime. Hepatic transaminases should be evaluated prior to initiation of ZYFLO and periodically during treatment (see **PRECAUTIONS, Hepatic**).

HOW SUPPLIED

ZYFLO Filmtab Tablets are available as 1 dosage strength: 600-mg white ovaloid tablets with single bisect, debossed on bisect side with Abbott logo and ZL (Abbo-Code), and 600 on the opposite side:

High-density polyethylene
bottles of 120.....(NDC 0074-8036-22)

Recommended storage: Store tablets at controlled room temperature between 20°-25°C, (68°-77°F). See USP. Protect from light.

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WARNINGS).

Co-administration of ZYFLO and propranolol results in a significant increase in propranolol concentrations. Administration of a single 80-mg dose of propranolol in 16 healthy male volunteers who received ZYFLO 600 mg every 6 hours for 5 days resulted in a 42% decrease in propranolol clearance. This resulted in an increase in propranolol C_{max}, AUC, and elimination half-life by 52%, 104%, and 25%, respectively. There was an increase in β-blockade and decrease in heart rate associated with the co-administration of these drugs. Patients on ZYFLO and propranolol should be closely monitored and the dose of propranolol reduced as necessary (see **WARNINGS**). No formal drug-drug interaction studies between ZYFLO and other beta-adrenergic blocking agents (i.e., β-blockers) have been conducted. It is reasonable to employ appropriate clinical monitoring when these drugs are co-administered with ZYFLO.

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Pregnancy: Pregnancy Category C: Developmental studies

* $p \leq 0.05$ vs placebo

Less common adverse events occurring at a frequency of greater than 1% and more commonly in ZYFLO-treated patients included: arthralgia, chest pain, conjunctivitis, constipation, dizziness, fever, flatulence, hypertonia, insomnia, lymphadenopathy, malaise, neck pain/rigidity, nervousness, pruritus, somnolence, urinary tract infection, vaginitis, and vomiting.

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The oral minimum lethal doses in mice and rats were 500-4000 and 300-1000 mg/kg in various preparations, respectively (providing greater than 3 and 9 times the systemic exposure [AUC] achieved at the maximum recommended human daily oral dose, respectively). No deaths occurred, but nephritis was reported in dogs at an oral dose of 1000 mg/kg (providing in excess of 12 times the systemic exposure [AUC] achieved at the maximum recommended human daily oral dose).

DOSAGE AND ADMINISTRATION

The recommended dosage of ZYFLO for the symptomatic treatment of patients with asthma is one 600-mg tablet four times a day for a total daily dose of 2400 mg. For ease of administration, ZYFLO may be taken with meals and at bedtime. Hepatic transaminases should be evaluated prior to initiation of ZYFLO and periodically during treatment (see **PRECAUTIONS, Hepatic**).

HOW SUPPLIED

ZYFLO Filmtab Tablets are available as 1 dosage strength: 600-mg white ovaloid tablets with single bisect, debossed on bisect side with Abbott logo and ZL (Abbo-Code), and 600 on the opposite side:

High-density polyethylene
bottles of 120.....(NDC 0074-8036-22)

Recommended storage: Store tablets at controlled room temperature between 20°-25°C, (68°-77°F). See USP. Protect from light.

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Filmtab - Film-sealed tablets, Abbott

Revised March 1998

ABBOTT LABORATORIES
NORTH CHICAGO, IL60064, U.S.A.

PRINTED IN U.S.A.

(71)

ZYFLO™ FILMTAB®
(zileuton tablets)
Patient Information

TEAR AT PERFORATION

"flu-like" symptoms, itching, yellow skin and/or yellow color in the whites of the eyes, or urine that is darker than normal.

If you notice these or any other symptoms that you think may be caused by Zyflo, call your doctor immediately. Once the medicine is stopped, these symptoms usually go away.

Even if you do not have any of these symptoms, you should continue to see your doctor for regular check-ups and liver enzyme tests.

Where should I keep my supply of Zyflo?

Keep Zyflo and all medicines out of the reach of children. In case of an accidental overdose, call your doctor or a Poison Control Center immediately.

Protect Zyflo from light and replace the child-resistant cap each time after use. Store Zyflo between 68° - 77°F (20° - 25°C).

If you would like more information about Zyflo, ask your doctor or pharmacist. If you have any questions or concerns about taking Zyflo, discuss them with your doctor.

Filmtab - Film-sealed tablets, Abbott

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Revised March, 1998

ABBOTT LABORATORIES
NORTH CHICAGO, IL60064, U.S.A.
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-471/S007

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEC 2 8 1998

NDA 20-471/S-007

Abbott Laboratories
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, IL 60064-3500

Attention: James D. Steck
Director
PPD Regulatory Affairs

Dear Mr. Steck:

We acknowledge the receipt of your September 23, 1998, submission containing final printed labeling in response to our September 4, 1998, letter approving your supplemental new drug application for Zyflo Tablets (zileuton tablets), 600 mg.

We have reviewed the labeling that you submitted in accordance with our September 4, 1998, letter, and we find it acceptable.

If you have any questions, contact Mr. David Hilfiker, Project Manager, at (301) 827-1084.

Sincerely,

John K. Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 20-471
HFD-570/Div. Files
HFD-570/Hilfiker
HFD-570/Schumaker
HF-2/Medwatch (with labeling)
HFD-102/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-95/DDMS (with labeling)
HFD-613/OGD (with labeling)
HFD-735/OPDRA (with labeling)
DISTRICT OFFICE

12-28-98

Drafted by: HFD-570/Hilfiker/December 28, 1998
Final by: HFD-570/Hilfiker/December 28, 1998
Filename: c:\my_documents\N20471\S007\98-12-28.arltr.doc

12/28/98

ACKNOWLEDGE AND RETAIN (AR)

12/28/98

FINAL PRINTED LABELING REVIEW

DEC 28 1998

Application #	20-471/S-007
Drug:	Zyflo Filmtabs (zileuton tablets), 600 mg
Applicant:	Abbott Laboratories, Abbott Park, IL

Supplement Letter Date:	March 31, 1998
Receipt Date:	April 1, 1998
Approval Date:	September 4, 1998
FPL Letter Date:	September 23, 1998
FPL Receipt Date:	September 23, 1998

Supplement Provides For: addition of rash and urticaria to the PRECAUTIONS, Post-Marketing Experience subsection of the package insert.

The September 23, 1998, final printed package insert was reviewed against the March 31, 1998, approved draft package insert submitted under supplement S-007. The September 23, 1998, final printed patient's instructions for use was reviewed against the December 26, 1996, final printed patient's instructions for use submitted under original NDA 20-471 and acknowledged and retained on January 17, 1997.

Comments:

The September 23, 1998, final printed package insert is identical to the March 31, 1998, approved draft labeling submitted for supplement 20-471/S-007. The September 23, 1998, final printed patient's instructions for use is identical to the originally approved patient's instructions for use, acknowledged and retained on January 17, 1997.

Conclusions:

The FPL submitted for supplement 20-471/S-007 on September 23, 1998, can be acknowledged and retained.

David Hilfiker
Project Manager
Division of Pulmonary Drug Products, HFD-570

Cc: Original NDA 20-471/S-007
HFD-570/Division File
HFD-570/Hilfiker
HFD-570/Schumaker

12-28-98

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PROJECT MANAGER LABELING REVIEW

Application: 20-471/S-007
Drug: Zyflo Filmtabs (zileuton tablets), 300 and 600 mg
Applicant: Abbott Laboratories

Supplement S-007 was submitted to FDA on March 31, 1998, received April 1, 1998, as a Changes-Being-Effected Labeling Supplement. The supplement provides for the addition of rash and urticaria to the ADVERSE REACTIONS, "Post-Marketing Experience" subsection of the package insert.

The medical officer noted on the cover letter that no action was indicated for this revision, and finds the addition acceptable.

The proposed draft package insert was reviewed against final printed labeling (FA) submitted on December 26, 1996, and acknowledged and retained on January 17, 1997. No other revisions have been made to the package insert.

The proposed language to be added to the "Post-Marketing Experience" subsection is acceptable.

ACTION: 20-471/S-007 should be approved (AP).

David Hilfiker
Project Manager

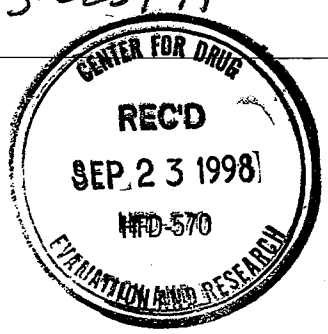
Cc: Original NDA 20-471/S-007
HFD-570/division file
HFD-570/Schumaker
HFD-570/Hilfiker

C:\my_documents\N20471\S007\98-08-26.rev.doc

ABBOTT

ORIGINAL

NDA SUPP AMEND
S-025 FA



Pharmaceutical Products Division

Abbott Laboratories
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, Illinois 60064-3500

September 23, 1998

John K. Jenkins, M.D., Division Director
Division of Pulmonary Drug Products
HFD-570, Room 10-B-03
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Zileuton Tablets **FPL for Approved Supplement**
NDA No. 20-471
Supplement No. S-007

Dear Dr. Jenkins:

Reference is made to your letter, dated September 4, 1998, indicating that our March 31, 1998 supplemental application S-007 to NDA 20-471 for Zyflo® Filmtab® (zileuton tablets) is approved.

This supplemental new drug application provides for the addition of rash and urticaria to the ADVERSE REACTIONS, "Post-Marketing Experience" subsection of the package insert.

As stipulated in the September 4, 1998 letter, we are submitting herein 20 copies of the final printed labeling (FPL) that is identical to the submitted draft labeling (package insert submitted March 31, 1998). Ten copies are individually mounted on heavy-weight paper as requested.

If there are any questions concerning this submission, please contact me at the telephone number listed below.

Sincerely,

ABBOTT LABORATORIES

James D. Steck

James D. Steck
Director, PPD Regulatory Affairs
Phone: (708) 937-0335
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JDS:kdh
Enclosures

Copy of Cover Letter to:
David Hilfiker, Project Manager
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Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

1 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 20-471
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