PRODUCT MONOGRAPH

Pr ACCOLATE®

(zafirlukast tablets)

Leukotriene Receptor Antagonist

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PRODUCT MONOGRAPH

NAME OF DRUG

Pr ACCOLATE®

(zafirlukast tablets)

Tablets 20 mg

THERAPEUTIC CLASSIFICATION

Leukotriene Receptor Antagonist

ACTIONS AND CLINICAL PHARMACOLOGY

Zafirlukast is a selective and competitive receptor antagonist of leukotriene D_4 and E_4 (LTD_4 and LTE_4). 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 Studies:

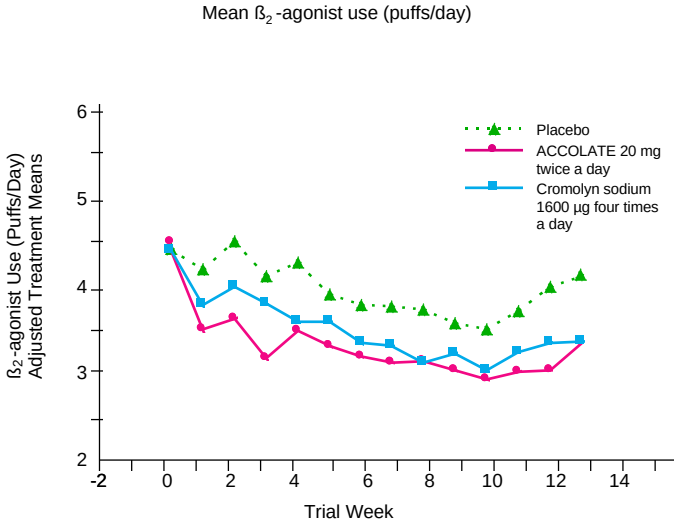
Three double-blind, randomized, placebo-controlled, 13-week clinical trials in 1,380 patients with mild-to-moderate asthma demonstrated that ACCOLATE (zafirlukast) improved daytime asthma symptoms, night time awakenings, mornings with asthma symptoms, rescue beta$_2$-agonist use, FEV_1, and morning peak expiratory flow rate (PEFR). 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 salbutamol 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	**Placebo**
Parameter		**N=514**	**N=248**
Daytime Asthma symptom score	(0-3 scale)	-0.44*	-0.25
Night time Awakenings	(number per week)	-1.27*	-0.43
Mornings with Asthma Symptoms	(days per week)	-1.32*	-0.75
Rescue β_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 sodium cromoglycate 1600 µg four times per day) and superior to placebo at endpoint for decreasing rescue beta-agonist use (figure below).



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.

Pharmacokinetics

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

Plasma kinetics and disposition: The mean terminal elimination half-life of zafirlukast is approximately 10 hours in both normal subjects and patients with asthma. Steady-state plasma concentrations of zafirlukast are proportional to the dose and predictable from single-dose pharmacokinetic data. In the concentration range of 0.25-10 μg/mL, zafirlukast is >99% bound to plasma proteins, predominantly albumin.

Biotransformation: Zafirlukast is extensively metabolized. Following oral administration of a radiolabeled dose, urinary excretion accounts for approximately 10% of the dose and the remainder is excreted in feces. Unmetabolized zafirlukast is not detected in urine. *In vitro* studies using human liver microsomes showed that the hydroxylated metabolites of zafirlukast are formed through the cytochrome P450 2C9 (CYP2C9) enzyme 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 plasma concentrations. The metabolites of zafirlukast found in plasma are at least 90 times less potent as LTD_4 receptor antagonists than zafirlukast in a standard in vitro test of activity.

Special Populations

Elderly: Cross-study comparisons in patients ranging from 7 years to greater than 65 years of age show that mean dose (mg/kg) normalized AUC and C_{max} increase and plasma clearance (CL) decreases with increasing 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.

Hepatic impairment: In a study of patients with hepatic impairment (biopsy-proven cirrhosis), there was a 50-60% greater C_{max} and AUC compared to normal subjects.

Renal impairment: Based on a cross-study comparison, there are no apparent differences in the pharmacokinetics of zafirlukast between renally impaired patients and normal subjects.

INDICATIONS AND CLINICAL USE

ACCOLATE (zafirlukast) is indicated for the prophylaxis and chronic treatment of asthma in adults and children 12 years of age and older.

ACCOLATE should be considered to be an add-on therapy following initial management with an "as needed" short-acting beta-agonist, an inhaled corticosteroid, or inhaled corticosteroid together with a long-acting beta agonist in patients who continue to experience asthma symptoms.

The clinical decision to use ACCOLATE must be based on assessing its risks and benefits for each individual patient.

CONTRAINDICATIONS

ACCOLATE (zafirlukast) is contraindicated in patients who have previously experienced hypersensitivity to the product or any of its ingredients.

ACCOLATE is also contraindicated in patients with hepatic impairment including hepatic cirrhosis and patients in whom ACCOLATE is discontinued due to hepatotoxicity where no other attributable cause is identified.

WARNINGS

ACCOLATE (zafirlukast) is not indicated for use in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus.

Warfarin Interaction: Warfarin coadministration with zafirlukast produces clinically significant increases 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).

Hepatic Effects:

Clinical Trials:

Rarely, elevations of one or more liver enzymes have occurred in patients receiving ACCOLATE in controlled clinical trials. In clinical trials, most of these cases have been observed in asymptomatic patients at doses four times higher than the recommended dose.

Post Marketing Experience:

The reporting rates of adverse events from the post-marketing experience are generally considered to significantly underestimate the incidence of the events.

Elevations in serum transaminases can occur during treatment with ACCOLATE. These were usually asymptomatic and transient but could represent early evidence of hepatotoxicity and have very rarely (less than 1 case / 10,000 patient years) been associated with more severe hepatocellular injury, fulminant hepatitis and liver failure resulting in some cases of liver transplantation and death**. In some post-marketing cases of more severe hepatic injury, no clinical symptoms or signs suggestive of liver dysfunction were reported to precede these observations.** The following hepatic events (which have occurred predominantly in females) have been reported from post-marketing adverse event surveillance of patients who have received the recommended dose of ACCOLATE (40 mg/day): very rare (less than 1 case /

10,000 patient years) cases of symptomatic hepatitis (with or without hyperbilirubinemia) without other attributable cause; and very rarely, hyperbilirubinemia without other elevated liver function tests. In most, but not all, post-marketing reports, the patient's symptoms abated and the liver enzymes returned to normal or near normal after stopping ACCOLATE. **In very rare (less than 1 case / 100,000 patient years) cases, patients have progressed to fulminant hepatitis and/or hepatic failure despite early detection of liver enzyme elevations or signs and symptoms and/or discontinuation of ACCOLATE.**

The table below lists the number and the main outcomes of post-marketing reports of specific hepatic events in patients receiving ACCOLATE through 23 December 2003 only and is not an illustration of any causality assessments of these outcomes. The reports are listed irrespective of pre-existing conditions and/or of concomitant therapies that may have contributed to the outcomes.

Type of Hepatic Event	Number of Reports	Recovered	Resolving / Not fully recovered at the time of the report	Death	Transplant	Unknown
Liver Failure*	14	2	4	5	2 (1 died)	1
Hepatitis**	46	16	22	1	0	7
Other significant liver dysfunction	59	20	20	1	0	18

* Includes 3 reports of fulminant hepatitis that progressed to liver failure; Two of these patients have died and one was not fully recovered at the time of the report.

** Hepatitis includes: hepatitis, hepatitis acute, hepatitis cholestatic, possible autoimmune hepatitis, hepatitis chronic active and chronic hepatitis.

For all patients who are to be treated with ACCOLATE, serum transaminase testing should be done at baseline and periodically during the treatment. However, note that periodic serum transaminase testing has not proven to prevent idiosyncratic liver injury. Particular caution should be used when patients are using a combination of ACCOLATE and concomitant medications known to be hepatotoxic. Such patients should be closely monitored for possible hepatotoxicity.

It is important that physicians be informed and subsequently inform their patients to be alert to the signs and symptoms of hepatic injury [e.g., right upper quadrant abdominal pain (enlarged liver), nausea, vomiting, fatigue, lethargy, pruritus, jaundice, 'flu-like' symptoms, anorexia, dark urine, discoloured and/or pale stools], and to seek immediate medical attention if these signs or symptoms develop. The appearance of signs and symptoms of hepatotoxicity or development of abnormal aminotransferase and/or bilirubin levels while on treatment is an indication for immediate termination of ACCOLATE treatment and close monitoring of patient. The serum transaminases, in particular serum ALT, should be measured immediately and the patient managed accordingly. **In very rare (less than 1 case / 100,000 patient years) cases, patients have progressed to fulminant hepatitis and/or hepatic failure despite early detection of liver enzyme elevations or signs and symptoms and/or discontinuation of**

ACCOLATE. If liver function tests are consistent with hepatic dysfunction, ACCOLATE therapy should not be resumed. Patients in whom ACCOLATE is discontinued due to hepatotoxicity where no other attributable cause is identified, should not be re-exposed to ACCOLATE. ACCOLATE is contraindicated for patients with hepatic impairment including hepatic cirrhosis (see CONTRAINDICATIONS).

PRECAUTIONS

General

ACCOLATE (zafirlukast) tablets should be taken regularly as prescribed, even during symptom-free periods. ACCOLATE therapy can be continued during acute exacerbations of asthma.

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.

Eosinophilic Conditions: In rare cases, patients with asthma on anti-leukotriene medications, including ACCOLATE may present with systemic eosinophilia, eosinophilic pneumonia or clinical features of systemic vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of steroid therapy.

Presentations may involve various body systems including vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. The possibility that leukotriene receptor antagonists, including ACCOLATE, may be associated with the emergence of Churg-Strauss syndrome can neither be excluded nor established. (see ADVERSE REACTIONS).

Hepatic Effects

See WARNINGS.

Pediatric Use

The efficacy and safety of ACCOLATE in children under 12 years has not been established.

Carcinogenesis and Mutagenicity

In two-year oral carcinogenicity studies, zafirlukast was administered at daily doses of 10-300 mg/kg to mice and 40-2000 mg/kg to rats. At 300 mg/kg/day male mice had an increased incidence of hepatocellular adenomas and female mice showed an increased incidence of whole body histocytic sarcomas as compared to concurrent controls. The plasma concentrations at these tumorigenic doses were approximately 220 times maximum recommended human daily oral dose. Male and female rats given 2000 mg/kg/day had an increased incidence of urinary bladder transitional cell papillomas as compared to concurrent controls. The plasma concentrations at these tumorigenic doses were approximately 200 times the plasma concentrations in humans at the maximum recommended human daily oral dose.

The data for both the mouse and rat demonstrate: large safety margins, a clear threshold over the no-effect level, and findings that are applicable or restricted to only one species. Further, ACCOLATE has no evident genotoxic potential. The bladder tumour induction seen in rats and liver tumour induction seen in mice are therefore unlikely to be relevant to humans (see TOXICOLOGY, Carcinogenicity and Mutagenicity).

No mutagenic potential was evident in point mutation assays or chromosomal aberrations clastogenic assays (see TOXICOLOGY, Carcinogenicity and Mutagenicity).

Reproduction and Fertility

Reproduction and fertility studies in rats showed no effect on fertility due to zafirlukast at doses up to 2000 mg/kg (approximately 400 times the maximum recommended human daily oral dose on mg/m^2 basis). In the one-year toxicity studies in dogs, zafirlukast produced an increase in absolute and relative uterine and ovarian weights at an oral dose of 150 mg/kg, resulting in approximately 85 times the systemic exposure ($AUC_{0\text{-}12h}$) in humans at the maximum recommended human oral daily dose.

Use in Pregnancy

The safety of ACCOLATE in human pregnancy has not been established. The potential risks should be weighed against the benefits of continuing therapy during pregnancy; ACCOLATE should be used only if clearly needed.

No teratogenicity was observed in the following species for the given oral doses (the approximate equivalence to the maximum recommended human daily oral dose on a mg/m^2 basis is given in brackets):

mice	1600 mg/kg/day	(160 times)
rats	2000 mg/kg/day	(400 times)
cynomolgus monkeys	2000 mg/kg/day	(800 times)

At these doses, maternal toxicity was manifested in rats (as deaths and increased incidence of early fetal resorption), and cynomolgus monkeys (as spontaneous abortions). 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 (see TOXICOLOGY, Reproduction and Teratology).

Nursing Mothers

Zafirlukast is excreted in human 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.

Geriatric Use

A total of 8,094 patients were exposed to zafirlukast in North American and European short-term placebo-controlled clinical trials. Of these, 243 patients were elderly (age 65 years and older). No overall difference in adverse events was seen in the elderly patients, except for an increase in the frequency of infection among zafirlukast treated elderly patients compared to placebo treated elderly patients (7.0% vs. 2.9%). The infections were not severe, occurred mostly in the lower respiratory tract, and did not necessitate withdrawal of therapy.

An open-label, uncontrolled, 4-week trial of 3759 asthma patients compared the safety and efficacy of Accolate 20 mg given twice daily in three patient age groups, adolescents (12-17 years), adults (18-65 years), and elderly (greater than 65 years). A higher percentage of elderly patients (n=384) reported adverse events when compared to adults and adolescents. These elderly patients showed less improvement in efficacy measures. In the elderly patients, adverse events occurring in greater than 1% of the population included headache (4.7%), diarrhea and nausea (1.8%) and pharyngitis (1.3%). The elderly reported the lowest percentage of infections of all three age groups in this study.

Drug Interactions

ACCOLATE may be administered with other therapies routinely used in the management of asthma and allergy. Examples of agents which have been co-administered with ACCOLATE without adverse interaction include inhaled steroids, inhaled and oral bronchodilator therapy, antihistamines and antibiotics.

Co-administration with:

- erythromycin will result in decreased plasma levels of zafirlukast. 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 40% due to a decrease in zafirlukast bioavailability.

- acetylsalicylic acid (e.g., Aspirin®) may result in increased plasma levels of zafirlukast. Co-administration of zafirlukast (40 mg/day) with acetylsalicylic acid (650 mg four times daily) resulted in mean increased plasma levels of zafirlukast by approximately 45%.

- theophylline may result in decreased plasma levels of zafirlukast, without effect on plasma theophylline levels. 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 resulted in decreased mean plasma levels of zafirlukast by approximately 30%, but no effect on plasma theophylline levels was observed. Paradoxically, post-marketing surveillance revealed rare cases of patients experiencing increased theophylline levels (with or without theophylline toxicity symptoms) when ACCOLATE was co-administered. The mechanism of action for this interaction is unknown.

- warfarin increases prothrombin time by approximately 35%. 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).

- fluconazole, a moderate CYP2C9 and CYP3A4 inhibitor, results in increased plasma levels of zafirlukast. In a drug interaction study in 12 healthy volunteers, co-administration of a single dose of 20 mg zafirlukast with fluconazole 200 mg administered once daily resulted in an increase in the mean AUC (60%) and C_{max} (50%) of zafirlukast.

- itraconazole, a strong CYP3A4 inhibitor, causes no change in plasma levels of zafirlukast as determined in a drug interaction study in 12 healthy volunteers administered a single dose of 20 mg zafirlukast with itraconazole 100 mg administered twice daily.

Oral contraceptives may be administered with ACCOLATE without adverse interaction. 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.

Cytochrome P450 enzyme inhibition: Zafirlukast is metabolized predominantly by CYP2C9 and has been shown to be an inhibitor of CYP3A4 *in vitro.* However, there is data that demonstrate zafirlukast does not inhibit CYP3A4 *in vivo.* Care should be exercised when ACCOLATE is co-administered with cytochrome P450 metabolised drugs such as:

- tolbutamide, phenytoin, carbamazepine (isozyme 2C9)

- dihydropyridine calcium-channel blockers, cyclosporin, cisapride (isozyme CYP 3A4).

Food interaction

ACCOLATE bioavailability may be altered when taken with a meal (see ACTIONS, CLINICAL PHARMACOLOGY, Pharmacokinetics).

ADVERSE REACTIONS

The adverse drug reactions that have been associated with ACCOLATE (zafirlukast) treatment in adults and children (12 years of age and older) are in the table below. Frequencies are based on pooled data from 45 randomized, double-blind, placebo-controlled studies and post-marketing data. The clinical trials involved more than 12, 000 patients treated with either ACCOLATE or placebo.

Frequency	System Organ Class	Reaction
Very Common ≥10% (>1/10)	Infections and Infestations	Infection
Common 1% to 10% (>1/100, <1/10)	Gastrointestinal Disorders	Nausea Vomiting Diarrhoea Abdominal Pain
	Hepatobiliary Disorders	Elevations in transaminase levels
	Musculoskeletal and Connective Tissue Disorders	Myalgia
	Nervous System Disorders	Headache
	Skin and Subcutaneous Tissue Disorders	Rash[1]
Uncommon 0.1% to 1% (>1/1,000, <1/100)	General disorders and administration site conditions	Oedema[1] Malaise[1]
	Immune System Disorders	Hypersensitivity[1]
	Hepatobiliary Disorders	Hyperbilirubinemia
	Musculoskeletal and Connective Tissue Disorders	Arthralgia
	Psychiatric Disorders	Insomnia[1]
	Skin and Subcutaneous Tissue Disorders	Pruritus[1] Urticaria[1]

Frequency	System Organ Class	Reaction
Rare ≥ 0.01% to < 0.1% (>1/10,000, <1/1,000)	Hepatobiliary Disorders	Hepatitis
	Immune System Disorders	Angioedema[1]
	Injury, Poisoning and Procedural Complications	Bruising[1]
	Skin and Subcutaneous Tissue Disorders	Blister[1]
	Blood and lymphatic system disorders	Bleeding disorders[1] (including thrombocytopenia, haemoptysis, haematemesis, haemorrhage and rectal bleeding)
Very rare < 0.01% (<1/10,000)	Blood and lymphatic system disorders	Agranulocytosis[1, 2]
	Hepatobiliary disorders	Fulminant hepatitis[2] Hepatic failure[2]

[1] These reactions have usually resolved following cessation of therapy.
[2] Frequency is based on post-marketing data.

Hepatic Effects: Elevations of one or more liver enzymes have occurred in patients receiving ACCOLATE in controlled clinical trials. In clinical trials, most of these cases have been observed in asymptomatic patients at doses four times higher than the recommended dose. Hepatic events (which have occurred predominantly in females) have been reported from post-marketing adverse event surveillance of patients (total exposure of more than 2.6 million patient years) who have received the recommended dose of ACCOLATE (40 mg/day). Rarely reports of symptomatic hepatitis (with or without hyperbilirubinemia) have been associated with the use of ACCOLATE. In most, but not all, post-marketing reports, the patient's symptoms abated and the liver enzymes returned to normal or near normal after stopping ACCOLATE. In very rare cases, patients have progressed to fulminant hepatitis and/or hepatic failure in some cases resulting in liver transplantation and/or death. (See WARNINGS).

Infections and age: In placebo-controlled clinical trials, an increased incidence of infection has been observed in elderly patients given ACCOLATE. These infections were mostly mild in intensity and predominantly affected the respiratory tract and did not necessitate withdrawal from ACCOLATE therapy.

Eosinophilic Conditions: In rare cases, patients with asthma on anti-leukotriene medications, including ACCOLATE, may present with systemic eosinophilia, eosinophilic pneumonia or

clinical features of systematic vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of steroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. The possibility that leukotriene receptor antagonists, including ACCOLATE, may be associated with the emergence of Churg-Strauss syndrome can neither be excluded nor established.(See PRECAUTIONS).

TREATMENT OF OVERDOSAGE

No deaths occurred at oral zafirlukast doses of 2000 mg/kg in mice (approximately 200 times the maximum recommended human daily oral dose on a mg/m^2 basis), 2000 mg/kg in rats (approximately 400 times the maximum recommended human daily oral dose on a mg/m^2 basis), and 500 mg/kg in dogs (approximately 330 times the maximum recommended human daily oral dose on a mg/m^2 basis).

Reports of overdose with ACCOLATE (zafirlukast) have been received. In reports with excessive ACCOLATE doses, no significant symptoms have been observed. 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.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

DOSAGE AND ADMINISTRATION

ACCOLATE (zafirlukast) 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.

Adults and Children Aged 12 Years and Over

The recommended dose of ACCOLATE is 20 mg, twice daily for a total daily dose of 40 mg.

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

Elderly

The clearance of zafirlukast is reduced in patients 65 years of age and older such that C_{max} and AUC are approximately 2- to 3-fold greater than those of younger patients. However, accumulation of zafirlukast is not evident in elderly patients.

No overall difference in adverse events was seen in the elderly patients, except for an increase in the frequency of infection among zafirlukast treated elderly patients compared to placebo-treated elderly patients (7.0% vs. 2.9%). The infections were not severe, occurred mostly in the lower respiratory tract and did not necessitate withdrawal of therapy. (See also PRECAUTIONS and ACTIONS AND CLINICAL PHARMACOLOGY)

Children

The safety and efficacy in children under 12 years have not been established.

Renal Impairment

Dosage adjustment is not required in patients with renal impairment.

Hepatic Impairment

ACCOLATE is contraindicated in patients with hepatic impairment, including hepatic cirrhosis.

The clearance of zafirlukast is reduced in patients with stable alcoholic cirrhosis such that C_{max} and AUC are approximately 50 - 60% greater than those of normal adults.

PHARMACEUTICAL INFORMATION

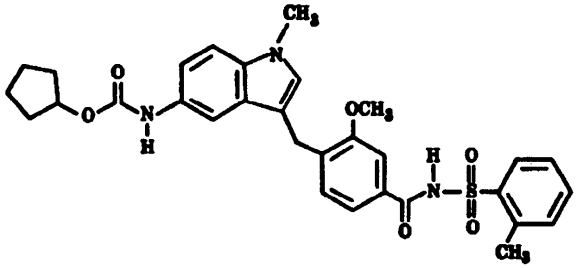
Drug Substance

Trade Name: ACCOLATE®

Proper Name: zafirlukast

Chemical Name: 4-(5-cyclopentyloxycarbonylamino-1-methylindol-3-ylmethyl)-3-methoxy-N-o-tolylsulfonylbenzamide

Structural Formula:



Molecular Formula: $C_{31}H_{33}N_3O_6S$

Molecular Weight: 575.7

Physical Form: White to off-white amorphous powder

Solubility: Practically insoluble in water. Slightly soluble in methanol.

pKa: 5.5 in water with 1% acetonitrile (amorphous form)

Melting Point: 119°C to 199°C (amorphous form)

Composition

Inactive Ingredients: The tablets are film coated and include croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, povidone, magnesium stearate, hypromellose and titanium dioxide.

Stability and Storage Recommendations

Store between 15 and 30°C.

AVAILABILITY OF DOSAGE FORMS

ACCOLATE (zafirlukast) 20 mg tablets are white to off-white, round, biconvex, film-coated tablets. The tablets are intagliated. Available in packs of 60.

PHARMACOLOGY

In Vitro and Animal Pharmacology

Zafirlukast is a potent, selective antagonist of receptors for the cysteinyl leukotrienes, LTC_4, LTD_4, and LTE_4 on human membranes, as demonstrated by direct receptor binding and functional studies in isolated tissues.

In vitro Studies

Zafirlukast competed with binding of the cysteinyl leukotriene receptor agonists $[^3H]LTD_4$ and $[^3H]LTE_4$ in membranes prepared from guinea pig and human lungs, with K_i values of 0.4 nM to 1.4 nM.

Zafirlukast competitively antagonized the contractile activity of both LTD_4 and LTE_4 on guinea pig isolated trachea. Zafirlukast also blocked the activity of LTC_4 in this preparation; however, when the metabolic conversion of LTC_4 to LTD_4 and LTE_4 was inhibited, zafirlukast failed to antagonize LTC_4-induced contractions. In contrast to the effects on guinea pig trachea, zafirlukast blocked the contractile activity of LTC_4 and LTD_4 with similar potency on human isolated bronchial smooth muscle.

Zafirlukast was evaluated in a range of *in vitro* tests in order to assess potential pharmacological actions unrelated to its intended therapeutic use. Concentrations ranged to 10,000 times the concentrations that cause 50% antagonism of the effects of the EC_{50} concentration of exogenous LTD_4. Zafirlukast had no effects at cholinergic, adrenergic, histaminergic or serotonergic receptors at a concentration of 0.1 μM. At 10 μM, zafirlukast caused relaxation of the guinea pig isolated trachea and noncompetitive antagonism of agonist responses in other smooth muscle preparations.

Since this concentration is some 10,000 times that required to antagonize the effects of cysteinyl leukotrienes, these effects are unlikely to be observed after administration to animals or humans.

In vivo Studies

In conscious guinea pigs exposed to an aerosol of LTD_4 to induce dyspnea, zafirlukast exhibited dose-related prolongation of time to dyspnea, when administered orally (0.17 to 0.58 mg/kg). The pharmacologic half-life was 916 min. Oral dosing of Zafirlukast (0.58 mg/kg per day) for 5 days provided no evidence of tolerance.

In studies of leukotriene-induced alterations of pulmonary mechanics in anaesthetized, spontaneously-breathing guinea pigs, zafirlukast in doses of 0.17 to 5.8 mg/kg orally produced significant dose-related antagonism in the i.v. LTC_4, LTD_4, and LTE_4 dose-response curves.

Zafirlukast inhibited LTD_4-induced eosinophil accumulation and tracheal edema in guinea pigs. Increases in pulmonary resistance and decreases in dynamic lung compliance in response to aerosol ovalbumin antigen administered to the guinea pig were prevented as well

as reversed by zafirlukast. Zafirlukast inhibited LTD_4-induced bronchoconstriction and lavagable protein in sheep in a dose-dependent manner. Zafirlukast, administered prior to, 4 hours after, and 24 hours after antigen in Ascaris suum-sensitive sheep, inhibited acute bronchoconstriction, late bronchoconstriction, and nonspecific airways hyper-reactivity.

Zafirlukast was evaluated in a range of *in vivo* tests covering the major physiological systems in order to assess potential pharmacological actions unrelated to its intended therapeutic use. Doses *in vivo* were approximately 10 times the projected therapeutic dose for antagonism of the effects of LTD_4. Zafirlukast was found to be without effect on autonomic, cardiovascular, central nervous system, gastrointestinal, renal, or reproductive function, at doses at least 10 times those effective in pharmacological tests.

Human Pharmacodynamics

The specificity of ACCOLATE (zafirlukast) was shown in clinical studies by its action on leukotriene receptors and not on prostaglandin, thromboxane, cholinergic or histamine receptors. ACCOLATE diminished the airway inflammatory response 48 hours after allergen challenge as demonstrated in a single placebo-controlled trial involving broncho-alveolar lavage following segmental allergen provocation. Compared to placebo, 20 mg of ACCOLATE led to a reduction in basophil ($p<0.01$) and lymphocyte ($p<0.01$) number and histamine release ($p<0.05$) in broncho-alveolar lavage fluid on day 7 of treatment (2 days after allergen challenge). ACCOLATE inhibited superoxide anion production from purified alveolar macrophages on day 7 ($p< 0.01$).

ACCOLATE attenuated the increase in bronchial hyperresponsiveness that follows inhaled allergen challenge and the bronchoconstriction induced by platelet activating factor (PAF). Furthermore, methacholine sensitivity was diminished by long-term dosing with ACCOLATE 20 mg b.i.d.

ACCOLATE shows a dose-dependent inhibition of bronchoconstriction induced by inhaled leukotriene D_4 (LTD_4). ACCOLATE, at recommended doses, enables an asthmatic patient to inhale 100 times more LTD_4 and continues to show significant protection at 12 and 24 hours after a single oral dose. (See also ACTIONS, CLINICAL PHARMACOLOGY.)

TOXICOLOGY

Acute Toxicity

THE LD_{50} values for zafirlukast in acute toxicity studies is summarized below:

Route	Species	Sex	LD_{50} (mg/kg)
Oral	Mouse	Male	> 2000
		Female	> 2000
	Rat	Male	> 2000
		Female	> 2000
	Dog	Male	> 500
		Female	> 500
Intraperitoneal	Mouse	Male	> 100
		Female	> 100
	Rat	Male	> 100
		Female	> 100
Intravenous	Mouse	Male	> 75
		Female	> 75
	Rat	Male	> 60
		Female	> 60

Repeat Dose Toxicity

Zafirlukast was well tolerated in the sub-acute and chronic studies in rats, dogs and mice. Liver enlargement was the most consistent observation and it was much greater in mice than rats and dogs. Hepatic changes in dogs were limited to increased glycogen deposition and, at very high exposures, hepatocyte degeneration.

Microscopic granulomatous infiltrates consisting primarily of enlarged histiocytic cells occurred in a wide range of tissues in dogs. They were not associated with any functional change, were not seen in any other species and were rarely reported in studies of more than six weeks duration. The granulomatous infiltrates may represent an enhancement of a normal macrophage response to inflammatory stimuli in this species.

For adult animals, the no toxic effect dose level after 12 months was 40 mg/kg for dogs and rats which corresponds to an exposure to zafirlukast of $AUC_{(0\text{-}24h)}$ of 50 +/- 12 μg.h/mL for dogs and $AUC_{(3\text{-}24h)}$ of 105 and 155 μg.h/mL for male and female rats respectively. These exposures afford a safety margin of approximately 20-fold over the $AUC_{(0\text{-}24h)}$ of 2.51 μg.h/mL for 20 mg ACCOLATE (zafirlukast) bid in humans.

Carcinogenicity and Mutagenicity

In two-year carcinogenicity studies, zafirlukast was administered at oral daily 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 of zafirlukast had a greater incidence of hepatocellular adenomas as compared to concurrent controls; female mice at this dose showed a greater incidence of whole body

histocytic sarcomas. Male and female rats given 2000 mg/kg/day of zafirlukast had a greater incidence of urinary bladder transitional cell papillomas as compared to concurrent controls. Pharmacokinetic data show that the plasma concentrations in mice at non-tumorigenic (100 mg/kg) and tumorigenic (300 mg/kg) doses of zafirlukast were approximately 70 times and 220 times, respectively, the plasma concentrations at the maximum recommended human daily oral dose. For rats, plasma concentrations at the non-tumorigenic (400 mg/kg) and tumorigenic (2000 mg/kg) doses of zafirlukast were approximately 170 times and 200 times, respectively, the plasma concentrations in humans at the maximum recommended human daily oral dose. The clinical significance of these findings for the long-term use of ACCOLATE is unknown.

In mutagenicity studies, there was no evidence of mutagenic potential in reverse (*S. typhimurium and E. coli*) or forward point mutation (CHO-HGPRT) assays or in two assays for chromosomal aberrations (human peripheral blood lymphocyte clastogenesis assay and the rat bone marrow erythrocyte micronucleus assay).

Reproduction and Teratology

No teratogenicity was observed at oral doses up to 1600 mg/kg/day in mice (approximately 160 times the maximum recommended human daily oral dose on a mg/m^2 basis), 2000 mg/kg/day in rats (approximately 400 times the maximum recommended human daily oral dose on a mg/m^2 basis) and 2000 mg/kg/day in cynomolgus monkeys (approximately 800 times the maximum recommended human daily oral dose on a mg/m^2 basis). At 2000 mg/kg/day 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 orally. 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.

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IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

Pr ACCOLATE®

zafirlukast tablets

This leaflet is part III of a three-part "Product Monograph" published when ACCOLATE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ACCOLATE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

REMEMBER: This medicine was prescribed only for **YOU**. Only a doctor knows who can use it safely. Never give it to someone else. It may harm them, even if their symptoms are the same as yours.

WHAT THE MEDICATION IS USED FOR:
ACCOLATE is used to control asthma symptoms, and prevent asthma from getting worse in adults and children 12 years and older.

ACCOLATE should be used as an add-on therapy to your current treatment for asthma (such as fast-acting relief medications or inhaled corticosteroids).

WHAT IT DOES:
ACCOLATE is a leukotriene receptor antagonist that blocks substances called leukotrienes. Leukotrienes cause a narrowing and swelling of airways in your lungs which results in asthma symptoms. Blocking leukotrienes improves asthma symptoms and helps prevent asthma attacks.

Improvement in your asthma symptoms should occur within one week of starting treatment with ACCOLATE. The effects of ACCOLATE last for up to 12 hours. Regular ACCOLATE use will help to control your symptoms.

WHEN IT SHOULD NOT BE USED:
You should not take ACCOLATE if you:
- Are allergic to zafirlukast or any of the ingredients in ACCOLATE tablets.
- Have problems with your liver.

WHAT THE MEDICINAL INGREDIENT IS:
zafirlukast

WHAT THE NONMEDICINAL INGREDIENTS ARE:
Film coated tablet: croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and titanium dioxide.

WHAT DOSAGE FORMS IT COMES IN:
Tablet: 20 mg

WARNINGS AND PRECAUTIONS

ACCOLATE is not for the treatment of asthma attacks.
ACCOLATE does not act quickly enough to be used as a relief medication. If you get a sudden attack of wheezing and breathlessness between doses of ACCOLATE, you should take one or two puffs from a fast-acting relief medication (e.g., terbutaline, salbutamol) that your doctor has given you.

Remember, if you have an attack that does not get better when you take the relief medication you should see your doctor right away. You may need emergency treatment.

You should tell your doctor as soon as possible if you:
- are getting more attacks of wheezing, breathlessness or chest tightness,
- are using an increasing amount of fast-acting relief medication,
- start to wake up at night with chest tightness, wheezing or shortness of breath.

Before using ACCOLATE, tell your doctor if:
- you suffer from liver problems;
- you are taking warfarin (blood thinner);
- you are pregnant, planning to become pregnant or breastfeeding.

If you go into hospital, let the medical staff know that you are taking ACCOLATE.

INTERACTIONS WITH THIS MEDICATION

BEFORE you use ACCOLATE, make sure your doctor knows about **all** other medicines you are taking (**including non-prescription or over the counter products**), especially blood thinners (warfarin), allergy medications, acetylsalicylic acid (Aspirin), antibiotics, antifungals and theophylline. This list is not complete and ACCOLATE may also interact with other medications.

PROPER USE OF THIS MEDICATION

Follow your doctor's instructions about when and how to take your tablets. Please READ THE LABEL on the package. Ask your doctor or pharmacist if you are not sure.

DO NOT stop taking or lower the amount of any other asthma medications you are taking while taking ACCOLATE unless instructed by your doctor.

USUAL DOSE:
For patients 12 years of age and older, the usual treatment with ACCOLATE is 20 mg (one tablet) twice daily (in the morning and evening).

- Swallow each tablet whole with a full glass of water.
- Do not take your tablet(s) with a meal (at least 1 hour before or 2 hours after meals).
- Try to take your medicine at the same times each day.

Using ACCOLATE twice a day, regularly, is very important. Your tablets come in blister cards of 10. All tablets in each card are the same. To help you remember your schedule, blisters are labelled with 2 spots per day, (a.m. and p.m.). You can start ACCOLATE at any time. When starting a card, note the day and time you took the tablet. Take your next tablet approximately 12 hours later, punching out the tablet that corresponds with the time (a.m. or p.m.). As you get to the end of your last card, call your pharmacist for a refill, preferably before using the last four tablets.

REMEMBER: ACCOLATE should be taken regularly. Do not stop taking your tablets even if you are feeling well, unless your doctor tells you.

OVERDOSE:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

MISSED DOSE:
If you forget to take a dose, do not worry. Take another tablet as soon as you remember. **BUT** if it is near the time for the next dose, wait until this dose is due. Then go on as before. **Do not take a double dose.**

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like any medication, ACCOLATE may cause side effects in some people. Tell your doctor or pharmacist if any of the following side effects bothers you, continues or gets worse:

The common side effects reported were:

- Nausea, vomiting, diarrhoea, stomach pain
- Muscle pain
- Rash
- Headache
- Infections (including respiratory infections)

Less common side effects reported were:

- Feelings of discomfort or of being unwell
- Swelling
- Blisters
- Pain in the joints
- Itching
- Sleeping difficulties (insomnia)

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
	Only if severe	In all cases	
Uncommon (frequency of 1 to 10 in 1,000 patients)			
Symptoms of allergic reactions such as swelling of the face, lips, tongue, and/or throat (which may cause difficulty in breathing or swallowing), hives, rash, and itching			X
Rare (frequency of 1 to 10 in 10,000 patients)			
Inflammation of the liver (hepatitis).–Symptoms may include: nausea, vomiting, tired or lack of energy, flu-like symptoms, loss of appetite, itching, pain on the right side of your stomach (just below your ribs), yellowing of the skin and eyes (jaundice), dark urine, and discoloured and/or pale stools.			X
Increased bleeding tendency or bruising		X	
Churg-Strauss syndromes: a flu-like illness, rash, pins and needles or numbness of arms or legs, joint pain and severe sinusitis and worsening lung or breathing problems.			X
Very Rare (frequency of less than 1 in 10,000)			

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
	Only if severe	In all cases	
Severe liver injury, including liver failure (which may result in liver transplantation or death). Symptoms may include: nausea, vomiting, tired or lack of energy, flu-like symptoms, loss of appetite, itching, pain on the right side of your stomach (just below your ribs), yellowing of the skin and eyes (jaundice), dark urine, and discoloured and/or pale stools.			X
Low white blood cell count. Symptoms may include: an increased risk of infection, as shown by a sudden fever, sore throat, chills, or mouth ulcers.			X

This is not a complete list of side effects. For any unexpected effects while taking ACCOLATE, contact your doctor or pharmacist.

HOW TO STORE IT

Keep out of reach and sight of children.

You should store your tablets between 15 and 30°C (room temperature). Keep your tablets in the original package.

If your doctor decides to stop your treatment, return your tablets to the pharmacist for disposal.

Do not take your tablets after the expiry date on the package.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found at:
www.astrazeneca.ca,
or by contacting the sponsor, AstraZeneca Canada Inc. at:
Customer Inquiries – 1 (800) 668-6000,
Renseignements – 1 (800) 461-3787.

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