



**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, zafirlukast should not be administered to mothers who are breast-feeding.

**Pediatric Use:**

The safety of zafirlukast at doses of 10 mg twice daily has been demonstrated in 205 pediatric patients 5 through 11 years of age 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 zafirlukast for the prophylaxis and chronic treatment of asthma in pediatric patients 5 through 11 years of age is based on an extrapolation of the demonstrated efficacy of zafirlukast 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 5 through 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 safety and effectiveness of zafirlukast for pediatric patients less than 5 years of age has not been established. The effect of zafirlukast on growth in children has not been determined.

**Geriatric Use:**

Based on cross-study comparison, the clearance of zafirlukast is reduced in patients 65 years of age and older such that C<sub>max</sub> and AUC are approximately 2- to 3-fold greater than those of younger patients (see  **DOSAGE AND ADMINISTRATION** and  **CLINICAL PHARMACOLOGY**).

A total of 8094 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 infections 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 zafirlukast 20 mg given twice daily in three patient age groups, adolescents (12 to 17 years), adults (18 to 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.

#### ADVERSE REACTIONS

**Adults and Children 12 years of age and older**

The safety database for zafirlukast consists of more than 4000 healthy volunteers and patients who received zafirlukast, of which 1723 were asthmatics enrolled in trials of 13 weeks duration or longer. A total of 671 patients received zafirlukast 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 zafirlukast.

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.

<b>Adverse Event</b>	<b>Zafirlukast N=4058</b>	<b>Placebo N=2032</b>
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 zafirlukast and placebo.

Rarely, elevations of one or more liver enzymes have occurred in patients receiving zafirlukast in controlled clinical trials. In clinical trials, most of these have been observed at doses four times higher than the recommended dose. The following hepatic events (which have occurred predominantly in females) have been reported from postmarketing adverse event surveillance of patients who have received the recommended dose of zafirlukast (40 mg/day): cases of symptomatic hepatitis (with or without hyperbilirubinemia) without other attributable cause; and 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 zafirlukast. In rare cases, patients have presented with fulminant hepatitis or progressed to hepatic failure, liver transplantation and death (see  **WARNINGS, Hepatototoxicity** and  **PRECAUTIONS, Information for Patients**)

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 with asthma on zafirlukast may present with systemic eosinophilia, eosinophilic pneumonia, or clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic steroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. These events have usually, but not always, been associated with reductions and/or withdrawal of steroid therapy. The possibility that zafirlukast may be associated with emergence of Churg-Strauss syndrome can neither be excluded nor established (see  **PRECAUTIONS, Eosinophilic Conditions**).

Neuropsychiatric adverse events, including insomnia and depression, have been reported in association with zafirlukast therapy (see  **PRECAUTIONS, Neuropsychiatric Events**). Hypersensitivity reactions, including urticaria, angioedema and rashes, with or without blistering, have also been reported in association with zafirlukast therapy. Additionally, there have been reports of patients experiencing agranulocytosis, bleeding, bruising, or edema, arthralgia, myalgia, malaise, and pruritus in association with zafirlukast therapy.

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

**Pediatric Patients 5 through 11 years of age**

Zafirlukast has been evaluated for safety in 788 pediatric patients 5 through 11 years of age. Cumulatively, 313 pediatric patients were treated with zafirlukast 10 mg twice daily 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 zafirlukast 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 zafirlukast 20 mg twice daily.

In pediatric patients receiving zafirlukast 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%).

The post-marketing experience in this age group is similar to that seen in adults, including hepatic dysfunction, which may lead to liver failure.

#### OVERDOSAGE

No deaths occurred at oral zafirlukast doses of 2000 mg/kg in mice (approximately 210 times the maximum recommended daily oral dose in adults and children on a mg/m² basis), 2000 mg/kg in rats (approximately 420 times the maximum recommended daily oral dose in adults and children on a mg/m² basis), and 500 mg/kg in dogs (approximately 350 times the maximum recommended daily oral dose in adults and children on a mg/m² basis).

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

Because food can reduce the bioavailability of zafirlukast, zafirlukast should be taken at least 1 hour before or 2 hours after meals.

**Adults and Children 12 years of age and older**

The recommended dose of zafirlukast in adults and children 12 years and older is 20 mg twice daily.

**Pediatric Patients 5 through 11 years of age**

The recommended dose of zafirlukast in children 5 through 11 years of age is 10 mg twice daily.

**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<sub>max</sub> 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**

Zafirlukast is contraindicated in patients with hepatic impairment including hepatic cirrhosis (see  **CONTRAINDICATIONS**). The clearance of zafirlukast is reduced in patients with stable alcoholic cirrhosis such that the C<sub>max</sub> and AUC are approximately 50 to 60% greater than those of normal adults. Zafirlukast 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

**Zafirlukast 10 mg Tablets**, (NDC 49884-549-02) white, round, biconvex, film-coated tablets debossed with “P” on one side and “10” on the other, are supplied in opaque HDPE bottles of 60 tablets.

**Zafirlukast 20 mg Tablets**, (NDC 49884-554-02) white, round, biconvex, film-coated tablets debossed with “P” on one side and “20” on the other, are supplied in opaque HDPE bottles of 60 tablets.

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

#### PATIENT INFORMATION

##### Zafirlukast Tablets

Read the Patient Information leaflet before you start taking zafirlukast and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

**What is Zafirlukast?**

Zafirlukast is a prescription medicine used to help prevent asthma attacks and for the long-term treatment of asthma symptoms in adults and children 5 years and older.

It is not known if zafirlukast is safe and effective when used in children under 5 years old. The effect of zafirlukast on growth in children has not been determined.

Do not take zafirlukast if you need relief right away for a sudden asthma attack. If you get an asthma attack, you should follow the instructions your healthcare provider gave you for treating asthma attacks.

**Who should not take Zafirlukast?**

Do not take zafirlukast if you:

- are allergic to zafirlukast or any of the ingredients in zafirlukast. See the end of this leaflet for a complete list of ingredients in zafirlukast.
- have problems with your liver.

**What should I tell my healthcare provider before taking Zafirlukast?**

**Before you take Zafirlukast, tell your healthcare provider if you:**

- have liver problems
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if zafirlukast will harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. Zafirlukast can pass into your milk; it is not known whether zafirlukast may harm your baby. Women who are breastfeeding should not take zafirlukast.

**Tell your healthcare provider about all the medicines you take**, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Zafirlukast may affect the way other medicines work, and other medicines may affect how zafirlukast works.

**Especially tell your healthcare provider if you take:**

- warfarin sodium (Coumadin, Jantoven)
- erythromycin (ERYC, ERY-TAB, PCE)
- theophylline (Elixophyllin, Theo-24, Theochron, Theolair, Uniphyll)
- fluconazole (Diflucan)

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

**How should I take Zafirlukast?**

- Take zafirlukast exactly as your healthcare provider tells you to take it.
- Take zafirlukast regularly, even if you do not have asthma symptoms. Do not change your dose or stop taking zafirlukast without talking to your healthcare provider.
- Do not stop taking or change the dose of your other asthma medicines unless your healthcare provider tells you to.
- Take your prescribed dose of zafirlukast by mouth at least 1 hour before or 2 hours after meals.
- Zafirlukast does not treat the symptoms of a sudden asthma attack. Always have a short-acting beta<sub>2</sub>-agonist medicine (rescue inhaler) with you to treat sudden symptoms. If you do not have a rescue inhaler medicine, talk to your healthcare provider to have one prescribed for you.
- If you take too much zafirlukast, call your healthcare provider or go to the nearest hospital emergency room right away.

**What are the possible side effects of Zafirlukast?**

**Zafirlukast may cause serious side effects, including:**

- Severe liver problems.** In some cases, these liver problems can lead to liver failure, the need for a liver transplant or death. Tell your healthcare provider right away if you have:
  - pain or tenderness in the right upper side of your stomach area (abdomen)
  - nausea
  - tiredness
  - itchiness
  - yellowing of your skin or the whites of your eyes
  - flu-like symptoms
  - loss of appetite
  - dark (tea colored) urine
- Inflammation of your blood vessels.** Rarely, this can happen in people with asthma who take zafirlukast. This usually, but not always, happens in people who also take a steroid medicine by mouth that is being stopped or the dose is being lowered. Tell your healthcare provider right away if you have:
  - a feeling of pins and needles or numbness of your arms or legs
  - flu like symptoms
  - rash
  - pain and swelling of your sinuses
- Changes in behaviour or mood.** Tell your healthcare provider if you have changes in your behaviour, problems sleeping or feel very sad.
- Hypersensitivity reactions.** Tell your healthcare provider if you have severe itching, breathing problems, skin rash, skin blisters, or skin redness, or swelling.

The most common side effects of zafirlukast in people 12 years and older include:

- headache
- infection
- nausea
- diarrhea
- pain (generalized)

The most common side effects of zafirlukast in children 5 to 11 years include:

- headache
- stomach pain

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of zafirlukast. For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Par Pharmaceutical at 1-800-828-9393.

**How should I store Zafirlukast?**

- Store zafirlukast at 68°F to 77°F (20°C to 25°C ).
- Keep zafirlukast tablets dry.
- Keep zafirlukast in a tight closed container and keep zafirlukast out of the light.
- Keep zafirlukast and all medicines out of the reach of children.

**General information about the safe and effective use of Zafirlukast.**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use zafirlukast for a condition for which it was not prescribed. Do not give zafirlukast to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about zafirlukast. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about zafirlukast that is written for healthcare professionals.

For more information, go to www.parpharm.com, or call 1-800-828-9393.

**What are the ingredients in Zafirlukast?**

**Active ingredient:** zafirlukast

**Inactive ingredients:** croscarmellose sodium, lactose, magnesium stearate, microcrystalline cellulose, povidone, hypromellose, and titanium dioxide.

**What do Zafirlukast tablets look like?**

- the 10 mg tablet is white and round with “P” marked on one side, and “10” on the other.
- the 20 mg tablet is white and round with “P” marked on one side, and “20” on the other.

	<p>Manufactured by: <b>Par Pharmaceutical</b> Chestnut Ridge, NY 10977</p>	
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