CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-547/S007

FINAL PRINTED LABELING

670200

Rev J 09/99

PROFESSIONAL INFORMATION BROCHURE

# ACCOLATE®

## ZAFIRLUKAST

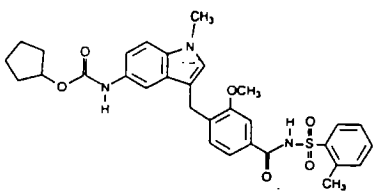
TABLETS

10.28.99

NOV - 2 1999

### DESCRIPTION

Zafirlukast is a synthetic, selective peptide leukotriene receptor antagonist (LTRA), with the chemical name 4-(5-cyclopentyloxy-carbonylamino-1-methyl-indol-3-ylmethyl)-3-methoxy-N-o-tolylsulfonylbenzamide. The molecular weight of zafirlukast is 575.7 and the structural formula is



The empirical formula is: $C_{31}H_{33}N_3O_6S$

Zafirlukast, a fine white to pale yellow amorphous powder, is practically insoluble in water. It is slightly soluble in methanol and freely soluble in tetrahydrofuran, 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 $D_4$ and $E_4$ ($LTD_4$ and $LTE_4$), components of slow-reacting substance of anaphylaxis (SRSA). 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 25-100 times more sensitive to the bronchoconstricting activity of inhaled $LTD_4$ than nonasthmatic subjects.

In vitro studies demonstrated that zafirlukast antagonized the contractile activity of three leukotrienes ($LTC_4$, $LTD_4$ and $LTE_4$) in conducting airway smooth muscle from laboratory animals and humans. Zafirlukast prevented intradermal $LTD_4$-induced increases in cutaneous vascular permeability and inhibited inhaled $LTD_4$-induced influx of eosinophils into animal lungs. Inhalational challenge studies in sensitized sheep showed that zafirlukast suppressed the airway responses to antigen; this included both the early- and late-phase response 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 reaction 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 inhaled allergen challenge.

Clinical Pharmacokinetics and Bioavailability:

Labeling: Original
NDA No. 20547 Rc'd. 10-19-99
Reviewed by: [151] 10-28-99

Labeling: Original
NDA No. 20547 Rc'd. 10-19-99
Reviewed by: 10-28-99

**Mechanism of Action:** Zafirlukast is a selective and competitive receptor antagonist of leukotriene $D_4$ and $E_4$ ($LTD_4$ and $LTE_4$), components of slow-reacting substance of anaphylaxis (SRSA). 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 25-100 times more sensitive to the bronchoconstricting activity of inhaled $LTD_4$ than nonasthmatic subjects.

In vitro studies demonstrated that zafirlukast antagonized the contractile activity of three leukotrienes ($LTC_4$, $LTD_4$ and $LTE_4$) in conducting airway smooth muscle from laboratory animals and humans. Zafirlukast prevented intradermal $LTD_4$-induced increases in cutaneous vascular permeability and inhibited inhaled $LTD_4$-induced influx of eosinophils into animal lungs. Inhalational challenge studies in sensitized sheep showed that zafirlukast suppressed the airway responses to antigen; this included both the early- and late-phase response 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 reaction 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 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 99% 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 ($V_{SS}/F$) 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 $LTD_4$ receptor antagonists than zafirlukast in a standard *in vitro* test of activity. *In vitro* studies using human liver microsomes showed that the hydroxylated metabolites of zafirlukast excreted in the feces are formed through the cytochrome P450 2C9 (CYP2C9) pathway. Additional *in vitro* studies utilizing human liver microsomes show that zafirlukast inhibits the cytochrome P450 CYP3A4 and CYP2C9 isoenzymes 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 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 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 with the table below.

**Mean (% Coefficient of Variation) pharmacokinetic parameters of zafirlukast following single 20 mg oral dose administration to male volunteers (n=36)**

| $C_{max}$ ng/ml | $t_{max}$[1] h | AUC ng.h/mL | t1/2 h | CL/f L/h |
|---|---|---|---|---|
| 326 (31.0) | 2 (0.5-5.0) | 1137 (34) | 13.3 (75.6) | 19.4 (32) |

[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.

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 $C_{max}$ 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 (% coefficient of variation) peak drug concentration of 601 ng/mL (45%) was obtained at about 2.5 hours. Zafirlukast systemic exposure as determined by mean AUC was 2027 ng.h/mL (38%). Weight unadjusted 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 [illegible] in plasma was similar to that

zafirlukast inhibits the cytochrome P450 isoenzyme CYP2C9 isoenzymes 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 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 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 with the table below.

**Mean (% Coefficient of Variation) pharmacokinetic parameters of zafirlukast following single 20 mg oral dose administration to male volunteers (n=36)**

| $C_{max}$ ng/ml | $t_{max}$[1] h | AUC ng.h/mL | t1/2 h | CL/f L/h |
|---|---|---|---|---|
| 326 (31.0) | 2 (0.5-5.0) | 1137 (34) | 13.3 (75.6) | 19.4 (32) |

[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.

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 $C_{max}$ 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 (% coefficient of variation) peak drug concentration of 601 ng/mL (45%) was obtained at about 2.5 hours. Zafirlukast systemic exposure as determined by mean AUC was 2027 ng h/mL (38%). Weight unadjusted 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 (biopsy-proven cirrhosis), there was a reduced clearance of zafirlukast resulting in a 50-60% greater $C_{max}$ 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 (160 mg/day) to steady state with a single 25 mg dose of warfarin (a substance of CYP2C9) resulted in a significant increase in the mean AUC (+63%) and half-life (+36%) of S-warfarin. The mean prothrombin time increased by approximately 35%. The 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 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.
- Co-administration 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.
- Co-administration 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.
- 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, 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, mornings with asthma symptoms, rescue beta$_2$-agonist use, $FEV_1$, and morning peak expiratory flow rate. In these studies, the patients had a mean baseline $FEV_1$ 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 largest of the trials are shown in the table

significant increase in the mean AUC (+63%) and half-life (+36%) of S-warfarin. The mean prothrombin time increased by approximately 35%. The 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 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.
- Co-administration 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.
- Co-administration 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
- 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, 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, mornings with asthma symptoms, rescue beta$_2$-agonist use, $FEV_1$, and morning peak expiratory flow rate. In these studies, the patients had a mean baseline $FEV_1$ 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 largest of the trials are shown in the table below

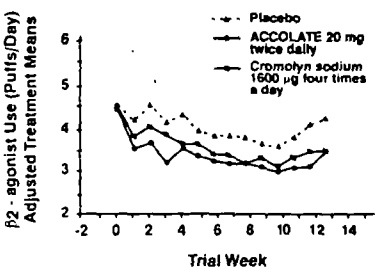
Table 1
Mean Change from Baseline at Study Endpoint

| | ACCOLATE 20 mg twice daily N=514 | Placebo N=248 |
|---|---|---|
| Daytime Asthma symptom score (0-3 scale) | -0.44* | -0.25 |
| Nighttime Awakenings (number per week) | -1.27* | -0.43 |
| Mornings with Asthma Symptoms (days per week) | -1.32* | -0.75 |
| Rescue $\beta_2$-agonist use (puffs per day) | -1.15* | -0.24 |
| $FEV_1$ (L) | +0.15* | +0.05 |
| Morning PEFR (L/min) | +22.06* | +7.63 |
| Evening PEFR (L/min) | +13.12 | +10.14 |

*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 1600 µg four times per day) and superior to placebo at endpoint for decreasing rescue beta-agonist use (figure below).

**Mean $\beta_2$ - agonist use (puffs/day)**




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 antiasthma therapy other than as-needed, inhaled beta$_2$-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 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.)

PRECAUTIONS


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 antiasthma therapy other than as-needed, inhaled beta$_2$-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 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.)

**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 antiasthma medications unless instructed by a physician. Women who are breast-feeding should be instructed not to take ACCOLATE (see PRECAUTIONS, Nursing Mothers). Alternative antiasthma medication 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/or 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 are 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 (40 mg/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.

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, Information for Patients 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, 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 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 (+63%) and half-life (+36%) of S-warfarin. The mean prothrombin time (PT) increased by approximately 35%. This interaction is probably due to an inhibition by zafirlukast of the cytochrome P450 2C9 isoenzyme 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 isoenzyme (e.g., tolbutamide, 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

(CONTINUED ON REVERSE SIDE)

zafirlukast by approximately 40% due to a decrease in zafirlukast bioavailability.

Co-administration 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.

Co-administration 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 levels of zafirlukast by approximately 30%, 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. dihydropyridine calcium-channel blockers, cyclosporin, cisapride) have been conducted. As ACCOLATE is known to be an inhibitor of CYP 3A4 in vitro, it is reasonable to employ appropriate 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 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 in children based on a comparison of the plasma area-under the curves [AUCs] values of total drug exposure) showed an increased incidence of hepatocellular adenomas; female mice at this dose showed a greater incidence of whole body histocytic sarcomas. Male and female rates 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 comparison of the AUC of total drug exposure) in mice and at dietary doses up to 400 mg/kg (approximately 550 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 microbial assay, in 2 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/m$^2$ 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/m$^2$ basis), 2000 mg/kg/day in rats (approximately 410 times the maximum recommended daily oral dose in adults on a mg/m$^2$ basis) and 2000 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/m$^2$ basis) in rats, maternal toxicity and deaths were seen with increased incidence of early fetal resorption. Spontaneous abortions occurred in cynomolgus monkeys at a maternally 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 179 patients in this age range 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 an extrapolation of the demonstrated efficacy of ACCOLATE in adults with asthma and the likelihood that the disease course, and pathophysiology and the drug's effect are substantially similar between the two populations. The recommended dose for the patients 7-11 years of age is based upon a

**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 in children based on a comparison of the plasma area-under the curves [AUCs] values of total drug exposure) showed an increased incidence of hepatocellular adenomas; female mice at this dose showed a greater incidence of whole body histocytic sarcomas. Male and female rates 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 comparison of the AUC of total drug exposure) in mice and at dietary doses up to 400 mg/kg (approximately 550 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 microbial assay, in 2 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/m$^2$ 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/m$^2$ basis), 2000 mg/kg/day in rats (approximately 410 times the maximum recommended daily oral dose in adults on a mg/m$^2$ basis) and 2000 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/m$^2$ basis) in rats, maternal toxicity and deaths were seen with increased incidence of early fetal resorption. Spontaneous abortions occurred in cynomolgus monkeys at a maternally 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 179 patients in this age range 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 an extrapolation of the demonstrated efficacy of ACCOLATE in adults with asthma and the likelihood that the disease course, and pathophysiology and the drug's effect 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 1723 were asthmatics enrolled in trials of 13 weeks duration or longer. A total of 671 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 2

| Adverse Event | ACCOLATE N=4058 | PLACEBO N=2032 |
|---|---|---|
| Headache | 12.9% | 11.7% |
| Infection | 3.5% | 3.4% |
| Nausea | 3.1% | 2.0% |
| Diarrhea | 2.8% | 2.1% |
| Pain (generalized) | 1.9% | 1.7% |
| Asthenia | 1.8% | 1.6% |
| Abdominal Pain | 1.8% | 1.1% |
| Accidental Injury | 1.6% | 1.5% |
| Dizziness | 1.6% | 1.5% |
| Myalgia | 1.6% | 1.5% |

similar between the two populations. The [illegible] 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 1723 were asthmatics enrolled in trials of 13 weeks duration or longer. A total of 671 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 2

| Adverse Event | ACCOLATE N=4058 | PLACEBO N=2032 |
|---|---|---|
| Headache | 12.9% | 11.7% |
| Infection | 3.5% | 3.4% |
| Nausea | 3.1% | 2.0% |
| Diarrhea | 2.8% | 2.1% |
| Pain (generalized) | 1.9% | 1.7% |
| Asthenia | 1.8% | 1.6% |
| Abdominal Pain | 1.8% | 1.1% |
| Accidental Injury | 1.6% | 1.5% |
| Dizziness | 1.6% | 1.5% |
| Myalgia | 1.6% | 1.5% |
| Fever | 1.6% | 1.1% |
| Back Pain | 1.5% | 1.2% |
| Vomiting | 1.5% | 1.1% |
| SGPT Elevation | 1.5% | 1.1% |
| Dyspepsia | 1.3% | 1.2% |

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 four times higher than the recommended dose. The clinical significance of these elevations are 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 milligrams of zafirlukast exposure, and were associated with coadministration 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 steroid 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 - Eosinophilic Conditions.)

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 bid 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% and more frequently than in pediatric patients who received placebo, regardless of causality assessment: headache (4.5 vs. 4.2%) and abdominal pain (2.8 vs. 2.3%).

## OVERDOSAGE

No deaths occurred at oral zafirlukast doses of 2000 mg/kg in mice (approximately 200 times the maximum recommended daily oral dose in adults on a mg/m$^2$ basis and

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 bid 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% and more frequently than in pediatric patients who received placebo, regardless of causality assessment: headache (4.5 vs. 4.2%) and abdominal pain (2.8 vs. 2.3%).

## OVERDOSAGE

No deaths occurred at oral zafirlukast doses of 2000 mg/kg in mice (approximately 200 times the maximum recommended daily oral dose in adults on a mg/m$^2$ basis and approximately 300 times the maximum recommended daily oral dose in children on a mg/m$^2$ basis), 2000 mg/kg in rats (approximately 410 times the maximum recommended daily oral dose in adults on a mg/m$^2$ basis and approximately 600 times the maximum recommended daily oral dose in children on a mg/m$^2$ basis), and 500 mg/kg in dogs (approximately 250 times the maximum recommended daily oral dose in adults on a mg/m$^2$ basis and approximately 500 times the maximum recommended daily oral dose in children on a mg/m$^2$ basis).

Overdosage with ACCOLATE has been reported in four patients surviving reported doses as high as 200 mg. The predominant symptoms reported following ACCOLATE overdose were rash and upset stomach. There were no acute toxic effects in humans that could be consistently ascribed to the administration of ACCOLATE. 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 required.

## DOSAGE 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 and older.

**Pediatric Patients 7 through 11 years of Age**

The recommended dose of ACCOLATE in children 7 through 11 years of age is 10 mg twice daily.

Since food reduces the bioavailability of zafirlukast, ACCOLATE should be taken at least 1 hour before or 2 hours after meals.

**Elderly Patients:** Based on cross-study comparisons, the clearance of zafirlukast is reduced in elderly patients (65 years of age and older), such that $C_{max}$ and AUC are approximately twice those of younger adults. In clinical trials, a dose of 20 mg twice daily was not associated with an increase in the overall incidence of adverse events or withdrawals because of adverse events in elderly patients.

**Patients with Hepatic Impairment:** The clearance of zafirlukast is reduced in patients with stable alcoholic cirrhosis such that the $C_{max}$ and AUC are approximately 50 - 60% greater than those of normal adults. ACCOLATE has not been evaluated in patients with hepatitis or in long-term studies of patients with cirrhosis.

**Patients with Renal Impairment:** Dosage adjustment is not required for patients with renal impairment.

## HOW SUPPLIED

**ACCOLATE 10 mg Tablets,** (NDC 0310-0401) white unflavored, round, biconvex, film-coated, mini-tablets identified with "ZENECA" debossed on one side and "ACCOLATE 10" debossed on the other side are supplied in opaque HDPE bottles of 60 tablets and hospital Unit Dose blister packages of 100 tablets.

**ACCOLATE 20 mg Tablets,** (NDC 0310-0402) white round, biconvex, coated tablets identified with "ZENECA" debossed on one side and "ACCOLATE 20" debossed on the other side are supplied in opaque HDPE bottles of 60 tablets and hospital Unit Dose blister packages of 100 tablets.

Store at controlled room temperature (20°-25°C) (68°-77°F) [see USP]. Protect from light and moisture. Dispense in the original air-tight container.

ZENECA

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

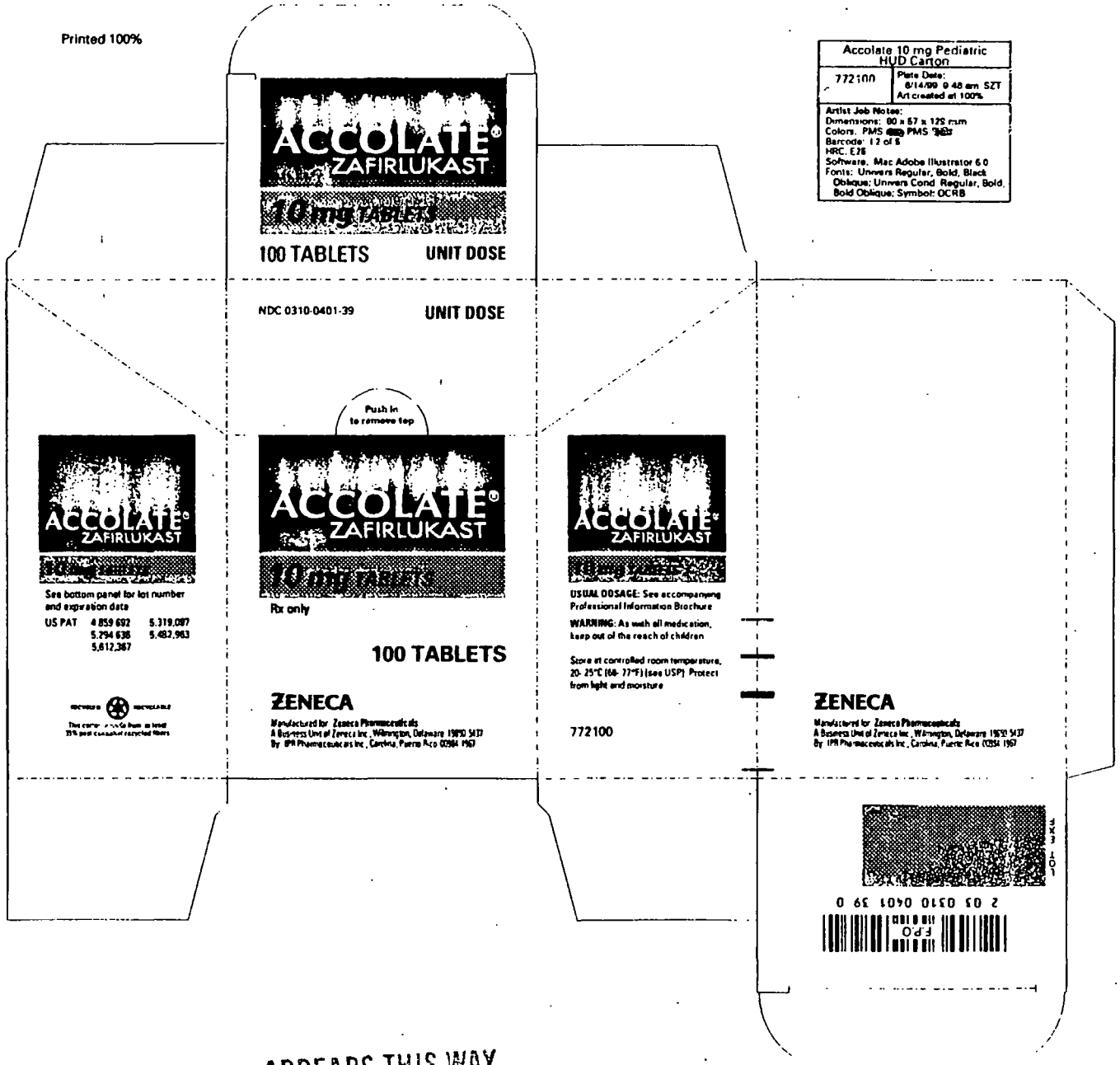
670200 Rev J 09/99

Printed 100%

Accolate 10 mg Pediatric
HUD Carton

772100 | Plate Date: 6/14/99 9:48 am SZT
Art created at 100%

Artist Job Notes:
Dimensions: 80 x 67 x 175 mm
Colors: PMS [redacted] PMS [redacted]
Barcode: I 2 of 5
HRC: E28
Software: Mac Adobe Illustrator 6.0
Fonts: Univers Regular, Bold, Black Oblique; Univers Cond Regular, Bold, Bold Oblique; Symbol; OCRB




APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Labeling: Original
NDA No. 20547 Rc'd. 10-19-97
Reviewed by: ISI 10-28-97

BEST POSSIBLE COPY

# ACCOLATE®
ZAFIRLUKAST

**10 mg TABLETS**

100 TABLETS **UNIT DOSE**

NDC 0310-0401-39 **UNIT DOSE**

ISI
10-28-97

NOV - ? 1997

Push in
to remove top

ACCOLATE®
ZAFIRLUKAST

**10 mg TABLETS**

Rx only

**100 TABLETS**

ZENECA

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

ACCOLATE®
ZAFIRLUKAST

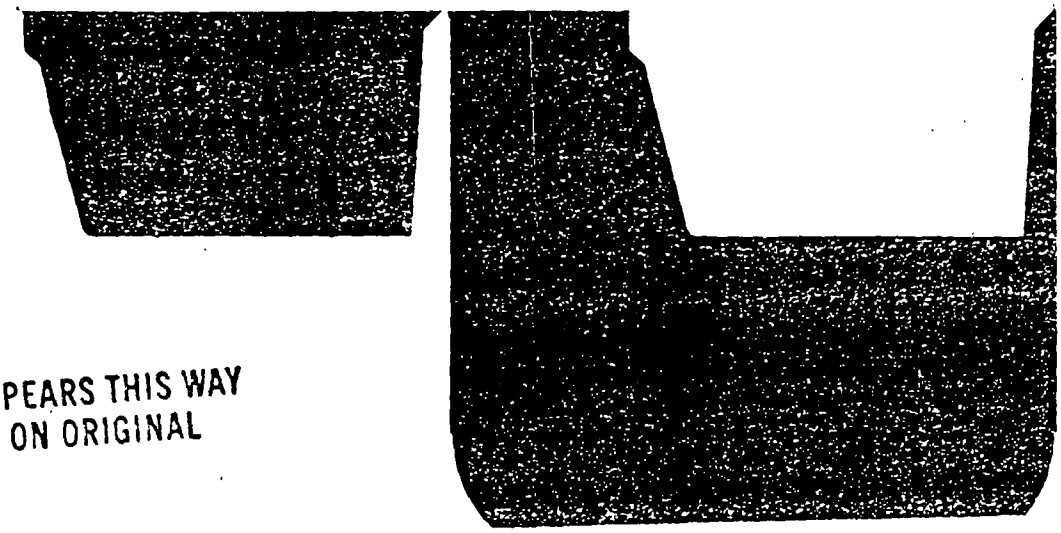
**10 mg TABLETS**

**USUAL DOSAGE:** See accompanying Professional Information Brochure.

**WARNING:** As with all medication, keep out of the reach of children.

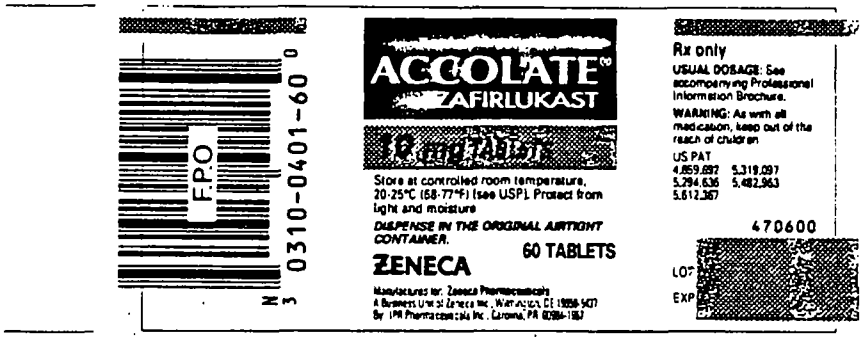
Store at controlled room temperature, 20- 25°C (68- 77°F) [see USP]. Protect from light and moisture.

772100



APPEARS THIS WAY
ON ORIGINAL

# BEST POSSIBLE COPY




| Accolate 10 mg Pediatric Label | |
|---|---|
| 470600 | Plate Date:<br>6/10/99 2:32 pm SZT<br>Art created at 100% |

**Artist Job Notes:**
Dimensions: 1-3/4" x 3-3/4""
Colors: PMS 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

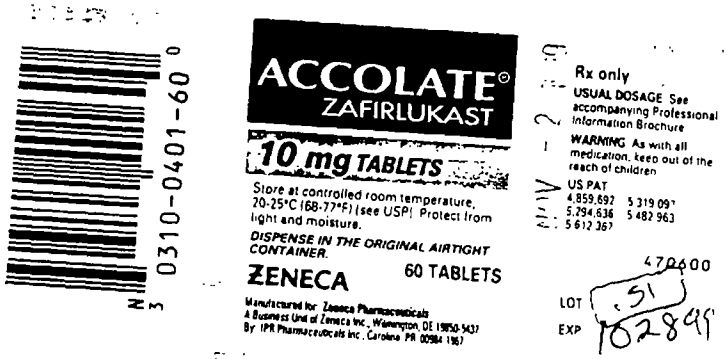
# BEST POSSIBLE COPY


| Accolate 10 mg 10-up Blisters | |
|---|---|
| 870400 | Plate Date:<br>6/14/99 2:45 pm SZT<br>Art created at 100% |

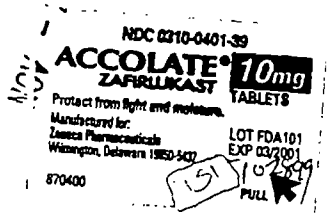
**Artist Job Notes:**
Dimensions: 25 x 37.5 mm ea., 10-up
Colors: Black
Software: Mac Adobe Illustrator 6.0
Fonts: Univers Regular, Bold, Bold Oblique, Black Oblique; Univers Cond. Bold Oblique; Helvetica Regular; Symbol; OCRB

APPEARS THIS WAY
ON ORIGINAL

# BEST POSSIBLE COPY




APPEARS THIS WAY
ON ORIGINAL




Labeling: Original
NDA No. 20547 Rc'd. 10-19-99
Reviewed by: 151 10-28-99

30 **Page(s) Redacted**

Draft

LABELING