ACCOLATE®
ZAFIRLUKAST
TABLETS

DESCRIPTION
Zafirlukast is a synthetic, selective peptide leukotriene receptor antagonist (LTRA), with the chemical name 6-(5-
elketo-2-(5-methyl-2,5-dihydrofuran-3-yl)pentyl)-8-oxo-1,2,3,4,8-
epoxy-4H-1-benzopyran-3-carboxylic acid tert-butyl ester. The molecular formula is C32H34N2O8S and the structural formula is:

![Structural formula of Zafirlukast]

The empirical formula is C32H32N2O8S.

Zafirlukast is a white, or pale yellow, amorphous powder, practically insoluble in water. It is slightly soluble in methanol and freely soluble in ethanol, dimethylsulfoxide, and acetone.

ACCOLATE is supplied as 10 and 20 mg tablets for oral administration.

Inactive ingredients: Film-coated tablets containing croscarmellose sodium, lactose, magnesium stearate, microcrystalline cellulose, povidone, hydroxypropylmethylcellulose and titanium dioxide.

CLINICAL PHARMACOLOGY
Mechanism of Action: Zafirlukast is a selective and competitive receptor antagonist of leukotriene D4 and E4 (LTD4 and LTE4), components of slow-reacting substance of anaphylaxis (SRS-A). Cysteinyl leukotriene production and receptor occupation have been correlated with the pathophysiology of asthma, including airway edema, smooth muscle constriction, and altered cellular activity associated with the inflammatory process, which contribute to the signs and symptoms of asthma. Patients with asthma were found in one study to be 2-5 times more sensitive to the bronchoconstricting activity of inhaled LTD4 than nonasthmatic subjects.

In vitro studies demonstrated that zafirlukast antagonized the contractile activity of these leukotrienes (LTC4, LTD4 and LTE4) in conducting airway smooth muscle from laboratory animals and humans. Zafirlukast prevented intradermal LTD4-induced increases in cutaneous vascular permeability and inhibited inhaled LTD4-induced influx of eosinophils into animal lungs. Intranasal challenge studies in sensitized sheep showed that zafirlukast suppressed the airway responses to antigen; this included both the early- and late-phase responses and the nonspecific hyperresponsiveness.

In humans, zafirlukast inhibited bronchoconstriction caused by several kinds of inhalational challenges. Pretreatment with single oral doses of zafirlukast inhibited the bronchoconstriction caused by sulfur dioxide and cold air in patients with asthma. Pretreatment with single doses of zafirlukast attenuated the early- and late-phase responses caused by inhalation of various antigens such as grass, cat dander, ragweed, and mixed antigens in patients with asthma. Zafirlukast also attenuated the increase in bronchial hyperresponsiveness to inhaled histamine that followed inhalation of allergen challenge.

Clinical Pharmacokinetics and Bioavailability:

Labeling: Original
NDANo. 20547
Rev. 10-19-99
Reviewed by. 10-28-99
Mechanism of Action: Zafirlukast is a selective and competitive leukotriene D4 (LTD4) receptor antagonist of leukotriene D4 (LTD4) in halting the biochemical cascade initiated by LTD4 in bronchial smooth muscle. LTD4 is a potent bronchoconstrictor and causes the release of histamine and other bronchoconstrictors which results in bronchial hyperreactivity and bronchoconstriction.

In vitro studies demonstrated that Zafirlukast antagonized the contractile activity of three leukotrienes (LTB4, LTD4, and LTE4) in inhibiting smooth muscle from laboratory animals and humans. Zafirlukast prevented nonselective LTD4-induced increases in canine airway vascular permeability and inhibited LTD4-induced influx of eosinophils into animal lung. Inhalational challenge studies in sensitized sheep showed that Zafirlukast suppressed the airway responses to antigen.

In humans, Zafirlukast inhibited bronchoconstriction caused by several kinds of inhalational challenges. Pre-treatment with single oral doses of Zafirlukast inhibited the bronchoconstriction caused by allergen (dust) and cold air in patients with asthma. Pre-treatment with single doses of Zafirlukast attenuated the early- and late-phase reaction caused by inhalation of various antigens such as grass, cat, dog, and ragweed, and mixed antigens in patients with asthma. Zafirlukast also attenuated the increase in bronchial hyperreactivity to inhaled histamine that followed inhaled allergen challenge.

Clinical Pharmacokinetics and Bioavailability:

Absorption:

Zafirlukast is rapidly absorbed following oral administration. Peak plasma concentrations are generally achieved 3 hours after oral administration. The absolute bioavailability of Zafirlukast is unknown. In two separate studies, one using a high-fat and the other a high-protein meal, administration of Zafirlukast with food reduced the mean bioavailability by approximately 40%.

Distribution:

Zafirlukast is more than 96% bound to plasma proteins, predominantly albumin. The degree of binding was independent of concentration in the clinically relevant range. The apparent steady-state volume of distribution (Vss) is approximately 70 L, suggesting moderate distribution into tissues. Studies in rats using radiolabeled Zafirlukast indicate minimal distribution across the blood-brain barrier.

Metabolism:

Zafirlukast is extensively metabolized. The most common metabolic products are hydroxylated metabolites which are excreted in the feces. The metabolites of Zafirlukast identified in plasma are at least 90 times less potent as LTD4 receptor antagonists than Zafirlukast itself. In in vitro studies using human liver microsomes, it was shown that the hydroxylated metabolites of Zafirlukast excreted in the feces are formed through the cytochrome P450 3A4 (CYP3A4) pathway. Additional in vitro studies utilizing human liver microsomes showed that Zafirlukast inhibits the cytochrome P450 3A4 (CYP3A4) and CYP2C9 monoxygenases at concentrations close to the clinically achieved total plasma concentrations. (see Drug Interactions).

Excretion:

The apparent oral clearance (CL/F) of Zafirlukast is approximately 20 L/h. Studies in the rat and dog suggest that urinary excretion is the primary route of excretion. Following oral administration of radiolabeled Zafirlukast to volunteers, urinary excretion accounts for approximately 10% of the dose and the remainder is excreted in feces. Zafirlukast is not detected in urine.

In the pivotal bioequivalence study, the mean terminal half-life of Zafirlukast is approximately 10 hours in both normal adult subjects and patients with asthma. In other studies, the mean plasma half-life of Zafirlukast ranged from approximately 8 to 16 hours in both normal subjects and patients with asthma. The pharmacokinetics of Zafirlukast are approximately linear over the range from 5 mg to 80 mg. Steady-state plasma concentrations of Zafirlukast are proportional to the dose and predictable from single-dose pharmacokinetic data. Accumulation of Zafirlukast in the plasma following twice daily dosing is approximately 45%.

The pharmacokinetic parameters of Zafirlukast 20 mg administered as a single dose to 36 male volunteers are shown in the table below.

<table>
<thead>
<tr>
<th>Gender</th>
<th>75% Coefficient of Variation</th>
<th>Pharmacokinetic Parameters</th>
<th>10/2 CL/F Mean</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>ng/mL</td>
<td>ng/mL h</td>
<td>AUC</td>
<td>ng/mL h</td>
<td>2.12</td>
<td>3.12</td>
</tr>
<tr>
<td>30 (10)</td>
<td>2.12 (5.58)</td>
<td>1.13 (3.46)</td>
<td>19.3 (5.36)</td>
<td>19.3 (5.36)</td>
<td></td>
</tr>
</tbody>
</table>

Median and range

Special Populations

Gender: The pharmacokinetics of Zafirlukast are similar in males and females. Weight-adjusted apparent oral clearance does not differ due to gender.

Race: No differences in the pharmacokinetics of Zafirlukast due to race have been observed.

Elderly: The apparent oral clearance of Zafirlukast decreases with age. In patients above 65 years of age, there is an approximately 2.3-fold greater mean and AUC compared to young adult patients.

Pediatric: Following administration of a 20 mg dose of Zafirlukast to 20 boys and girls between 7 and 11 years of age, a mean % coefficient of variation peak drug concentration of 60% (46%) was obtained at about 2.5 hours. Zafirlukast systemic exposure as determined by mean AUC was 207 mg·h/mL (38%). Weight-unadjusted apparent clearance was 11.4 L/h (24%) which resulted in lower systemic drug exposure than that obtained in adults for an identical dose. Zafirlukast disposition was unchanged after multiple dosing (20 mg twice daily) in children and the peak concentrations observed were similar to that.
The apparent oral clearance (CL/F) of zafirlukast is approximately 20 L/h. Studies in the rat and dog suggest that biliary excretion is the primary route of excretion. Following oral administration of radiolabeled zafirlukast to volunteers, urinary excretion accounts for approximately 10% of the dose and the remainder is excreted in feces. Zafirlukast is not detected in urine.

In the present bioequivalence study, the mean terminal halflife of zafirlukast is approximately 10 hours in both normal adult subjects and patients with asthma. In other studies, the mean plasma halflife of zafirlukast ranged from approximately 8 to 16 hours in both normal subjects and patients with asthma. The pharmacokinetics of zafirlukast are approximately linear over the range from 5 mg to 80 mg. Steady-state plasma concentrations of zafirlukast are proportional to the dose and predictable from single-dose pharmacokinetic data. Accumulation of zafirlukast in the plasma following twice daily dosing is approximately 45%.

The pharmacokinetic parameters of zafirlukast 20 mg administered as a single dose to 56 male volunteers are shown in the table below.

<table>
<thead>
<tr>
<th>Cmax</th>
<th>tmax</th>
<th>AUC</th>
<th>CL/F</th>
</tr>
</thead>
<tbody>
<tr>
<td>nmol/L</td>
<td>h</td>
<td>ng.h/ml</td>
<td>h L/h</td>
</tr>
<tr>
<td>32 (31-33)</td>
<td>2.05 (1.6-2.6)</td>
<td>117 (94-140)</td>
<td>132 (75-215)</td>
</tr>
</tbody>
</table>

<1 Median and range

Special populations
- Gender: The pharmacokinetics of zafirlukast are similar in males and females. Weight-adjusted apparent oral clearance does not differ due to gender.
- Race: No differences in the pharmacokinetics of zafirlukast due to race have been observed.
- Ethnicity: The apparent oral clearance of zafirlukast decreases with age. In patients above 65 years of age, there is an approximately 2.3 fold greater Cmax and AUC compared to young adult patients.
- Children: Following administration of a 20 mg dose of zafirlukast to 20 boys and girls between 7 and 11 years of age, a mean (SD) of 616.1 (147.0) nmol/L was obtained at about 2 hours. Zafirlukast systemic exposure as determined by mean AUC was 2072 ng.h/ml (38%). Weight-adjusted apparent clearance was 11.4 L/h (42%) which resulted in greater systemic drug exposure than that obtained in adults for an identical dose. Zafirlukast disposition was unchanged after multiple dosing (20 mg twice daily) in children and the degree of accumulation in plasma was similar to that observed in adults.
- Hepatic insufficiency: In a study of patients with hepatic impairment (defined as Child's C), there was a reduced clearance of zafirlukast resulting in a 50-60% greater Cmax and AUC compared to normal subjects.
- Renal insufficiency: Based on a cross-study comparison, there are no apparent differences in the pharmacokinetics of zafirlukast between renally-impaired patients and normal subjects.

Drug Interactions: The following drug interaction studies have been conducted with zafirlukast. (see PRECAUTIONS: Drug Interactions)
- Co-administration of multiple doses of zafirlukast (150 mg/day) to steady state with a single 25 mg dose of warfarin (a substrate of CYP2C9) resulted in a significant increase in the mean AUC (+63%) and half-life (+96%) of S-warfarin. The mean prothrombin time increased by approximately 35%. No pharmacokinetics of zafirlukast were unaffected by coadministration with warfarin.
- Co-administration of zafirlukast (80 mg/day) at steady state with a single dose of a diuretic-containing preparation (5 mg/kg) in 13 asthmatic patients. 18 to 44 years of age, resulted in decreased mean plasma concentrations of zafirlukast by approximately 30%, but no effect on plasma theophylline concentrations was observed.
- Co-administration of zafirlukast (20 mg/day) or placebo at steady state with a single dose of sustained release theophylline preparation (15 mg/kg) in 16 healthy boys and girls (8 through 11 years of age) resulted in no significant differences in the pharmacokinetic parameters of theophylline.
- Co-administration of zafirlukast at 40 mg twice daily in a single-blind, parallel-group, 3-week study in 39 healthy female subjects taking oral contraceptives, resulted in no significant effect on ethinyl estradiol plasma concentrations or contraceptive efficacy.
- Co-administration of zafirlukast (40 mg/day) with aspirin (650 mg four times daily) resulted in mean increased plasma concentrations of zafirlukast by approximately 45%.
- Co-administration of a single dose of zafirlukast (40 mg) with erythromycin (500 mg three times daily for 5 days) to steady state in 11 asthmatic patients, resulted in decreased mean plasma concentrations of zafirlukast by approximately 40% due to a decrease in zafirlukast bioavailability.

Clinical Studies:
- Three U.S. double-blind, randomized, placebo-controlled, 12-week clinical trials in 1,368 adults and children 12 years of age and older with mild-to-moderate asthma demonstrated that ACCOLADE improved daytime asthma symptoms, nighttime awakenings, morning with asthma symptoms, rescue beta-agonist use, FEV1, and morning peak expiratory flow rate. In these studies, the patients had a mean baseline FEV1 of approximately 75% of predicted normal and a mean baseline beta-agonist requirement of approximately 4.5 puffs of albuterol per day. The results of the serum of the trials are shown in the table.
significant increase in the mean AUC (+63%) and halflife (+36%) of S-warfarin. The mean prothrombin time increased by approximately 35%.

The pharmacokinetics of zafirlukast were unaffected by coadministration with warfarin.

- Coadministration of zafirlukast (80 mg/day) at steady state with a single dose of a liquid theophylline preparation (6 mg/kg) in 13 asthmatic patients, 18 to 44 years of age, resulted in decreased mean plasma concentrations of zafirlukast by approximately 30%, but no effect on plasma theophylline concentrations was observed.

- Coadministration of zafirlukast (20 mg/day) or placebo at steady state with a single dose of sustained-release theophylline preparation (16 mg/kg) in 16 healthy boys and girls (6 through 11 years of age) resulted in no significant differences in the pharmacokinetic parameters of theophylline.

- Coadministration of zafirlukast dosed at 40 mg twice daily in a single-blind, parallel-group, 3-week study in 39 healthy female subjects taking oral contraceptives, resulted in no significant effect on ethinyl estradiol plasma concentrations or contraceptive efficacy.

- Coadministration of zafirlukast (40 mg/day) with aspirin (650 mg four times daily) resulted in mean increased plasma concentrations of zafirlukast by approximately 45%.

- Coadministration of a single dose of zafirlukast (40 mg) with erythromycin (500 mg three times daily for 5 days) to steady state in 11 asthmatic patients, resulted in decreased mean plasma concentrations of zafirlukast by approximately 40% due to a decrease in zafirlukast bioavailability.

**Clinical Studies:**
Three U.S. double-blind, randomized, placebo-controlled, 13-week clinical trials in 1,380 adults and children 12 years of age and older with mild-to-moderate asthma demonstrated that ACCOLATE improved daytime asthma symptoms, nighttime awakenings, morilings with asthma symptoms, rescue beta-agonist use, PEV, and morning peak expiratory flow rate. In these studies, the patient had a mean baseline FEV, of approximately 75% of predicted normal and a mean baseline beta-agonist requirement of approximately 4.5 puffs of albuterol per day.

The results of the trials are shown in the table below.

<table>
<thead>
<tr>
<th>Table 1: Mean Change from Baseline at Study Endpoint</th>
<th>ACCOLATE</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime Asthma symptom score (0-3 scale)</td>
<td>-0.44*</td>
<td>-0.25</td>
</tr>
<tr>
<td>Nighttime Awakenings (number per week)</td>
<td>-1.27</td>
<td>-0.43</td>
</tr>
<tr>
<td>Morings with Asthma Symptoms (days per week)</td>
<td>-1.32</td>
<td>-0.75</td>
</tr>
<tr>
<td>Rescue beta-agonist use (puffs per day)</td>
<td>-1.15</td>
<td>-0.24</td>
</tr>
<tr>
<td>PEV (L)</td>
<td>+0.15</td>
<td>+0.05</td>
</tr>
<tr>
<td>Morning PEFR (L/min)</td>
<td>+2.56*</td>
<td>+7.63</td>
</tr>
<tr>
<td>Evening PEFR (L/min)</td>
<td>+13.12</td>
<td>+10.14</td>
</tr>
</tbody>
</table>

*p<0.05 compared to placebo.

In a second and smaller study, the effect of ACCOLATE on most efficacy parameters was comparable to the active control (inhaled cromolyn sodium 1500 µg four times per day) and superior to placebo at endpoint for decreasing rescue beta-agonist use (figure below).

**Mean β₂ agonist use (puffs/day)***

![Graph showing mean β₂ agonist use (puffs/day) over trial weeks.](image)

In these trials, improvements in asthma symptoms occurred within one week of initiating treatment with ACCOLATE. The use of ACCOLATE in the management of patients with more severe asthma, patients receiving antiasthma therapy other than as-needed, inhaled beta-agonists, or as inhaler or inhaled corticosteroid-sparing agent remains to be fully characterized.

**INDICATIONS AND USAGE**

ACCOLATE is indicated for the prophylaxis and chronic treatment of asthma in adults and children 7 years of age and older.

**CONTRAINDICATIONS**

ACCOLATE is contraindicated in patients who are hypersensitive to zafirlukast or any of its inactive ingredients.

**WARNINGS**

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

Coadministration of zafirlukast with warfarin results in a clinically significant increase in prothrombin time (PT). Patients on oral warfarin anticoagulant therapy and ACCOLATE should have their prothrombin times monitored closely and anticoagulant dose adjusted accordingly. (See PRECAUTIONS, Drug Interactions.)
In these trials, improvement in asthma symptoms occurred within one week of initiating treatment with ACCOLATE. The role of ACCOLATE in the management of patients with more severe asthma, patients receiving concomitant therapy other than as-needed, inhaled beta-agonists, or as an oral or inhaled corticosteroid-sparing agent remains to be fully characterized.

INDICATIONS AND USAGE

ACCOLATE is indicated for the prophylaxis and chronic treatment of asthma in adults and children 7 years of age and older.

CONTRAINDICATIONS

ACCOLATE is contraindicated in patients who are hypersensitive to zafirlukast or any of its inactive ingredients.

WARNINGS

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

Coadministration of zafirlukast with warfarin results in a clinically significant increase in prothrombin time (PT). Patients on oral warfarin anticoagulant therapy and ACCOLATE should have their prothrombin times monitored closely and anticoagulant dose adjusted accordingly. (See PRECAUTIONS, Drug Interactions.)

PRECAUTIONS

Information for Patients: ACCOLATE is indicated for the chronic treatment of asthma and should be taken regularly as prescribed, even during symptom-free periods. ACCOLATE is not a bronchodilator and should not be used to treat acute episodes of asthma. Patients receiving ACCOLATE should be instructed not to decrease the dose or stop taking any other asthma medications unless instructed by a physician. Women who are breast-feeding should be instructed not to take ACCOLATE (see PRECAUTIONS, Nursing Mothers). Alternative asthma medications should be considered in such patients.

The bioavailability of ACCOLATE may be decreased when taken with food. Patients should be instructed to take ACCOLATE at least 1 hour before or 2 hours after meals.

Patients should be told that a rare side effect of ACCOLATE is elevation of liver enzymes and that if they experience signs and symptoms of liver dysfunction (e.g., right upper quadrant abdominal pain, nausea, fatigue, lethargy, pruritus, jaundice, and flu-like symptoms), they should contact their physician immediately.

Hepatic: Rarely, elevations of one or more liver enzymes may occur during ACCOLATE therapy. Most of these have been observed in clinical trials with ACCOLATE at doses four times higher than the recommended dose. The clinical significance of these elevations is unknown. Cases of asymptomatic hepatitis and hyperbilirubinemia without other attributable cause, have been reported from the post-marketing experience in patients who have received the recommended dose of ACCOLATE (40 mg/day). In rare cases, patients have progressed to hepatic failure. In most cases, patients have recovered from hepatic failure, but not all patients, the clinical symptoms abated and the liver enzymes returned to normal or near normal after stopping ACCOLATE.

If clinical signs or symptoms of liver dysfunction (e.g., right upper quadrant abdominal pain, nausea, fatigue, lethargy, pruritus, jaundice, and flu-like symptoms) are noted, it is reasonable to recommend that standard liver tests be obtained and the patient managed accordingly. A decision to discontinue ACCOLATE should be individualized to the patient's condition weighing the risk of hepatic dysfunction against the clinical benefit of ACCOLATE to the patient. (See PRECAUTIONS, Drug Interactions, and ADVERSE REACTIONS sections.)

Eosinophilic Conditions: In rare cases, patients on ACCOLATE therapy may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic steroid therapy. These events usually, but not always, have been associated with the reduction of oral steroid therapy. Physicians should be alert to eosinophilia, vasculitis rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between ACCOLATE and these underlying conditions has not been established. (See ADVERSE REACTIONS.)

Drug Interactions: In a drug interaction study in 16 healthy male volunteers, coadministration of multiple doses of zafirlukast (160 mg/day) to steady state with a single 25-mg dose of warfarin resulted in a significant increase in the mean AUC (+32%) and half-life (+36%) of S-warfarin. The mean prothrombin time (PT) increased by approximately 32%. This interaction is probably due to an inhibition by zafirlukast of the cytochrome P450 2C9 isozyme system. Patients on oral warfarin anticoagulant therapy and ACCOLATE should have their prothrombin times monitored closely and anticoagulant dose adjusted accordingly. (See WARNINGS.) No formal drug-drug interaction studies with ACCOLATE and other drugs known to be metabolized by the cytochrome P450 2C9 isozyme (e.g., lithium, phenytoin, carbamazepine) have been conducted; however, care should be exercised when ACCOLATE is co-administered with these drugs.

In a drug interaction study in 11 asthmatic patients, co-administration of a single dose of zafirlukast (40 mg) with erythromycin (500 mg three times daily for 5 days) to steady state resulted in decreased mean plasma levels of...
zafirlukast by approximately 45% due to a decrease in zafirlukast bioavailability.

Co-administration of zafirlukast (30 mg/day) or placebo at steady state with a single dose of sustained release theophylline preparation (15 mg/kg) in 16 healthy boys and girls (6 through 11 years of age) resulted in no significant differences in the pharmacokinetic parameters of theophylline.

Co-administration of zafirlukast (80 mg/day) at steady state with a single dose of a lozol theophylline preparation (6 mg/kg) in 13 asthmatic patients, 18 to 44 years of age, resulted in decreased mean plasma levels of zafirlukast by approximately 50%, but no effect on plasma theophylline levels was observed.

Rare cases of patients experiencing increased theophylline levels with or without clinical signs or symptoms of theophylline toxicity after the addition of ACCOLATE to an existing theophylline regimen have been reported. The mechanism of the interaction between ACCOLATE and theophylline in these patients is unknown (see ADVERSE REACTIONS).

Co-administration of zafirlukast (40 mg/day) with aspirin (650 mg four times daily) resulted in mean increased plasma levels of zafirlukast by approximately 45%.

In a single-blind, parallel-group, 3-week study in 39 healthy female subjects taking oral contraceptives, 40 mg twice daily of zafirlukast had no significant effect on ethinyl estradiol plasma concentrations or contraceptive efficacy.

No formal drug-drug interaction studies between ACCOLATE and marketed drugs known to be metabolized by the P450 3A4 (CYP 3A4) isoenzyme (e.g. ciprofloxacin, calcium-channel blockers, hydralazine, clonidine) have been conducted. As ACCOLATE is known to be an inhibitor of CYP 3A4 in vitro, it is reasonable to employ proper clinical monitoring when these drugs are coadministered with ACCOLATE.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In two-year carcinogenicity studies, zafirlukast was administered at dietary doses of 10, 100, and 300 mg/kg to male and 40, 400, and 2000 mg/kg to rats. Male mice given 300 mg/kg/day (approximately 75 times the maximum recommended daily oral dose in adults and in children based on a comparison of the plasma area-under-the-curve (AUC) values of total drug exposure) showed an increased incidence of hepatocellular adenomas, a female mice at this dose showed a greater incidence of whole body histiocytic sarcomas. Male and female rats given a dietary dose of 2000 mg/kg/day (approximately 630 times the maximum recommended daily oral dose in adults and in children based on a comparison of the AUCs of total drug exposure) of zafirlukast showed an increased incidence of urinary bladder transitional cell papillomas.

Zafirlukast was not tumorigenic at dietary doses up to 100 mg/kg (approximately 40 times the maximum recommended daily oral dose in adults and in children based on a comparison of the AUCs of total drug exposure) in mice and at dietary doses up to 400 mg/kg (approximately 150 times the maximum recommended daily oral dose in adults and in children based on a comparison of the AUCs of total drug exposure) in rats. The clinical significance of these findings for the long-term use of ACCOLATE is unknown.

Zafirlukast showed no evidence of mutagenic potential in the reverse mutation assay, in two forward point mutation (CHO-HGPRT and mouse lymphoma) assays or in two assays for chromosomal aberrations (an in vitro human peripheral blood lymphocyte clastogenic assay and a rat bone marrow micronucleus assay).

No evidence of impairment of fertility and reproduction was seen in male and female rats treated with zafirlukast at oral doses up to 2000 mg/kg (approximately 410 times the maximum recommended daily oral dose in adults on a mg/m² basis).

Pregnancy Category B: No teratogenicity was observed at oral doses up to 1600 mg/kg/day in mice (approximately 150 times the maximum recommended daily oral dose in adults on a mg/m² basis), 2000 mg/kg/day in rats (approximately 410 times the maximum recommended daily oral dose in adults on a mg/m² basis) and 2000 mg/kg/day in cynomolgous monkeys (approximately 120 times the maximum recommended daily oral dose in adults based on comparison of the AUC of total drug exposure). At an oral dose of 2000 mg/kg/day (approximately 410 times the maximum recommended daily oral dose in adults on a mg/m² basis) in rats, maternal toxicity and litters were seen with increased incidence of male fetal resorption. Spontaneous abortions occurred in cynomolgous monkeys at a maternal toxic dose of 2000 mg/kg/day. There are no adequate and well-controlled trials in pregnant women. Because animal reproduction studies are not always predictive of human response, ACCOLATE should be used during pregnancy only if clearly needed.

Nursing Mothers: Zafirlukast is excreted in breast milk. Following repeated 40-mg twice-a-day dosing in healthy women, average steady-state concentrations of zafirlukast in breast milk were 50 ng/ml, compared to 255 ng/ml in plasma. Because of the potential for tumorigenicity shown for zafirlukast in mouse and rat studies and the enhanced sensitivity of neonatal rats and dogs to the adverse effects of zafirlukast, ACCOLATE should not be administered to mothers who are breast-feeding.

Pediatric Use: The safety of ACCOLATE at doses of 10 mg twice daily has been demonstrated in 205 pediatric patients aged 5 through 11 years in placebo-controlled trials lasting up to six weeks and with 175 patients in this age range participating in 28 weeks of treatment in an open-label extension.

The effectiveness of ACCOLATE for the prophylaxis and chronic treatment of asthma in pediatric patients aged 7 to 11 years is based on an extrapolation of the demonstrated efficacy of ACCOLATE in adults with asthma and the likelihood that the disease course, pathophysiology and the drug's effect are substantially similar between the two populations. The recommended
Carcinogenesis, Mutagenesis, Impairment of Fertility: In two-year carcinogenicity studies, zafirlukast was administered at dietary doses of 10, 100, and 300 mg/kg to mice and 40, 400, and 2000 mg/kg to rats. Male mice given 300 mg/kg/day (approximately 75 times the maximum recommended daily oral dose in adults) and female mice at this dose showed increased incidence of hemolymphoid hyperplasia and lymphoid nodules in lymphoid tissues. In rats, male mice given 2000 mg/kg/day (approximately 630 times the maximum recommended oral dose in adults) and female mice at this dose showed increased incidence of hemolymphoid hyperplasia, and lymphoid nodules in lymphoid tissues. Zafirlukast was not tumorigenic at dietary doses up to 100 mg/kg (approximately 40 times the maximum recommended daily oral dose in adults) and in children based on the comparison of the AUCs of total drug exposure and the AUCs of total drug exposure in adult rats and in children based on the comparison of the AUCs of total drug exposure at a dose of 2000 mg/kg (approximately 10 times the maximum recommended daily oral dose in adults and in children based on the comparison of the AUCs of total drug exposure) in rats and at dietary doses up to 400 mg/kg (approximately 50 times the maximum recommended daily oral dose in adults and in children based on the comparison of the AUCs of total drug exposure) in rats. The clinical significance of these findings for the long-term use of ACCOLATE is unknown.

Zafirlukast showed no evidence of mutagenic potential in the reverse mutation assay, in two forward point mutation (CHO-HGPRT and mouse lymphoma) assays or in two assays for chromosomal aberrations (in vitro human peripheral blood lymphocyte clastogenic assay and a rat bone marrow micronucleus assay).

No evidence of impairment of fertility and reproduction was seen in male and female rats treated with zafirlukast at oral doses up to 2000 mg/kg (approximately 410 times the maximum recommended daily oral dose in adults on a mg/m² basis).

Pregnancy Category B: No teratogenicity was observed at oral doses up to 1600 mg/kg/day in mice (approximately 160 times the maximum recommended daily oral dose in adults on a mg/m² basis), 2000 mg/kg/day in rats (approximately 410 times the maximum recommended daily oral dose in adults on a mg/m² basis), and 3000 mg/kg/day in cynomolgus monkeys (approximately 120 times the maximum recommended daily oral dose in adults based on comparison of the AUCs of total drug exposure). At an oral dose of 2000 mg/kg/day (approximately 410 times the maximum recommended daily oral dose in adults on a mg/m² basis) in rats, maternal toxicity and developmental defects were seen with increased incidence of early fetal resorption. Spontaneous abortions occurred in cynomolgus monkeys at a maximally toxic dose of 2000 mg/kg/day. There were no adequate and well-controlled trials in pregnant women. Because animal reproduction studies are not always predictive of human response, ACCOLATE should be used during pregnancy only if clearly needed.

Nursing Mothers: Zafirlukast is secreted in breast milk. Following repeated 40-mg twice-a-day dosing in healthy women, average steady-state concentrations of zafirlukast in breast milk were 50 ng/ml compared to 255 ng/ml in plasma. Because of the potential for tumorigenicity shown for zafirlukast in mouse and rat studies and the enhanced sensitivity of neonatal rats and dogs to the adverse effects of zafirlukast, ACCOLATE should not be administered to mothers who are breast-feeding.

Pediatric Use: The safety of ACCOLATE at doses of 10 mg twice daily has been demonstrated in 205 pediatric patients aged 5 through 11 years in placebo-controlled trials lasting up to six weeks and with 178 patients in this age group participating in 52 weeks of treatment in an open-label extension. The effectiveness of ACCOLATE for the prophylaxis and chronic treatment of asthma in pediatric patients aged 7 to 11 years is based on extrapolation of the demonstrated efficacy of ACCOLATE in adults with asthma and the likelihood that the disease course, pathophysiology and the drug's affect are substantially similar between the two populations. The recommended dose for the patients 7-11 years of age is based upon a cross-study comparison of the pharmacokinetics of zafirlukast in adults and pediatric subjects, and on the safety profile of zafirlukast in both adult and pediatric patients at doses equal to or higher than the recommended dose.

The effective dose of zafirlukast in pediatric patients 5 and 6 years of age has not yet been established. The safety and effectiveness of zafirlukast for pediatric patients less than 5 years of age has not been established.

ADVERSE REACTIONS

Adults and Children 12 years of age and older: The safety database for ACCOLATE consists of more than 4,000 healthy volunteers and patients who received ACCOLATE, of which 39,723 were asthmatics enrolled in trials of 13 weeks duration or longer. A total of 672 patients received ACCOLATE for 1 year or longer. The majority of the patients were 18 years of age or older; however, 222 patients between the age of 12 and 18 years received ACCOLATE.

A comparison of adverse events reported by ≥1% of zafirlukast-treated patients, and at rates numerically greater than in placebo-treated patients, is shown for all trials in the table below.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>ACCOLATE N=4958</th>
<th>PLACEBO N=3032</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>12.9%</td>
<td>11.7%</td>
</tr>
<tr>
<td>Infection</td>
<td>3.5%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Nausea</td>
<td>3.1%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2.8%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Pain (generalized)</td>
<td>1.9%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1.8%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>1.8%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Adiposephic Injury</td>
<td>1.6%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.6%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1.6%</td>
<td>1.5%</td>
</tr>
</tbody>
</table>
dose for the patients 7-11 years of age is based upon a cross-study comparison of the pharmacokinetics of zafirlukast in adults and pediatric subjects, and on the safety profile of zafirlukast in both adult and pediatric patients at doses equal to or higher than the recommended dose.

The effectiveness of zafirlukast in pediatric patients 5 and 6 years of age has not yet been established. The safety and effectiveness of zafirlukast for pediatric patients less than 5 years of age has not been established.

ADVERSE REACTIONS

Adults and Children 12 years of age and older

The safety database for ACCOLATE consists of more than 4,000 healthy volunteers and patients who received ACCOLATE, of which 1,723 were evaluated in trials of 13 weeks duration or longer. A total of 971 patients received ACCOLATE for 1 year or longer. The majority of the patients were 18 years of age or older; however, 222 patients between the age of 12 and 16 years received ACCOLATE. A comparison of adverse events reported by ≥ 1% of zafirlukast-treated patients, and at rates numerically greater than in placebo-treated patients, is shown for all trials in the table below.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Adverse Event</th>
<th>ACCOLATE</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACCOLATE N=408</td>
<td>PLACEBO N=2032</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>12.9%</td>
<td>11.7%</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>3.5%</td>
<td>3.4%</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>3.1%</td>
<td>2.0%</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2.6%</td>
<td>2.1%</td>
<td></td>
</tr>
<tr>
<td>Pain (generalized)</td>
<td>1.9%</td>
<td>1.7%</td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>1.8%</td>
<td>1.6%</td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>1.6%</td>
<td>1.2%</td>
<td></td>
</tr>
<tr>
<td>Accidental Injury</td>
<td>1.9%</td>
<td>1.5%</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.6%</td>
<td>1.5%</td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>1.5%</td>
<td>1.5%</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>1.6%</td>
<td>1.1%</td>
<td></td>
</tr>
<tr>
<td>Back Pain</td>
<td>1.5%</td>
<td>1.2%</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.5%</td>
<td>1.1%</td>
<td></td>
</tr>
<tr>
<td>SGPT Elevation</td>
<td>1.5%</td>
<td>1.1%</td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1.3%</td>
<td>1.2%</td>
<td></td>
</tr>
</tbody>
</table>

The frequency of less common adverse events was comparable between ACCOLATE and placebo. Rarely, elevations of one or more liver enzymes have occurred in patients receiving ACCOLATE in controlled clinical trials. Most of these have been observed in asymptomatic patients at doses 4 times higher than the recommended dose. The clinical significance of these elevations is unknown. Cases of symptomatic hepatitis and hyperbilirubinemia, without other attributable cause, have been reported from the post-marketing experience in patients who have received the recommended dose of ACCOLATE (40mg/day). In rare cases, patients have progressed to hepatic failure. In most, but not all patients, the clinical symptoms abated and the liver enzymes returned to normal or near normal after stopping ACCOLATE.

In clinical trials, an increased proportion of zafirlukast patients over the age of 55 years reported infections as compared to placebo-treated patients. A similar finding was not observed in other age groups studied. These infections were mostly mild or moderate in intensity and predominantly affected the respiratory tract. Infections occurred equally in both sexes, were dose-proportional to total milligramms of zafirlukast exposure, and were associated with concomitant use of inhaled corticosteroids. The clinical significance of this finding is unknown.

In rare cases, patients on ACCOLATE therapy may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic steroids therapy. These events usually, but not always, have been associated with the reduction of oral steroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between ACCOLATE and these underlying conditions has not been established.

(See PRECAUTIONS - Endocrine Considerations.)

Hypersensitivity reactions, including urticaria, angioedema and rashes, with or without blistering, have been reported in association with ACCOLATE therapy. Additionally, there have been reports of patients experiencing agranulocytosis, bleeding, bruising, or edema in association with ACCOLATE therapy.

Rare cases of patients experiencing increased theophylline levels with or without clinical signs or symptoms of theophylline toxicity after the addition of ACCOLATE to an existing theophylline regimen have been reported. The mechanism of the interaction between ACCOLATE and theophylline in these patients is unknown and not predicted by available in vitro metabolism data and the results two clinical drug interaction studies. (see CLINICAL PHARMACOLOGY and PRECAUTIONS - Drug Interactions sections.)

Pediatric Patients 5 through 11 years of Age

ACCOLATE has been evaluated for safety in 788 pediatric patients 5 through 11 years of age. Cumulatively, 313 pediatric patients were treated with ACCOLATE 10 mg bd or higher for at least 6 months, and 113 of them were treated for one year or longer in clinical trials. The safety profile of ACCOLATE 10 mg twice daily versus placebo in the 4 and 6-week double-blind trials was generally similar to that observed in the adult clinical trials with ACCOLATE 20 mg twice daily.

In pediatric patients receiving ACCOLATE in multi-dose clinical trials, the following events occurred with a frequency of 2% or more frequently than in pediatric patients who received placebo, regardless of causality assessment: headache (4.5% vs. 2.5%) and abdominal pain (2.5% vs. 2.5%).

OVERDOSAGE

No deaths occurred at oral zafirlukast doses of 2000 mg/kg in mice (approximately 200 times the maximum recommended daily dose in adults on a mg/m² basis and
PEDIATRIC PATIENTS 5 THROUGH 11 YEARS OF AGE

ACCOLATE has not been evaluated for safety in children. In 1 study, 21 children aged 3-12 years of age were treated with ACCOLATE 75 mg/m² twice daily for a mean duration of 8 months. Children aged 5-11 years of age were treated for 3-6 months, and children aged 3-4 years of age were treated for 2-6 months. Although the safety and effectiveness of ACCOLATE were demonstrated in this study, longer-term clinical trials are needed to determine the long-term safety and effectiveness of ACCOLATE in children. The recommended dose for children aged 5-11 years of age is 75 mg/m² twice daily. The recommended dose for children aged 3-4 years of age is 60 mg/m² twice daily. The maximum recommended daily dose of ACCOLATE for children aged 5-11 years of age is 150 mg/m². The maximum recommended daily dose of ACCOLATE for children aged 3-4 years of age is 120 mg/m².

DOSE ADMINISTRATION

Adults and Children 12 years of age and older

The recommended dose of ACCOLATE is 20 mg twice daily in adults and children 12 years of age and older. The recommended dose of ACCOLATE in children aged 5-11 years of age is 75 mg/m² twice daily. The maximum recommended daily dose of ACCOLATE in children aged 5-11 years of age is 150 mg/m². The maximum recommended daily dose of ACCOLATE in children aged 3-4 years of age is 60 mg/m² twice daily. The maximum recommended daily dose of ACCOLATE in children aged 3-4 years of age is 120 mg/m².

OVERDOSAGE

Overdose cases occurred at oral zaltikasat doses of 2000 mg in adults and 1000 mg in children. The maximum recommended daily oral dose is 20 mg/m² in adults and 75 mg/m² in children. The maximum recommended daily oral dose is 100 mg/m² in children. Overdosage with ACCOLATE has been reported in patients taking multiple doses as high as 200 mg. The predominant symptoms reported following overdoses were rash and skin rash. There were no acute toxic effects in humans that could be consistently ascribed to the administration of ACCOLATE. In case of an overdose, it is reasonable to employ the usual supportive measures in the event of an overdose, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy if necessary.

DOSE AND ADMINISTRATION

Adults and Children 12 years of age and older

The recommended dose of ACCOLATE is 20 mg twice daily in adults and children 12 years of age and older. The recommended dose of ACCOLATE in children 5-11 years of age is 75 mg/m² twice daily. The maximum recommended daily dose of ACCOLATE in children 5-11 years of age is 150 mg/m². The maximum recommended daily dose of ACCOLATE in children 3-4 years of age is 60 mg/m² twice daily. The maximum recommended daily dose of ACCOLATE in children 3-4 years of age is 120 mg/m².

OVERDOSAGE

Overdose cases occurred at oral zaltikasat doses of 2000 mg in adults and 1000 mg in children. The maximum recommended daily oral dose is 20 mg/m² in adults and 75 mg/m² in children. The maximum recommended daily oral dose is 100 mg/m² in children. Overdosage with ACCOLATE has been reported in patients taking multiple doses as high as 200 mg. The predominant symptoms reported following overdoses were rash and skin rash. There were no acute toxic effects in humans that could be consistently ascribed to the administration of ACCOLATE. In case of an overdose, it is reasonable to employ the usual supportive measures in the event of an overdose, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy if necessary.

DOSE AND ADMINISTRATION

Adults and Children 12 years of age and older

The recommended dose of ACCOLATE is 20 mg twice daily in adults and children 12 years of age and older. The recommended dose of ACCOLATE in children 5-11 years of age is 75 mg/m² twice daily. The maximum recommended daily dose of ACCOLATE in children 5-11 years of age is 150 mg/m². The maximum recommended daily dose of ACCOLATE in children 3-4 years of age is 60 mg/m² twice daily. The maximum recommended daily dose of ACCOLATE in children 3-4 years of age is 120 mg/m².

OVERDOSAGE

Overdose cases occurred at oral zaltikasat doses of 2000 mg in adults and 1000 mg in children. The maximum recommended daily oral dose is 20 mg/m² in adults and 75 mg/m² in children. The maximum recommended daily oral dose is 100 mg/m² in children. Overdosage with ACCOLATE has been reported in patients taking multiple doses as high as 200 mg. The predominant symptoms reported following overdoses were rash and skin rash. There were no acute toxic effects in humans that could be consistently ascribed to the administration of ACCOLATE. In case of an overdose, it is reasonable to employ the usual supportive measures in the event of an overdose, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy if necessary.

DOSE AND ADMINISTRATION

Adults and Children 12 years of age and older

The recommended dose of ACCOLATE is 20 mg twice daily in adults and children 12 years of age and older. The recommended dose of ACCOLATE in children 5-11 years of age is 75 mg/m² twice daily. The maximum recommended daily dose of ACCOLATE in children 5-11 years of age is 150 mg/m². The maximum recommended daily dose of ACCOLATE in children 3-4 years of age is 60 mg/m² twice daily. The maximum recommended daily dose of ACCOLATE in children 3-4 years of age is 120 mg/m².

OVERDOSAGE

Overdose cases occurred at oral zaltikasat doses of 2000 mg in adults and 1000 mg in children. The maximum recommended daily oral dose is 20 mg/m² in adults and 75 mg/m² in children. The maximum recommended daily oral dose is 100 mg/m² in children. Overdosage with ACCOLATE has been reported in patients taking multiple doses as high as 200 mg. The predominant symptoms reported following overdoses were rash and skin rash. There were no acute toxic effects in humans that could be consistently ascribed to the administration of ACCOLATE. In case of an overdose, it is reasonable to employ the usual supportive measures in the event of an overdose, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy if necessary.
ACCOLATE®
ZAFIRLUKAST

10 mg TABLETS
100 TABLETS
UNIT DOSE

NDC 0310-0401-39
UNIT DOSE

Push in to remove top

ACCOLATE®
ZAFIRLUKAST

10 mg TABLETS
Rx only

100 TABLETS

ZENECA
Manufactured for: Zeneva Pharmaceuticals
A Business Unit of Zeneva Inc., Wilmington, Delaware 19850-5437
By: IPR Pharmaceuticals Inc., Carolina, Puerto Rico 00984-1967

772100

USUAL DOSAGE: See accompanying Professional Information Brochure.
WARNING: As with all medication, keep out of the reach of children.

Store at controlled room temperature, 20-25°C (68-77°F) [see USP]. Protect from light and moisture.
BEST POSSIBLE COPY

Accolate 10 mg Pediatric Label

- 470600 Plate Date: 6/10/99 2:32 pm, SZT Art created at 100%

Artist Job Notes:
Dimensions: 1-3/4" x 3-3/4"
Colors: PMS
Barcode: UPC
Software: Mac Adobe Illustrator 6.0 Fonts: Univers Regular, Bold, Bold Oblique, Black Oblique; Univers Cond. Bold Oblique; Helvetica Regular; Symbol; OCRB

APPEARS THIS WAY ON ORIGINAL
# Accolate 10 mg 10-up Blisters

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Amount</th>
<th>Lot</th>
<th>Expiry</th>
<th>Manufacturer</th>
<th>Place</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>870400</td>
<td>Accolate 10 mg 10-up Blisters</td>
<td>10 mg</td>
<td>LOT XXXXXX</td>
<td>EXP XXXXXX</td>
<td>Jeans Pharmaceuticals, Milwaukee, Wisconsin 53262</td>
<td>E70402</td>
<td>NDC 0310-0401-39</td>
</tr>
</tbody>
</table>

**Artwork Job Notes:**
- Dimensions: 25 x 37.5 mm ea., 10-up
- Colors: Black
- Software: Mac Adobe Illustrator 8.0
- Fonts: Univers Regular, Bold, Oblique, Black Oblique; Univers Cond. Bold Oblique; Helvetica Regular; Symbol: OCR-B8

*Appears This Way On Original*
30 Page(s) Redacted

Draft

LABELING