

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-052

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZYFLO CR™ safely and effectively. See full prescribing information for ZYFLO CR.

**ZYFLO CR (zileuton) extended-release tablets
Initial U.S. Approval: 1996**

INDICATIONS AND USAGE

ZYFLO CR is a leukotriene synthesis inhibitor indicated for the prophylaxis and chronic treatment of asthma in adults and children 12 years of age and older. (1)

Do not use ZYFLO CR to treat an acute asthma attack (1)

DOSAGE AND ADMINISTRATION

Adults and children 12 years of age and older: The recommended dose of ZYFLO CR is two 600 mg extended-release tablets twice daily, within one hour after morning and evening meals, for a total daily dose of 2400 mg. (2)

Monitoring: Assess hepatic function enzymes prior to initiation of ZYFLO CR and monitor periodically during treatment. (2, 5.1)

DOSAGE FORMS AND STRENGTHS

Extended-release tablets: 600 mg (3)

CONTRAINDICATIONS

- Active liver disease or persistent hepatic function enzyme elevations ≥ 3 times the upper limit of normal (4, 5.1)
- History of allergic reaction to zileuton or any of the ingredients of ZYFLO CR. (4)

WARNINGS AND PRECAUTIONS

Hepatotoxicity: Elevations of one or more hepatic function enzymes and bilirubin may occur with ZYFLO CR. Assess hepatic function enzymes prior to initiation of ZYFLO CR, monthly for the first 3 months, every 2-3 months for the remainder of the first year, and periodically thereafter. Use ZYFLO CR with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. (5)

ADVERSE REACTIONS

Most common adverse reactions ($\geq 5\%$) included: sinusitis, nausea, and pharyngolaryngeal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Critical Therapeutics at 1-866-835-8216 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Zileuton increases theophylline levels. Reduce theophylline dose and monitor levels. (7.1)
- Zileuton increases warfarin levels. Monitor prothrombin time and adjust warfarin dose accordingly. (7.2)
- Zileuton increases propranolol levels and beta-blocker activity. Monitor appropriately. (7.3)

USE IN SPECIFIC POPULATIONS

Hepatic Impairment: ZYFLO CR is contraindicated in patients with active liver disease and in patients with elevated hepatic function enzymes ≥ 3 times the upper limit of normal. (4, 5, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: month/year

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

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

2 DOSAGE AND ADMINISTRATION

The recommended dosage of ZYFLO CR for the treatment of patients with asthma is two 600 mg extended-release tablets twice daily, within one hour after morning and evening meals, for a total daily dose of 2400 mg. Tablets should not be chewed, cut or crushed. If a dose is missed, the patient should take the next dose at the scheduled time and not double the dose. Assess hepatic function enzymes prior to initiation of ZYFLO CR and periodically during treatment [see *Contraindications (4), Warnings and Precautions (5), and Use in Specific Populations (8.7)*].

3 DOSAGE FORMS AND STRENGTHS

Extended-release tablets, 600 mg

4 CONTRAINDICATIONS

The use of ZYFLO CR is contraindicated in patients with:

- Active liver disease or persistent hepatic function enzyme elevations greater than or equal to 3 times the upper limit of normal ($\geq 3 \times \text{ULN}$) [see *Warnings and Precautions (5), and Use in Specific Populations (8.7)*].
- A history of allergic reaction to zileuton or any of the ingredients of ZYFLO CR (e.g., rash, eosinophilia, etc.).

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

Elevations of one or more hepatic function enzymes and bilirubin may occur during ZYFLO CR therapy. These laboratory abnormalities may progress to clinically significant liver injury, remain unchanged, or resolve with continued treatment, usually within three weeks. The ALT (SGPT) test is considered the most sensitive indicator of liver injury for ZYFLO CR.

Assess hepatic function enzymes prior to initiation of, and during therapy with, ZYFLO CR. Assess serum ALT before treatment begins, once a month for the first 3 months, every 2-3 months for the remainder of the first year, and periodically thereafter for patients receiving long-term ZYFLO CR therapy. If clinical signs and/or symptoms of liver dysfunction develop (e.g., right upper quadrant pain, nausea, fatigue, lethargy, pruritus, **jaundice, or “flu-like” symptoms**) or **transaminase elevations $\geq 5 \times \text{ULN}$** occur, discontinue ZYFLO CR and follow hepatic function enzymes until normal.

In controlled and open-label clinical studies involving more than 5000 patients treated with zileuton immediate-release tablets, the overall rate of ALT elevation $\geq 3 \times \text{ULN}$ 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 $3 \times \text{ULN}$. There was no evidence of hypersensitivity or other alternative etiologies for these findings.

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

6 ADVERSE REACTIONS

Hepatotoxicity: Elevations of one or more hepatic function enzymes and bilirubin may occur during ZYFLO CR therapy [see *Warnings and Precautions (5)*].

The most commonly occurring adverse reactions ($\geq 5\%$) with ZYFLO CR are sinusitis, nausea, and pharyngolaryngeal pain.

6.1 Short-Term Clinical Studies Experience

The safety data described below reflect exposure to ZYFLO CR in 199 patients for 12 weeks duration. In a 12-week, randomized, double-blind, placebo-controlled trial in adults and adolescents 12 years of age and older with asthma, patients received ZYFLO CR two 600 mg tablets ($n=199$) or placebo ($n=198$) twice daily by mouth. Eighty-three percent of patients were white, 48% were male, and the mean age was 34 years.

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The most commonly reported adverse reactions (occurring at a frequency of $\geq 5\%$) in ZYFLO CR-treated patients and at a frequency greater than placebo-treated patients are reflected in Table 1.

Table 1
Adverse Reactions with $\geq 5\%$ Incidence in a 12-Week Placebo-Controlled Trial in Patients with Asthma

Adverse Reaction	ZYFLO CR 600 mg 2 Tablets Twice Daily N=199	Placebo 2 Tablets Twice Daily N=198
	n (%)	n (%)
Sinusitis	13 (6.5)	8 (4.0)
Nausea	10 (5.0)	3 (1.5)
Pharyngolaryngeal pain	10 (5.0)	8 (4.0)

Less common adverse reactions occurring at a frequency $\geq 1\%$ and more often in the ZYFLO CR group than in the placebo group included gastrointestinal disorders (upper abdominal pain, diarrhea, dyspepsia, vomiting), rash, hypersensitivity, and hepatotoxicity.

There were no differences in the incidence of adverse reactions based upon gender. The clinical trials did not include sufficient numbers of patients <18 years of age or non-Caucasians to determine whether there is any difference in adverse reactions based upon age or race.

Hepatotoxicity

In the 12-week placebo-controlled trial, the incidence of ALT elevations ($\geq 3 \times \text{ULN}$) was 2.5% (5 of 199) in the ZYFLO CR group, compared to 0.5% (1 of 198) in the placebo group. In the ZYFLO CR group, the majority of ALT elevations (60%) occurred in the first month of treatment, and in 2 of the 5 patients in the ZYFLO CR group, ALT elevations were detected 14 days after completion of the 3-month study treatment. The levels returned to $< 2 \times \text{ULN}$ or normal within 9 and 12 days, respectively. The ALT elevations in the other 3 patients were observed to return to $< 2 \times \text{ULN}$ or normal within 15, 19, and 31 days after ZYFLO CR discontinuation. There appeared to be no clinically relevant relationship between the time of onset and the magnitude of the first elevation or the magnitude of first elevation and time to resolution. The hepatic function enzyme elevations attributed to ZYFLO CR did not result in any cases of jaundice, development of chronic liver disease, or death in this clinical trial.

6.2 Long-Term Clinical Studies Experience

The safety of ZYFLO CR was evaluated in one 6-month, randomized, double-blind, placebo-controlled clinical trial in adults and adolescents 12 years of age and older with asthma. Patients received two 600 mg ZYFLO CR tablets (n=619) or placebo (n=307) twice daily by mouth along with usual asthma care. Eighty-six percent of patients were white, 40% were male, and the overall mean age was 36.

The rate and type of adverse reactions observed in this study were comparable to the adverse reactions observed in the 12-week study. Other commonly reported adverse reactions (occurring at a frequency of $\geq 5\%$) in ZYFLO CR-treated patients and at a frequency greater than placebo-treated patients included the following: headache (23%), upper respiratory tract infection (9%), myalgia (7%), and diarrhea (5%) compared to 21%, 7%, 5% and 2%, respectively, in the placebo-treated group.

ALT elevations ($\geq 3 \times \text{ULN}$) were observed in 1.8% of patients treated with ZYFLO CR compared to 0.7% in patients treated with placebo. The majority of elevations (82%) were reported within the first 3 months of treatment and resolved within 21 days for most of these patients after discontinuation of the drug. The hepatic function enzyme elevations attributed to ZYFLO CR did not result in any cases of jaundice, development of chronic liver disease, or death in this clinical trial.

Occurrences of low white blood cell (WBC) count ($< 3.0 \times 10^9/\text{L}$) were observed in 2.6% (15 of 619) of the ZYFLO CR-treated patients and in 1.7% (5 of 307) of the placebo-treated patients. The WBC counts returned to normal or baseline following discontinuation of ZYFLO CR. The clinical significance of these findings is not known.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of zileuton immediate-release tablets and may be applicable to ZYFLO CR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship.

Cases of severe hepatic injury have been reported in patients taking zileuton immediate-release tablets. These cases included death, life-threatening liver injury with recovery, symptomatic jaundice, hyperbilirubinemia, and elevations of ALT $> 8 \times \text{ULN}$.

7 DRUG INTERACTIONS

The following study results were obtained using zileuton immediate-release tablets but the conclusions also apply to ZYFLO CR.

7.1 Theophylline

In a drug-interaction study in 16 healthy subjects, co-administration of multiple doses of zileuton immediate-release tablets (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 reactions were observed more frequently than after theophylline alone. Upon initiation of ZYFLO CR 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 CR, the maintenance dose and/or dosing interval of theophylline should be adjusted accordingly and guided by serum theophylline determinations.

7.2 Warfarin

Concomitant administration of multiple doses of zileuton immediate-release tablets (600 mg every 6 hours) and warfarin (fixed daily dose obtained by titration in each subject) to 30 healthy male subjects 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 CR and warfarin therapy.

7.3 Propranolol

Co-administration of zileuton immediate-release tablets and propranolol results in a significant increase in propranolol concentrations. Administration of a single 80 mg dose of propranolol in 16 healthy male subjects who received zileuton immediate-release tablets 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 as shown by a decrease in heart rate associated with the co-administration of these drugs. Patients concomitantly on ZYFLO CR and propranolol should be closely monitored and the dose of propranolol reduced as necessary. No formal drug-drug interaction studies between zileuton 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 CR.

7.4 Other Concomitant Drug Therapy

Drug-drug interaction studies conducted in healthy subjects between zileuton immediate-release tablets and prednisone and ethinyl estradiol (oral contraceptive), drugs known to be metabolized by the CYP3A4 isoenzyme, have shown no significant interaction. However, no formal drug-drug interaction studies between zileuton and CYP3A4 inhibitors, such as ketoconazole, have been conducted. It is reasonable to employ appropriate clinical monitoring when these drugs are co-administered with ZYFLO CR.

Drug-drug interaction studies in healthy subjects have been conducted with zileuton immediate-release tablets and digoxin, phenytoin, sulfasalazine, and naproxen. There was no significant interaction between zileuton and any of these drugs.

8 USE IN SPECIFIC POPULATIONS

Information on specific populations is based on studies conducted with zileuton immediate-release tablets and is applicable to ZYFLO CR.

8.1 Pregnancy

Pregnancy Category C:

Developmental studies indicated adverse effects (reduced body weight and increased skeletal variations) in rats at an oral dose of 300 mg/kg/day (providing greater than 10 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/m² basis). There are no adequate and well-controlled studies in pregnant women. ZYFLO CR

should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 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 zileuton 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.

8.4 Pediatric Use

The safety and effectiveness of ZYFLO CR in pediatric patients under 12 years of age have not been established. ZYFLO CR is not appropriate for children less than 12 years of age.

8.5 Geriatric Use

Subgroup analysis of controlled and open-label clinical studies with zileuton immediate-release tablets suggests that females ≥ 65 years of age appear to be at increased risk of ALT elevations. In ZYFLO CR placebo-controlled studies there were no discernable trends in ALT elevations noted in subset analyses for patients ≥ 65 years of age, although the database may not have been sufficiently large to detect a trend [see *Pharmacokinetics (12.3)*].

8.6 Renal Impairment

Dosing adjustment in patients with renal dysfunction or patients undergoing hemodialysis is not necessary [see *Pharmacokinetics (12.3)*].

8.7 Hepatic Impairment

ZYFLO CR is contraindicated in patients with active liver disease or persistent ALT elevations $\geq 3 \times \text{ULN}$ [see *Warnings and Precautions (5)* and *Pharmacokinetics (12.3)*].

10 OVERDOSAGE

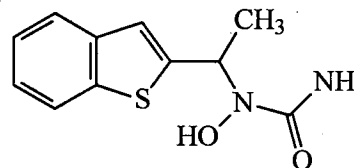
Human experience of acute overdose with zileuton is limited. A patient in a clinical study took between 6.6 and 9.0 grams of zileuton immediate-release tablets in a single dose. Vomiting was induced and the patient recovered without sequelae. Zileuton is not removed by dialysis. Should an overdose occur, 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 CR.

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

11 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 (\pm)-1-(1-Benzo[b]thien-2-ylethyl)-1-hydroxyurea and the following chemical structure:



Zileuton has the molecular formula $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_2\text{S}$ 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 CR (zileuton) extended-release tablets for oral administration are triple-layer tablets comprised of an immediate-release layer, a middle (barrier) layer, and an extended-release layer. ZYFLO CR tablets are oblong, film-coated tablets with one red layer between two white layers, **debossed on one side with "CT2"**. Each tablet contains 600 mg of zileuton and the following inactive ingredients: crospovidone, ferric oxide, glyceryl behenate, hydroxypropyl cellulose, hypromellose, magnesium stearate, mannitol, microcrystalline cellulose, povidone, pregelatinized starch, propylene glycol, sodium starch glycolate, and talc.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Zileuton is an inhibitor of 5-lipoxygenase and thus inhibits leukotriene (LTB₄, LTC₄, LTD₄ and LTE₄) formation. Both the R(+) and S(-) enantiomers are pharmacologically active as 5-lipoxygenase inhibitors in *in vitro* and *in vivo* 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. LTB₄, a chemoattractant for neutrophils and eosinophils, and cysteinyl leukotrienes (LTC₄, LTD₄, LTE₄) can be measured in a number of biological fluids including bronchoalveolar lavage fluid (BALF), blood, urine and sputum from asthmatic patients.

Zileuton is an orally active inhibitor of *ex vivo* LTB₄ formation in several species, including mice, rats, rabbits, dogs, sheep, and monkeys. 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. In a mouse model of allergic inflammation, zileuton inhibited neutrophil and eosinophil influx, reduced the levels of multiple cytokines in the BALF, and reduced serum IgE levels. 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. The clinical relevance of these findings is unknown.

12.2 Pharmacodynamics

Zileuton is an orally active inhibitor of *ex vivo* LTB₄ formation in humans. The inhibition of LTB₄ formation in whole blood is directly related to zileuton plasma levels. In patients with asthma, the IC₅₀ is estimated to be 0.46 µg/mL, and maximum inhibition ≥80% is reached at a zileuton concentration of 2 µg/mL. In patients with asthma receiving zileuton immediate-release tablets 600 mg four times daily, peak plasma levels averaging 5.9 µg/mL were associated with a mean LTB₄ inhibition of 98%. Zileuton inhibits the synthesis

of cysteinyl leukotrienes as demonstrated by reduced urinary LTE₄ levels.

12.3 Pharmacokinetics

Information on the pharmacokinetics of zileuton following the administration of zileuton immediate-release tablets is available in healthy subjects. The results of two clinical pharmacology studies using ZYFLO CR are described below.

Absorption

A three-way crossover study was conducted in healthy male and female subjects (n=23) with a mean age of 33 (range 20-55) following single dose of 1200 mg (2 x 600 mg) ZYFLO CR tablets under fasted and fed conditions, and two doses of 600 mg zileuton immediate-release tablets every 6 hours under fasted conditions. Food increased the peak mean plasma concentrations (C_{max}) and the mean extent of absorption (AUC) of ZYFLO CR by 18 and 34%, respectively, and prolonged T_{max} from 2.1 hours to 4.3 hours. The relative bioavailability of ZYFLO CR to zileuton immediate-release tablets with respect to C_{max} and AUC under fasted conditions were 0.39 (90% CI: 0.36, 0.43) and 0.57 (90% CI: 0.52, 0.62), respectively. Similarly, relative bioavailability of ZYFLO CR to zileuton immediate-release tablets with respect to C_{max} and AUC under fed conditions were 0.45 (90% CI: 0.41, 0.49) and 0.76 (90% CI: 0.70, 0.83), respectively.

A three-way crossover study was conducted in healthy male and female subjects (n=24) with a mean age of 35 (range 19-56) following multiple doses of 1200 mg (2 x 600 mg) ZYFLO CR tablets administered every 12 hours under fasted and fed conditions, and 600 mg zileuton immediate-release tablets every 6 hours under fed conditions until steady state zileuton levels were achieved. Food increased AUC and C_{min} of ZYFLO CR by 43% and 170%, respectively, but had no effect on C_{max}. Therefore, ZYFLO CR is recommended to be administered with food [see *Dosage and Administration (2)*]. At steady state, relative bioavailability of ZYFLO CR to zileuton immediate-release tablets with respect to C_{max}, C_{min}, and AUC were 0.65 (90% CI: 0.60, 0.71), 1.05 (90% CI: 0.88, 1.25) and 0.85 (90% CI: 0.78, 0.92) respectively. These data indicate that at steady state under fed conditions the C_{max} of ZYFLO CR is about 35% lower than that of zileuton immediate-release tablets but the C_{min} and AUC are similar for both formulations

Distribution

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 α 1-acid glycoprotein.

Elimination

Elimination of zileuton is predominantly via metabolism with a mean terminal half-life of 3.2 hours. Apparent oral clearance (CL/F) of zileuton is 669 mL/min. Zileuton activity is primarily due to the parent drug. Studies with radiolabeled drug have 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.

Metabolism

In vitro studies utilizing human liver microsomes have shown that zileuton and its N-dehydroxylated metabolite can be oxidatively metabolized by CYP1A2, CYP2C9 and CYP3A4.

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 (A-66193) of zileuton. The urinary excretion of the inactive A-66193 metabolite and unchanged zileuton each accounted for less than 0.5% of the single radiolabeled dose. Multiple doses of 1200 mg ZYFLO CR twice daily resulted in peak plasma levels of 4.9 μ g/mL of the inactive metabolite A-66193 with an AUC of 93 μ g·hr/mL, showing large inter-subject variability. This inactive metabolite has been shown to be formed by the gastrointestinal microflora prior to the absorption of zileuton and its formation increases with delayed absorption of zileuton.

Renal Impairment

The pharmacokinetics of zileuton immediate-release tablets 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 Impairment

The pharmacokinetics of zileuton immediate-release tablets were compared between subjects with mild and moderate chronic hepatic insufficiency. The mean apparent plasma clearance of total zileuton in subjects with hepatic impairment was approximately half the value of the healthy subjects. The percent binding of zileuton to plasma proteins after multiple dosing was significantly reduced in patients with moderate hepatic impairment. ZYFLO CR is contraindicated in patients with active liver disease or persistent ALT elevations $\geq 3 \times$ ULN [see *Warnings and Precautions* (5)].

Geriatric Use

The pharmacokinetics of zileuton immediate-release tablets were investigated in healthy elderly subjects (ages 65 to 81 years, 9 males, 9 females) and healthy young subjects (ages 20 to 40 years, 5 males, 4 females) after single and multiple oral doses of 600 mg zileuton every 6 hours. Zileuton pharmacokinetics were similar in healthy elderly subjects (≥ 65 years) compared to healthy younger adults (20 to 40 years).

13 NONCLINICAL TOXICOLOGY

13.1 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 toward an increase in the incidence of liver tumors in male mice were observed at 450 mg/kg/day (providing approximately 5 times [females] or 8 times [males] the systemic exposure [AUC=64 μ g·hr/mL] 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 2-3 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 8 times [males] or 16 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 7 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 Aroclor-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 12 times [male rats] and greater than 10 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 10 times the systemic exposure [AUC] achieved at the maximum recommended human daily oral dose). These effects were not seen at an estimated 4 times clinical exposure. Increases in gestation length, prolongation of estrus cycle, and increases in stillbirths were observed at oral doses of 70 mg/kg/day and higher (providing approximately 3 times the systemic exposure [AUC] achieved at the maximum recommended human daily oral dose). In a perinatal/postnatal study in rats, reduced pup survival and growth were noted at an oral dose of 300 mg/kg/day (providing approximately greater than 10 times the systemic exposure [AUC] achieved at the maximum recommended human daily oral dose).

14 CLINICAL STUDIES

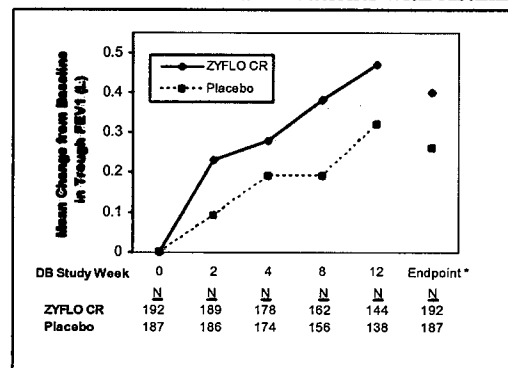
The efficacy of ZYFLO CR was evaluated in a randomized, double-blind, parallel-group, placebo-controlled, multicenter trial of 12 weeks duration in patients 12 years of age and older with asthma. The 12-week trial included 199 patients randomized to ZYFLO CR (two 600 mg tablets twice daily) and 198 to placebo. Eighty-three percent of patients were white, 48% were male,

and the mean age was 34 years. The mean baseline FEV₁ percent predicted was 58.5%.

Assessment of efficacy was based upon forced expiratory volume in one second (FEV₁) at 12 weeks. ZYFLO CR demonstrated a significantly greater improvement in mean change from baseline trough FEV₁ at 12 weeks compared to placebo (0.39 L vs. 0.27 L; p=0.021). The mean change from baseline FEV₁ over the course of the 12-week study is shown in Figure 1. Secondary endpoints (PEFR and rescue beta-agonist use) were supportive of efficacy.

Examination of gender subgroups did not identify differences in response between men and women. The database was not large enough to assess whether there were differences in response in age or racial subgroups.

Figure 1
Mean Change from Baseline in Trough FEV₁ in 12-Week Clinical Trial in Patients with Asthma



*p ≤ 0.050. Endpoint analysis based on last-observation-carried-forward (LOCF) methodology.

16 HOW SUPPLIED/STORAGE AND HANDLING

ZYFLO CR (zileuton) extended-release tablets are debossed on one side with "CT2"; they are available in bottles of 120 tablets (NDC 68734-710-10).

Store between 20 and 25°C (68-77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from light.

17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients

Patients should be told that:

- ZYFLO CR is indicated for the chronic treatment of asthma and should be taken regularly as prescribed, even during symptom-free periods.
- ZYFLO CR is a leukotriene synthesis inhibitor which works by inhibiting the formation of leukotrienes.
- ZYFLO CR should be taken within one hour after morning and evening meals.
- ZYFLO CR tablets should not be cut, chewed or crushed.
- ZYFLO CR is not a bronchodilator and should not be used to treat acute episodes of asthma.
- When taking ZYFLO CR, they should not decrease the dose or stop taking any other antiasthma medications unless instructed by a health care provider. If a dose is missed, they should take the next dose at the scheduled time and not double the dose.
- While using ZYFLO CR, 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 CR is potential elevation of liver enzymes (in 2% of patients) and that, while taking ZYFLO CR, 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 health care provider immediately.
- ZYFLO CR can interact with other drugs and that, while taking ZYFLO CR, they should consult their health care provider before starting or stopping any prescription or non-prescription medicines.
- A patient leaflet is included with the tablets.

17.2 FDA-Approved Patient Labeling ZYFLO (zy'-flo) CR (zileuton) extended-release tablets

Read the Patient Information that comes with ZYFLO CR carefully before you start taking it and read it each time you get a refill. There may be new information. This leaflet does not take the place of talking with your health care provider about your medical condition or your treatment.

What is ZYFLO CR?

ZYFLO CR is a medicine that is used to prevent asthma attacks and for long-term management of asthma in adults and children 12 years of age and older. ZYFLO CR blocks the production of leukotrienes. Leukotrienes are substances that may contribute to your asthma.

ZYFLO CR is not a rescue medicine (it is not a bronchodilator) and should not be used if you need relief right away for an asthma attack.

Who should not take ZYFLO CR?

Do not take ZYFLO CR if you have:

- active liver disease or repeated blood tests showing elevated liver enzymes (substances released by the liver).
- ever had an allergic reaction to ZYFLO CR or any of the ingredients in ZYFLO CR.

What should I tell my health care provider before taking ZYFLO CR?

ZYFLO CR may not be right for you. Tell your health care provider if you:

- have ever had liver problems, including hepatitis, jaundice (yellow eyes or skin), or dark urine.
- drink alcohol. Tell your health care provider how much and how often you drink alcohol.
- have difficulty swallowing pills
- are pregnant or planning to become pregnant. It is not known if ZYFLO CR will harm your unborn baby. Do not take ZYFLO CR during pregnancy unless you and your health care provider decide that taking the medicine is more important than the possible risk to your unborn baby.
- are breastfeeding. It is not known if ZYFLO CR passes into your breast milk. You and your health care provider should decide if you will take ZYFLO CR or breast feed. You should not do both.

Tell your health care provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. ZYFLO CR and other medicines may affect each other causing side effects. Your health care provider may need to adjust the doses of certain medicines while you are taking ZYFLO CR. Talk with your health care provider before starting or stopping any prescription or nonprescription medicine.

Know the medicines you take. Keep a list of your medicines and show it to your health care provider and pharmacist when you get a new medicine.

How should I take ZYFLO CR?

- Take ZYFLO CR exactly as prescribed by your health care provider. Do not decrease the dose of ZYFLO CR or stop taking the medicine without talking to your health care provider first, even if you have no asthma symptoms.

- Take two ZYFLO CR tablets two times each day within one hour after your morning and evening meals.

- Swallow ZYFLO CR whole. **Do not chew, cut or crush ZYFLO CR tablets.** Tell your health care provider if you cannot swallow the tablets whole.

- **Follow your health care provider's** instructions for what to do if you get sudden symptoms of an asthma attack. You can continue taking ZYFLO CR during asthma attacks.

- Get medical help right away if you need to use your rescue medicine more often than usual or **if you use the highest number of "puffs" prescribed** for one 24-hour period. These could be signs that your asthma is getting worse. This means that your asthma therapy may need to be changed.

- Keep taking your other asthma medicines as directed while taking ZYFLO CR.

- If you miss a dose, just take your next scheduled dose when it is due. Do not double the dose.

- If you take too much ZYFLO CR, call your health care provider or a Poison Control Center right away.

What are the possible side effects of ZYFLO CR?

ZYFLO CR can cause serious side effects.

Liver problems. Liver function enzymes and bilirubin can increase while taking ZYFLO CR, and severe liver injury can occur.

- Keep all of your **health care provider's** appointments and be sure to follow all of your **health care provider's instructions.** Have your blood tests done as ordered to check your liver enzymes.

- Tell your health care provider right away if you get any of the following signs or symptoms: pain on the right side of your abdomen (stomach area), nausea, tiredness, lack of energy, itching, yellow skin or yellow color in the whites of your **eyes, dark urine, or "flu-like" symptoms.**

Some of the most common side effects are:

- nose and throat irritation
- sinusitis
- upper respiratory infection
- throat pain
- headache
- muscle aches

- nausea
- diarrhea

Allergic reactions can happen while taking ZYFLO CR. Tell your health care provider right away if you get any of the following signs or symptoms: rash or hives.

Tell your health care provider if you have any new or unusual symptoms that bother you or do not go away while taking ZYFLO CR.

These are not all of the possible side effects of ZYFLO CR. For more information, ask your health care provider or pharmacist.

How should I store ZYFLO CR?

- Store ZYFLO CR between 68°F and 77°F (20°C-25°C).

- Protect ZYFLO CR from light and replace the cap each time after use.

Keep ZYFLO CR and all medicines out of the reach of children.

General Information about ZYFLO CR:

Medicines are sometimes prescribed for conditions that are not mentioned in the patient leaflet. Do not use ZYFLO CR for a condition for which it was not prescribed. Do not give ZYFLO CR to other people, even if they have the same symptoms you have. It may harm them.

This patient information leaflet summarizes the most important information about ZYFLO CR. If you would like more information about ZYFLO CR, talk with your health care provider or pharmacist. You can ask your health care provider or pharmacist for information about ZYFLO CR that is written for health professionals.

For more information go to www.ZYFLOCR.com or call 1-866-835-8216.

What are the ingredients in ZYFLO CR?

Active ingredient: zileuton

Inactive ingredients: crospovidone, ferric oxide, glyceryl behenate, hydroxypropyl cellulose, hypromellose, magnesium stearate, mannitol, microcrystalline cellulose, povidone, pregelatinized starch, propylene glycol, sodium starch glycolate, and talc.

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