Zafirlukast is a leukotriene receptor antagonist (LTRA), with the chemical name 4-(5-
1H-indol-3-yl)-3,4-dihydro-2H-1,4-benzoxazin-2-one. This medication is approved for the 
treatment of asthma symptoms, nighttime awakenings, mornings with asthma demonstrated 
that ACOLATE improved daytime lung function (FEV1) at 24-hour post-dosing.

**Clinical Pharmacology**

Absorption: Peak plasma concentrations are generally achieved within 3 hours 
after oral administration. The apparent steady-state volume of distribution predominantlj 
albumin. The degree of binding was approximately 40%.

Distribution: The apparent oral clearance of zafirlukast decreases with age. In 
patients above 65 years of age, reduced clearance of zafirlukast resulting in a 50-60% 
lower Cmax and AUC compared to normal subjects. No differences in the 
pharmacokinetics of zafirlukast due to race have been observed.

Excretion: Zafirlukast is extensively metabolized. The most common metabolites 
are hydroxylated metabolites which are excreted in the feces. The total 
excretion is approximately 8 to 16 hours in both normal subjects and volunteers, 
urinary excretion accounts for approximately 45%.

Following oral administration of radiolabeled zafirlukast to healthy male and 
female volunteers, urinary excretion accounts for approximately 45%.

Mean Cmax and AUC values for zafirlukast 20 mg administered following single 
dose administration to male volunteers (n=36) are shown with the table below.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Variation</th>
<th>Coefficient of Variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>756 (39%)</td>
<td>601 (45%)</td>
</tr>
<tr>
<td>AUC (ng•h/mL)</td>
<td>2458 (34%)</td>
<td>2027 (48%)</td>
</tr>
</tbody>
</table>

### Special Populations

- **Elderly:** The apparent oral clearance of zafirlukast decreases with age. In 
patients above 65 years of age, reduced clearance of zafirlukast resulting in a 50-60% 
lower Cmax and AUC compared to normal subjects. No differences in the 
pharmacokinetics of zafirlukast due to race have been observed.
- **Children:** Following administration of a single 20 mg oral dose of 
zafirlukast to children 5-11 years of age, resulted in decreased mean plasma 
concentration and AUC compared to adults, a dose of 10 mg twice daily is recom-
mended in children 5-11 years of age.
- **Race:** No differences in the pharmacokinetics of zafirlukast were 
observed between races.

### Interactions

- **Drug Interactions:** Pulmonary irritants, such as ethinyl estradiol (oral contraceptives), 
during acute exacerbations of asthma.
- **Coadministration of a single dose of zafirlukast 40 mg with erythromycin (500 mg three times 
daily) to healthy male volunteers resulted in no significant effect on ethinyl estradiol 
release and a small increase in mean AUC (+37%).
- **Concomitant Steroid Administration:** In a second and smaller study, the effect of 
ACOLATE (20 mg twice daily) on the pharmacokinetics of dexamethasone was 
investigated in 11 asthmatic patients, 18 to 44 years of age, who were taking 
a constant dose of inhaled beclomethasone dipropionate. The pharmacokinetics of 
dexamethasone were unaffected by the concomitant administration of ACOLATE.

### WARNINGS

- **Clinical Importances:** The role of ACOLATE in the management of asthma symptoms, nighttime 
awakenings, mornings with asthma demonstrated that ACOLATE improved daytime 
lung function (FEV1) at 24-hour post-dosing.

### Adverse Reactions

- **Hypersensitivity Reactions:** Patients should be told that a rare side effect of 
ACOLATE is anaphylaxis, which is usually associated with cross-reactivity. 
If such reactions are suspected, patients should seek immediate medical attention.

### Nursing Mothers

- **Nursing Mothers:** Nursing mothers should be instructed not to breast-feed 
while taking ACOLATE, as it is not known whether the drug is excreted in 
maternal milk. If the patient is breast-feeding, they should be advised to 
choose another method of contraception.

### Precautions

- **Information for Patients:** Patients should be advised to be alert for signs 
and symptoms of liver dysfunction (eg, right upper quadrant abdominal pain, 
astryx, nausea, fatigue, lethargy, pruritus, jaundice, flu-like symptoms) and to 
consult their physician immediately if they experience symptoms of 
hepatic dysfunction (eg. right upper quadrant abdominal pain, fatigue, 
nausea, jaundice, flu-like symptoms). If liver dysfunction is suspected based 
upon clinical signs and symptoms, the suspect drug should be withdrawn 
from post-marketing adverse event surveillance of patients attributable cause 
is identified should not be re-exposed to the drug.

### Drug Information

- **Contraindications:** ACOLATE is contraindicated in patients who are 
hypersensitive to zafirlukast or any of its inactive ingredients.

### Administration

- **Dosage and Administration:** ACOLATE is supplied as 10 and 20 mg tablets for oral 
dosage. The tablets should be swallowed whole and should be taken at least 1 hour 
before or 2 hours after a meal. The tablets should be stored at room temperature.

- **Adults:** The recommended dosage is 10 mg twice daily, taken at 
least 1 hour before or 2 hours after meals. The dosage may be 
increased to 20 mg twice daily if necessary.

- **Children:** Following administration of a single 20 mg oral dose of 
zafirlukast to children 5-11 years of age, resulted in decreased mean plasma 
concentration and AUC compared to adults, a dose of 10 mg twice daily is recom-
mended in children 5-11 years of age (see DOSAGE AND 
ADMINISTRATION).

The role of ACOLATE in the management of asthma symptoms, nighttime 
awakenings, mornings with asthma demonstrated that ACOLATE improved daytime 
lung function (FEV1) at 24-hour post-dosing.
the clearance of zafirlukast is reduced in elderly patients.

In mouse and rat studies, the enhanced levels in breast milk were 50 ng/mL compared to 255 ng/mL in healthy patients at doses equal to or higher than the recommended dose.

A comparison of adverse events reported by adults and children revealed a higher percentage of adverse events in the elderly groups, adolescents (12-17 years), adults (18-65 years), and elderly (greater than 65 years). A higher percentage of infections were seen in the elderly patients, except for adverse events in the respiratory tract and did not necessitate withdrawal of therapy.

Overdosage with ACCOLATE has been reported in four children, one adult, and one teenager. There were no deaths observed at oral zafirlukast doses of up to 1600 mg/kg/day in mice and rats. A single 25 mg dose of warfarin resulted in a significant inhibition by zafirlukast of the cytochrome P450 2C9 isoenzyme (e.g., tolbutamide).

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Hepatocellular adenomas were induced in female mice and pituitary tumors were induced in male mice at the maternally toxic oral dose of 2000 mg/kg/day. There were no deaths observed at oral zafirlukast doses of up to 1600 mg/kg/day in mice and rats.

In rare cases, patients on ACCOLATE therapy may present with systemic eosinophilia, vasculitic rash, hypocomplementemia, and/or neuropathy presenting in their patients. A causal relationship between zafirlukast and these conditions has not been established.

Physicians should be alert to eosinophilia, vasculitic rash, hypocomplementemia, and/or neuropathy presenting in their patients. A causal relationship between zafirlukast and these conditions has not been established.

The safety and effectiveness of zafirlukast for acute exacerbations of asthma in pediatric patients 5 through 11 years of age is 10 mg twice daily.