CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-471/S009

Trade Name: Zyflo Filmtab

Generic Name: (zileutin tablets)

Sponsor: Abbott Laboratories

Approval Date: December 16, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-471/S009

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-471/S009

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-471/S-009

Abbott Laboratories
D-491/AP6B-1
100 Abbott Park Road
Abbott Park IL 60064-6108

Attention: Ernesto J. Rivera, Pharm.D.
Regulatory Affairs Project Manager

Dear Dr. Rivera:

Please refer to your supplemental new drug application dated August 22, 2001, received August 23, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyflo (zileutin tablets) Filmtab.

This supplemental new drug application provide for the addition of a Geriatric Use subsection to the WARNING section, and revisions to the Special Population subsecton of the CLINICL PHARMACOLOGY section of the package insert.

We completed our review of this application. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the submitted labeling (package insert submitted August 22, 2001).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper 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-009." Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), 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 reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Ms. Colette Jackson, Regulatory Project Manager, at (301) 827-5580.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Acting Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Badrul Chowdhury
12/16/02 05:00:17 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

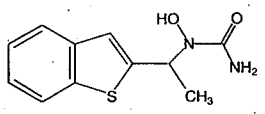
NDA 20-471/S009

LABELING

/FLO® FILMTAB®
euton tablets)

:RIPTION

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



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

ive Ingredients: crospovidone, hydroxypropyl cellulose, mellose, magnesium stearate, microcrystalline cellulose, latinized starch, propylene glycol, sodium starch glycolate, nd titanium dioxide.

ICAL PHARMACOLOGY

anism of Action:

ton is a specific inhibitor of 5-lipoxygenase and thus inhibits triene (LTB_4, LTC_4, LTD_4, and LTE_4) formation. Both the and S(-) enantiomers are pharmacologically active as oxygenase inhibitors in *in vitro* systems. Leukotrienes are ances that induce numerous biological effects including entation of neutrophil and eosinophil migration, neutrophil monocyte aggregation, leukocyte adhesion, increased ary permeability, and smooth muscle contraction. These s contribute to inflammation, edema, mucus secretion, and hoconstriction in the airways of asthmatic patients. Sulfido-le leukotrienes (LTC_4, LTD_4, LTE_4, also known as the slow-ing substances of anaphylaxis) and LTB_4, a chemoattractant eutrophils and eosinophils, can be measured in a number of gical fluids including bronchoalveolar lavage fluid (BALF) asthmatic patients.

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

euton inhibits leukotriene-dependent smooth muscle actions *in vitro* in guinea pig and human airways. The ound inhibits leukotriene-dependent bronchospasm in n and arachidonic acid-challenged guinea pigs. In antigen-nged sheep, zileuton inhibits late-phase bronchocon-on and airway hyperreactivity. In humans, pretreatment zileuton attenuated bronchoconstriction caused by cold air nge in patients with asthma.

MACOKINETICS

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

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

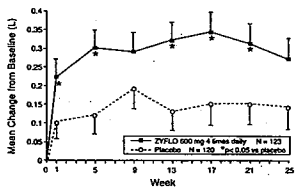
nination of zileuton is predominantly via metabolism with a terminal half-life of 2.5 hours. Apparent oral clearance of on is 7.0 mL/min/kg. ZYFLO activity is primarily due to the t drug. Studies with radiolabeled drug demonstrated that administered zileuton is well absorbed into the systemic ation with 94.5% and 2.2% of the radiolabeled dose ered in urine and feces, respectively. Several zileuton olites have been identified in human plasma and urine. include two diastereomeric O-glucuronide conjugates e metabolites) and an N-dehydroxylated metabolite of on. The urinary excretion of the inactive N-dehydroxylated olite and unchanged zileuton each accounted for less than of the dose. *In vitro* studies utilizing human liver

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
ß-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

ZYFLO® FILMTAB®
(zileuton tablets)

Patient Information Leaflet
Zyflo® Filmtab® Tablets
Generic Name: zileuton

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

This leaflet provides important information about taking Zyflo. It is not meant to take place of your doctor's specific instructions. Talk to your doctor if you have any quest about Zyflo. Your doctor or pharmacist can also provide you with additional informa 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 an 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 n "puffs" of your bronchodilator inhaler than normal or if you use the maximum numbe "puffs" prescribed for one 24-hour period. These could be a sign of worsening asthma w 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 che cals (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?

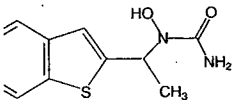
You should tell your doctor if you:

- 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 d of some of your other medicines while you are taking Zyflo.
- if you are taking theophylline for your asthma, the blood-thinning medication warfari the blood-pressure medication propranolol. Your doctor may need to change the dose 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 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 prescri by your doctor. Zyflo WILL NOT relieve an asthma attack that has already started. W taking Zyflo, it is important to keep taking your other asthma medicines as directed an follow all of your doctor's instructions.
- Even if you have no asthma symptoms, do not decrease the dose of Zyflo or stop tal

ucture:



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KINETICS

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ulations:

The pharmacokinetics of zileuton were investigated elderly volunteers (ages 65 to 81 years, 9 males, and healthy young volunteers (ages 20 to 40 years, 14 females) after single and multiple oral doses of ery 6 hours of zileuton. Zileuton pharmacokinetics r in healthy elderly subjects (≥65 years) compared to nger adults (18 to 40 years).

nder: Across several studies, no significant gender observed on the pharmacokinetics of zileuton.

fficiency: The pharmacokinetics of zileuton were ealthy subjects and in subjects with mild, moderate, renal insufficiency. In subjects with renal failure emodialysis, zileuton pharmacokinetics were not hemodialysis and a very small percentage of the d zileuton dose (<0.5%) was removed by is. Hence, dosing adjustment in patients with renal or undergoing hemodialysis is not necessary.

fficiency: ZYFLO is contraindicated in patients with r disease (see **CONTRAINDICATIONS** and **TIONS, Hepatic**).

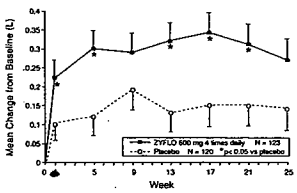
TUDIES

e-blind, parallel, placebo-controlled, multi-center established the efficacy of ZYFLO in the treatment Three hundred seventy-three (373) patients were the 6-month, double-blind phase of Study 1, and were enrolled in the 3-month double-blind phase of these studies, the patients were mild-to-moderate who had a mean baseline FEV_1 of approximately d who used inhaled beta-agonists as needed, the mean ximately 6 puffs of albuterol per day from a metered- r. In each study, patients were randomized to receive LO 400 mg four times daily, ZYFLO 600 mg four or placebo. Only the ZYFLO 600 mg four times daily men was shown to be efficacious by demonstrating significant improvement across several parameters. ndpoints measured in Study 1 are shown in Table 1 ean change from baseline to the end of the study). Statistically significant differences from placebo at level are indicated by an asterisk(*). Similar results ed 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.

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.

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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 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

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

ould be taken regularly as prescribed, even during symptom-ee periods.

YFLO is not a bronchodilator and should not be used to treat ute episodes of asthma.

hen taking ZYFLO, they should not decrease the dose or stop king any other antiasthma medications unless instructed by a ysician.

hile using ZYFLO, medical attention should be sought if ort-acting bronchodilators are needed more often than usual, if more than the maximum number of inhalations of short-ting bronchodilator treatment prescribed for a 24-hour period e needed.

he most serious side effect of ZYFLO is elevation of liver zyme tests and that, while taking ZYFLO, they must return for ver enzyme test monitoring on a regular basis.

they experience signs and/or symptoms of liver dysfunction .g., right upper quadrant pain, nausea, fatigue, lethargy, uritus, jaundice, or "flu-like" symptoms), they should contact eir physician immediately.

YFLO can interact with other drugs and that, while taking YFLO, they should consult their doctor before starting or opping any prescription or non-prescription medicines.

atient leaflet is included with the tablets.

ug Interactions: In a drug-interaction study in 16 healthy unteers, co-administration of multiple doses of zileuton 0 mg every 12 hours) and theophylline (200 mg every 6 hours) 5 days resulted in a significant decrease (approximately 50%) steady-state clearance of theophylline, an approximate ubling of theophylline AUC, and an increase in theophylline ax (by 73%). The elimination half-life of theophylline was reased by 24%. Also, during co-administration, theophylline-ated adverse events were observed more frequently than after ophylline alone. Upon initiation of ZYFLO in patients eiving theophylline, the theophylline dosage should be reduced approximately one-half and plasma theophylline con-ntrations monitored. Similarly, when initiating therapy with ophylline in a patient receiving ZYFLO, the maintenance dose /or dosing interval of theophylline should be adjusted cordingly and guided by serum theophylline determinations e **WARNINGS**).

Concomitant administration of multiple doses of ZYFLO 0 mg every 6 hours) and warfarin (fixed daily dose obtained by ation in each subject) to 30 healthy male volunteers resulted in .5% decrease in R-warfarin clearance and an increase in AUC 22%. The pharmacokinetics of S-warfarin were not affected. ese pharmacokinetic changes were accompanied by a clinically nificant increase in prothrombin times. Monitoring of othrombin time, or other suitable coagulation tests, with the propriate dose titration of warfarin is recommended in patients ceiving concomitant ZYFLO and warfarin therapy (see **ARNINGS**).

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

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

Drug-drug interaction studies conducted in healthy volunteers tween ZYFLO and prednisone and ethinyl estradiol (oral ntraceptive), drugs known to be metabolized by the P450 3A4 YP3A4) isoenzyme, have shown no significant interaction. owever, no formal drug-drug interaction studies between YFLO and dihydropyridine, calcium channel blockers, closporine, cisapride, and astemizole, also metabolized by YP3A4, have been conducted. It is reasonable to employ propriate clinical monitoring when these drugs are co-lministered with ZYFLO.

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

arcinogenesis, Mutagenesis, Impairment of Fertility: In -year carcinogenicity studies, increases in the incidence of liver, dney, and vascular tumors in female mice and a trend towards n increase in the incidence of liver tumors in male mice were served at 450 mg/kg/day (providing approximately 4 times emales] or 7 times [males] the systemic exposure [AUC] hieved at the maximum recommended human daily oral dose). o increase in the incidence of tumors was observed at 50 mg/kg/day (providing approximately 2 times the systemic posure [AUC] achieved at the maximum recommended human aily oral dose). In rats, an increase in the incidence of kidney mors was observed in both sexes at 170 mg/kg/day (providing proximately 6 times [males] or 14 times [females] the systemic posure [AUC] achieved at the maximum recommended human aily oral dose). No increased incidence of kidney tumors was en at 80 mg/kg/day (providing approximately 4 times [males] or times [females] the systemic exposure [AUC] achieved at the aximum recommended human daily oral dose). Although a se-related increased incidence of benign Leydig cell tumors as observed, Leydig cell tumorigenesis was prevented by pplementing male rats with testosterone.

Zileuton was negative in genotoxicity studies including acterial reverse mutation (Ames) using *S. typhimurium* and *. coli*, chromosome aberration in human lymphocytes, *in vitro* nscheduled DNA synthesis (UDS), in rat hepatocytes with or ithout zileuton pretreatment and in mouse and rat kidney cells ith zileuton pretreatment, and mouse micronucleus assays. lowever, a dose-related increase in DNA adduct formation was ported in kidneys and livers of female mice treated with ileuton. Although some evidence of DNA damage was observed a UDS assay in hepatocytes isolated from Aroclor-1254 treated ats, no such finding was noticed in hepatocytes isolated from onkeys, where the metabolic profile of zileuton is more similar that of humans.

In reproductive performance/fertility studies, zileuton produced o 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 aximum recommended human daily oral dose). Comparative ystemic exposure (AUC) is based on measurements in male rats r nonpregnant female rats at similar dosages. However, reduction a fetal implants was observed at oral doses of 50 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.

Geriatric Use: In subset analyses, females over the age of 65 appeared to be at an increased risk for ALT elevations. Zileuton pharmacokinetics were similar in healthy elderly subjects (≥ 65 years) compared to healthy younger adults (18 to 40 years) (see **CLINICAL PHARMACOLOGY** - ***Special populations:*** Effect of age).

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 (≤ 2.8 x 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

TEAR AT PERFORATION

ZYFLO® FILMTAB®
(zileuton tablets)
Patient Information Leaflet

If you notice these or any other symptoms that you think may be caused by Zyflo, cal 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 doct 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 ove call your doctor or a Poison Control Center immediately.

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

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

Filmtab - Film-sealed tablets, Abbott

Revised January, 2003

ABBOTT LABORATORIES
NORTH CHICAGO, IL 60064, U.S.A.

PRINTED IN U.S.A.

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ncy: Pregnancy Category C: Developmental studies

Asthenia	3.6	2.9
Accidental Injury	3.4	2.0
DIGESTIVE SYSTEM		
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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.

Filmtab - Film-sealed tablets, Abbott

03-5247-R4-Rev. January, 2003

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

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

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

Filmtab - Film-sealed tablets, Abbott

Revised January, 2003

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-471/S009

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Project Manager Labeling Review

NDA 20-471/S-009/Zyflo Filmtab (zileuton tablets)

SPONSOR: Abbott Laboratories

SUBMISSION DATED: August 22, 2001

This supplemental application contains revised labeling in response to the August 27, 1997, Federal Register requesting the addition of a Geriatric Use subsection to the package insert. Abbott states that they have performed a complete analysis of the available data and that there is no new data regarding Zyflo in the Geriatric population. The currently approved package insert contains a statement in the PRECAUTIONS section that is specific to female elderly patients and a statement in the Special Population subsection of the CLINICAL PHARMACOLOGY section that is specific to the geriatrics population. They believe that in light of the above information paragraphs 21 201.57(f)(10)(ii)(9C) and CFR 201.57(f)(10)(iii)(A) would apply. Abbott proposes to expand the Special Population subsection of the CLINICAL PHARMACOLOGY section to included additional information on the referenced study and add a Geriatric Use Subsection to the PRECAUTIONS section.

The Special Population subsection of the CLINICAL PHARMACOLOGY section would be worded as follows: Effect of age: The pharmacokinetics of zileuton were investigated in healthy elderly volunteers (ages 65 to 81 years, 9 Males and 4 Females) and healthy young volunteers (ages 20 to 40 years, 5 Males and 4 Females) after single and multiple oral doses of 600 mg every 6 hours of zileuton. Zileuton pharmacokinetics were similar in healthy elderly subjects (≥65 years) compared to healthy younger adults (18 to 40 years).

The Geriatric Use Subsection to the PRECAUTIONS section would read: In a subset analyses, females over the age of 65 appeared to be at an increased risk for ALT elevations. Zileuton pharmacokinetics were similar in healthy elderly subjects (≥65 years) compared to healthy younger adults (18 to 40 years) (see **Clinical Pharmacology-Special Populations**: Effect of age).

No other changes have been made to the package insert other then those provide for by this supplemental application. This supplemental application should be approved and the letter should contain a request for FPL.

Sandy Barnes
Chief, Project Management Staff

RD initial by M.Mann 12/4/02

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

/s/

Sandra Barnes
12/16/02 04:07:17 PM
CSO

ABBOTT

Pharmaceutical Products Division

Abbott Laboratories
200 Abbott Park Road
D-491, AP30-1E
Abbott Park, Illinois 60064-6157

ORIGINAL

February 28, 2003

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FDR/CDER

Badrul A. Chowdhury, M.D., Ph.D., Acting Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II, CDER
Food and Drug Administration
Fishers Document Room
Parklawn Building, Room 8 B 45
5600 Fishers Lane
Rockville, MD 20857

S LR009 (FA)

Re: Zyflo® Filmtab®
(zileuton tablets)
NDA 20-471

FINAL PRINTED LABELING (FPL) for Approved Supplement S-009

Dear Dr. Chowdhury:

Reference is made to the December 16, 2002 approval letter for the above cited supplemental new drug application (S-009) for the addition of a Geriatric Use subsection to the Warning section, and revisions to the Special Population subsection of the Clinical Pharmacology section of the physician package insert. The purpose of this submission is to provide final printed labeling (FPL) for the approved supplement (S-009).

Please note that the final printed labeling (FPL) is identical to the draft labeling (package insert submitted August 22, 2001) with the exception of a change in the name of an inactive ingredient, hydroxypropyl methylcellulose. The name of hydroxypropyl methylcellulose has been changed to hypromellose in accordance with the United States Pharmacopeia (USP 26-NF 21, September 1, 2002) and is reflected in the final printed labeling (Commodity No. 03-5247-R4-Rev. January, 2003) that is submitted herein.

Accordingly, please find 20 paper copies of final printed labeling, ten of which are individually mounted, in FDA copy 1. FDA copy 2 contains a single copy.

If you have any questions regarding this submission, please contact me at the number listed below.

Sincerely,

Ernesto J. Rivera, Pharm.D.
Regulatory Affairs Project Manager
Phone: (847) 937-7847
Fax: (847) 937-8002

Copy of this cover letter:
Ms. Colette Jackson, Regulatory Project Manager
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II, CDER
Food and Drug Administration
Fishers Document Room
Parklawn Building, Room 8 B 45
5600 Fishers Lane
Rockville, MD 20857

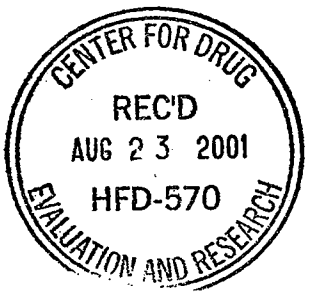
ABBOTT

ORIGINAL

Pharmaceutical Products Division

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

NDA NO. 20471 REF NO. 009
NDA SUPPL FOR SLR



August 22, 2001

Robert J. Meyer, M.D., Director
Division of Pulmonary Drug Products
HFD-570, Room 10B-45/PKLN
Office of Drug Evaluation, II CDER
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Zyflo® Filmtab®
(zileuton tablets)
NDA No. 20-471
Supplement S-009

Prior Approval
Supplement-Geriatric Labeling

Dear Dr. Meyer:

The sponsor, Abbott Laboratories, hereby submits a prior approval supplement to NDA 20-471 in accordance with the August 27, 1997 Federal Register Notice {62 FR 45313} which added a "Geriatric Use" subsection under 21 CFR 201.57(f)(10). The purpose of this submission is to provide information pertinent to the use of Zyflo® Filmtab® (zileuton tablets) in elderly patients (persons ages 65 years and over), in a new "Geriatric Use" subsection to the labeling.

In accordance with the final rule an analysis of all available data on Zyflo® Filmtab® tablets has been conducted. As submitted herein, the following paragraphs of 21 CFR 201.57 (f)(10)(ii)(C) and 201.57 (f)(10)(iii)(A) apply.

Clinical Studies Database

Currently, there is no "Geriatric Use" subsection in the Precautions section of the Zyflo® Filmtab® Tablets labeling. However, there is currently a statement in the precautions section of the labeling that is specific to female elderly patients. Furthermore, under the Clinical Pharmacology section of the package insert, the Special Populations subsection, there is a pharmacokinetic statement that is specific to the geriatric population.

The PRECAUTIONS section of the zileuton package insert contains the following statement: "In subset analyses, females over the age of 65 appeared to be at increased risk for ALT elevations." The basis for this statement stems form the results of clinical trial M94-199, entitled: "Long Term Surveillance Study of Zileuton Plus Usual Care in Patients with Asthma." Data supporting this statement may be found in the M94-199 interim study report that was submitted to the NDA on August 17, 1995. Two later updates to this study report were submitted to IND 30,661 (November 14, 1997, Serial No. 334; and November 18, 1998, Serial No. 340).

The M94-199 study was a 12-month, open-label, randomized, multi-center trial of zileuton plus usual care versus usual care. The M94-199 trial contained the greatest number (n=275) and the most information regarding geriatric subjects. Hence, the most comprehensive adverse event data on patients $\geq$ 65 who received zileuton comes from study M94-199. A Review of adverse events from this study was performed, stratifying the events by patients' age $\geq$ 65 and patients age <65. There were thirteen costart terms that had a reporting rate of $\geq$ 5% in the patients $\geq$65 who received zileuton and for which the reporting rate was greater than that for patients < 65 who received zileuton (excluding events with a higher reporting rate in the patients $\geq$ 65 in the usual care group). These were 'abdominal pain", "aggravation reaction", "asthenia", "chest pain", "pain", "constipation", "dyspepsia", "liver function tests abnormal", "nausea", "dizziness", "insomnia", "somnolence", and "cough increased". Interaction analyses of treatment and age group were performed on this set of adverse events and showed only "cough increased" to have a significant interaction p-value. On further review of the "cough increased" events, the significant interaction was caused by a reporting rate of 8.4% in patients $\leq$ 65 in the usual care group and a reporting rate of 0% in the patients $\geq$ 65 in the usual care group. Therefore, there does not appear to be evidence of increased risk of "cough increased" in subjects $\geq$ 65 who receive zileuton. A copy of the listing of Treatment-Emergent Adverse Events Grouped by body system and costart term subset by age is included as a reference in Section I of this submission.

In the current Zyflo Filmtab package insert, under the Clinical Pharmacology section of the following statement already exists "Special populations: Effect of Age:" "Zileuton pharmacokinetics were similar in healthy elderly subjects (> 65 years) compared to healthy younger adults (18 to 40 years)." The basis for this statement came from a Drug Metabolism Report No. 49 for Clinical Protocol M90-529, entitled: "Comparison of the Pharmacokinetics of Zileuton between Elderly and Younger Subjects," which was submitted to our original NDA 20-471 (July 18, 1994, Volume 94, Page 1).

In conclusion, the review of the clinical trial database did not reveal any new or significant findings. Hence, the reviewer is referred to NDA 20-471 and IND 30,661, if additional information is required.

Post-Marketing Database

A total of 34 Zyflo post-marketing reports on geriatric patients (≥ 65 years) have been received between 12/09/96 to 12/31/00. All of the reports are domestic. More than three quarters (76.5%) of reports were triaged as non-serious. There were more reports on female patients (61.8%) than on male patients. Section II of this submission, entitled: "Spontaneous Geriatric Reports of Zyflo in Post-Marketing Database, 12/09/96-11/30/00, N=34," provides a summary of the post marketing data that were reviewed. Based on the review, there were no significant differences found in the patterns of adverse events reported in the population age < 65 years versus ≥ 65 and over group.

Medical Literature

An extensive literature search was conducted on April 19, 2001. The list of databases that were searched, are listed below. The dates (month/year) covered by each search are included. Please note that the months are approximations.

Information Source	Beginning Date Covered by Search	End date
Medline	January 1966	April 2001
Aidsline	January 1980	December 2000
Cancerlit	January 1975	November 2000
Derwent Drug File	January 1983	April 2001
Embase	June 1974	April 2001

A search of the published medical literature for well-documented studies found no difference between elderly and younger (<65 years) patients. A copy of the titles and abstracts of the articles from the literature search are included in this submission under Section III.

Applicable Regulations:

Section 21 CFR 201.57(f)(10)(ii)(C) "If evidence from clinical studies and other reported clinical experience available to the sponsor indicated that use of the drug in the elderly patients is associated with differences in safety or effectiveness, or requires specific monitoring or dosage adjustment, the 'Geriatric use' subsection of the labeling shall contain a brief description of observed differences." This regulation applies to Zyflo® Filmtab® and there are currently two statements in the Zyflo package insert that meet the intent of this regulation. These statements are combined into a short paragraph to comprise the Geriatric Use subsection.

Section 21 CFR 201.57(f)(10)(iii)(A) "If specific pharmacokinetic or pharmacodynamic studies have been carried out in the elderly, they shall be briefly described in the 'Geriatric use' subsection of the labeling and in detail under the clinical pharmacology section." The first sentence in the proposed labeling (Clinical Pharmacology) provides detailed information on the number and gender of subjects who participated in the M90-529 study, entitled: "Comparison of the Pharmacokinetics of Zileuton Between Healthy Elderly and Younger Subjects." The second statement is already present in the Zyflo® Filmtab® labeling. However, please note that the "(> 65 years)" text has been changed to "(≥ 65 years)." A brief summary of the pharmacokinetic information is also provided in Section I as a reference.

Proposed Labeling

PRECAUTIONS

Geriatric Use: *In subset analyses, females over the age of 65 appeared to be at an increased risk for ALT elevations. Zileuton pharmacokinetics were similar in healthy elderly subjects (≥65 years) compared to healthy younger adults (18 to 40 years) (see* ***Clinical Pharmacology-Special Populations****: Effect of age).*

CLINICAL PHARMACOLOGY

Special Populations:

Effect of age: The pharmacokinetics of zileuton were investigated in healthy elderly volunteers (ages 65 to 81 years, 9 Males, 7 Females) and healthy young volunteers (ages 20 to 40 years, 5 Males and 4 Females) after single and multiple oral doses of 600 mg every 6 hours of zileuton. Zileuton pharmacokinetics were similar in healthy elderly subjects (≥65 years) compared to healthy younger adults (18 to 40 years).

b(4)

Applicability of User Fees to Geriatric Labeling Supplements

In accordance with the December 1998, draft Guidance for Industry, entitled: "Content and Format for Geriatric Labeling," section VII, Applicability of User Fees to Geriatric Labeling Supplements, there is no User Fee provided in this supplement because it does not require clinical data for review. The proposed changes to the package insert are based on data from the original NDA 20-471. Furthermore, most of changes consist of information that is relocated from the approved labeling. The only exception was the addition of the number of subjects, gender, and age ranges for participants in the pharmacokinetic study (M90-529) that compared the elderly and younger patient populations. Also, the "(> 65 years)" text has been changed to "(≥ 65 years)" in the proposed labeling to better reflect the age population that was studied.

A copy of the draft labeling, number DN0659V1, can be found in Section IV of this submission.

Accordingly, the table below provides the section numbers, titles, and page numbers for the information contained in this submission.

Section	Title	Page No.
I	Listing of Treatment-Emergent Adverse Events Grouped By Body System and Costart Term for Study M94-199 and Pharmacokinetic Summary	002
III	Spontaneous Geriatric Reports of Zyflo In Post Marketing Database, 12/09/96-11/30/00, N=34	031
III	Zyflo (Zileuton) Geriatric Use, Abstracts and Titles of Primary Literature	038
IV	Zyflo® Filmtab® Tablets, Draft Labeling, No. DN0659V1	053

If you have any questions regarding this submission, please contact me at the number listed below.

Sincerely,
ABBOTT LABORATORIES

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