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Zafirlukast

A Review of its Pharmacology and Therapeutic Potential in the Management of Asthma

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Synopsis

Zafirlukast is a competitive and selective leukotriene receptor antagonist indicated for the prophylaxis and treatment of chronic asthma. The rationale for the development of leukotriene antagonists was based on in vitro *and* in vivo *data demonstrating the extensive role of the cysteinyl leukotrienes C_4 (LTC_4), D_4 (LTD_4) and E_4 (LTE_4) in the pathogenesis of asthma.*

Initial data have demonstrated an improvement in pulmonary function and symptom control and a reduction in the use of short-acting inhaled β_2-adrenoceptor agonist therapy in patients with mild to moderate asthma treated with oral zafirlukast at the recommended dosage of 20mg twice daily. Available data also suggest that zafirlukast may significantly reduce the incidence of asthma exacerbations.

Data on the comparative efficacy of zafirlukast and existing antiasthma medications are limited. Results from 2 double-blind randomised studies comparing zafirlukast 20mg twice daily with sodium cromoglycate aerosol or dry powder inhalation reported similar efficacy for both drugs. In a comparison with inhaled beclomethasone dipropionate (0.2 to 0.25mg twice daily), improvements in morning peak expiratory flow rate, forced expiratory volume in 1 second and daytime symptom score were significantly less with zafirlukast 20mg twice daily for 6 weeks. However, available data suggest that patient compliance and patient preference may be greater with oral zafirlukast 20mg twice daily than with twice-daily inhaled corticosteroid therapy.

Confounding results from 2 studies preclude any clear conclusions regarding the potential steroid-sparing effect of zafirlukast at the recommended dosage of 20mg twice daily. Furthermore, Churg-Strauss syndrome has been reported in 6 patients who were being withdrawn from oral corticosteroid therapy while receiving treatment with oral zafirlukast. It is, therefore, recommended that zafirlukast-treated patients who require a reduction in their oral corticosteroid therapy are closely monitored.

Zafirlukast is generally well tolerated. Reports of elevated liver enzymes in patients receiving high dosages of zafirlukast (80mg twice daily) preclude the use of dosages exceeding 40mg twice daily. Careful monitoring is necessary in zafirlukast-treated patients receiving concomitant therapy with drugs such as warfarin, terfenadine and erythromycin because of the potential for drug interactions.

Thus, zafirlukast is a potentially useful addition to current antiasthma therapies in patients with mild to moderate asthma. Because zafirlukast is administered orally, it may be particularly beneficial in patients poorly compliant with asthma therapy as a result of poor inhaler technique. Further investigation of the efficacy of zafirlukast is expected to more clearly define its position in the management of asthma.

Pharmacodynamic Properties

The cysteinyl leukotrienes C_4 (LTC_4), D_4 (LTD_4) and E_4 (LTE_4) are important inflammatory mediators clearly implicated in the pathogenesis of asthma. Zafirlukast is a competitive inhibitor of LTD_4 and LTE_4. *In vitro*, zafirlukast antagonised the contractile response of guinea-pig and human airway smooth muscle to LTD_4 and LTE_4 and competitively inhibited the binding of LTD_4 and LTE_4 to guinea-pig lung parenchymal membrane. Zafirlukast is selective for cysteinyl leukotriene receptors and demonstrated minimal affinity for a variety of

other receptor types, including α- and β-adrenoceptors and muscarinic receptors in isolated tissue.

In vivo, zafirlukast antagonised the pulmonary effects of LTC_4 and LTD_4 and showed potential anti-inflammatory activity in guinea-pig airways with inhibition of the eosinophil chemotactic responses to LTC_4, LTD_4 and LTE_4 and a reduction in LTD_4-induced oedema.

Bronchial challenge studies in humans have demonstrated the protective efficacy of oral zafirlukast against bronchoconstriction induced by various stimuli, including LTD_4, exercise and cold air. Similarly, oral administration of zafirlukast showed protective efficacy relative to placebo against the early and late bronchoconstrictive response to allergen challenge. Zafirlukast has also been reported to reduce cellular infiltration into the airways after allergen challenge. However, further investigations are necessary to clearly determine the extent of the protection conferred by zafirlukast against increased bronchial hyperresponsiveness associated with the late phase response.

Pharmacokinetic Properties

The pharmacokinetics of zafirlukast are best described by a 2-compartment model. Maximum plasma concentrations (C_{max}) were achieved 3 hours after single-dose oral administration of zafirlukast 20 or 40mg to healthy volunteers. The absolute bioavailability of zafirlukast is unknown; however, coadministration with food produced an approximately 40% reduction in the bioavailability of the drug. The drug binds extensively to plasma proteins (>99%), predominantly to albumin and has a mean terminal elimination half-life of approximately 10 hours in both healthy volunteers and patients with asthma.

Zafirlukast undergoes extensive hepatic metabolism. Hydroxylation by cytochrome P450 CYP2C9 is the major biotransformation pathway for the drug. The metabolites of zafirlukast appear to contribute little to its overall activity. The faeces are the main route of elimination, with urinary excretion accounting for <10% of an orally administered dose.

Because hepatic metabolism is extensive, clearance of zafirlukast is reduced in patients with hepatic impairment. In patients with stable alcoholic cirrhosis, the C_{max} and area under the plasma concentration-time curve for zafirlukast were increased by 50 to 60% compared with healthy volunteers.

Inhibition of the cytochrome P450 CYP2C9 and CYP3A isoenzymes by zafirlukast has been reported *in vitro*. Because there is the potential for drug interactions to occur with other agents which compete for these enzymes, appropriate clinical monitoring is required when zafirlukast is coadministered with these agents. Zafirlukast interacts with warfarin to produce a clinically significant increase in prothrombin time but it does not significantly alter the pharmacokinetic profile of terfenadine carboxylate, the active metabolite of terfenadine. Plasma concentrations of zafirlukast decreased when the drug was administered concomitantly with erythromycin, theophylline or terfenadine and increased when it was coadministered with aspirin.

Therapeutic Potential

The therapeutic efficacy of oral zafirlukast has been investigated in patients aged ≥12 years with predominantly mild to moderate asthma. Most studies evaluated zafirlukast 20mg twice daily for up to 13 weeks and included both an objective assessment of pulmonary function and a subjective assessment of symptom control as a measurement of therapeutic efficacy. Although many of the investigations included large patient numbers (n > 100), most of the data from these studies are available in abstract form only.

In double-blind randomised studies, oral zafirlukast 20mg twice daily generally produced significantly greater improvements in asthma symptom scores, nocturnal awakenings, forced expiratory volume in 1 second (FEV_1) and peak expiratory flow (PEF) than placebo and significantly reduced the need for as-required short-acting inhaled β_2-adrenoceptor agonist therapy. Favourable quality-of-life benefits were also reported in 1 study during treatment with zafirlukast 20mg twice daily for 13 weeks. In a meta-analysis of 5 double-blind placebo-controlled multicentre trials comparing zafirlukast (4 to 80mg twice daily) with placebo, zafirlukast also significantly reduced the incidence of asthma exacerbations.

Comparative data on the efficacy of zafirlukast and other antiasthma medications are limited. Zafirlukast 20mg twice daily has been compared with sodium cromoglycate aerosol (1.6mg 4 times daily) or dry powder inhalation (40mg daily) in patients with mild to moderate asthma in 2 double-blind randomised studies. Neither study demonstrated a significant difference between the 2 treatments in terms of pulmonary function or symptom control and 1 study showed no overall significant benefit with the active drugs compared to placebo in patients with mild asthma. In a comparison with inhaled beclomethasone dipropionate therapy (0.2 to 0.25mg twice daily for 6 weeks), improvements in morning PEF, FEV_1 and daytime symptom score were significantly less with zafirlukast 20mg twice daily. However, initial results suggest that patient preference and compliance may be greater with oral zafirlukast 20mg twice daily than with twice-daily inhaled corticosteroid therapy.

Because of confounding results from 2 studies, no clear conclusions can be drawn regarding the potential steroid-sparing effect of zafirlukast 20mg twice daily. In another investigation, concomitant treatment with high-dose zafirlukast therapy (80mg twice daily), which is outside recommended treatment guidelines, was associated with a significant improvement in pulmonary function and symptom control in patients with moderate to severe asthma who were symptomatic despite receiving high-dose inhaled corticosteroid therapy.

Pharmacoeconomic Considerations

Treatment with zafirlukast 20mg twice daily plus as-required short-acting inhaled β_2-adrenoceptor agonist therapy was more effective clinically and associated with a marked reduction in the use of healthcare resources (number of healthcare contacts, absenteeism from school or work, use of inhaled β_2-adrenoceptor agonist therapy and non-asthma medication) compared with placebo plus as-required β_2-adrenoceptor agonist therapy. Furthermore, considerable cost savings have also been demonstrated for patients treated with zafirlukast compared with placebo as a result of a reduction in the incidence of asthma exacerbations leading to study withdrawal. However, well designed pharmacoeconomic studies that compare zafirlukast with other antiasthma drugs are necessary before the potential benefit of zafirlukast can be fully evaluated in economic terms.

Tolerability

According to data from 7761 patients recruited to controlled clinical trials, the profile and incidence of adverse events were similar among patients treated with short term (≤20 weeks) zafirlukast therapy (n = 5188; typically 20mg twice daily) or placebo (n = 2573). The most frequent adverse events associated with zafirlukast therapy were pharyngitis (16%), headache (12%) and worsening of asthma (8%). Other adverse events including infection, rhinitis, flu syndrome, nausea and cough developed in 3 to 4% of patients. Longer term zafirlukast therapy (21 weeks to >2 years; n = 1120) was associated with a similar profile but a higher

incidence of adverse events (pharyngitis 46%, worsening of asthma 28%, headache 16%, infection 16%, flu syndrome 10% and rhinitis 8%) than over the short term. The incidence of serious adverse events during long term therapy was low, the most frequent being worsening of asthma (1.5%) and infection (0.8%).

Infrequent asymptomatic elevations in serum liver enzymes have been reported with high dosages of zafirlukast (80mg twice daily). These elevations returned to normal after cessation of therapy. However, because of these findings, the administration of zafirlukast dosages exceeding 40mg twice daily is not recommended.

Postmarketing surveillance studies have revealed a very small number of cases of Churg-Strauss syndrome (n = 6) in patients who were being withdrawn from oral corticosteroid therapy while receiving treatment with zafirlukast.

Dosage and Administration

In the prophylaxis and treatment of asthma, the recommended oral dosage regimen for zafirlukast is 20mg twice daily. Dosage guidelines are currently unavailable for the use of zafirlukast in children aged <12 years. Zafirlukast should be administered at regular intervals and should not be taken with food.

Because zafirlukast is excreted in breast milk, the drug should not be administered to women who are breast feeding. Furthermore, zafirlukast should not be used during pregnancy. Dosage reductions for zafirlukast do not appear to be necessary in the elderly or in patients with renal impairment. However, dosage modification may be necessary in patients with hepatic impairment, although specific dosage recommendations have yet to be devised for this patient group. If a patient experiences symptoms of liver dysfunction, medical attention should be sought immediately. Because of a small number of reports of Churg-Strauss syndrome in zafirlukast-treated patients in association with a reduction in oral corticosteroid dosage, individuals who require tapering of their oral corticosteroid dosage while receiving treatment with zafirlukast should be monitored closely.

Zafirlukast (fig. 1) is a leukotriene receptor antagonist approved for the treatment of asthma. The important contributory role of the leukotrienes in the pathogenesis of asthma has provided the rationale for the development of agents that interfere with the activity of these mediators. This has resulted in the first new class of antiasthma drugs to be introduced for many years. The pharmacology of zafirlukast and the preliminary clinical findings of studies evaluating its efficacy and tolerability in the treatment of asthma are the focus of this review.

1. Leukotrienes and Their Role in Asthma

Leukotrienes are inflammatory mediators and may be divided into 2 classes: the non-peptide leukotrienes [leukotrienes A_4 (LTA_4) and B_4 (LTB_4)] and the cysteinyl or sulphidopeptide leukotrienes [leukotrienes C_4 (LTC_4), D_4 (LTD_4) and E_4 (LTE_4)]. The cysteinyl leukotrienes were formerly collectively known as the slow-reacting substance of anaphylaxis.

Leukotrienes are lipoxygenase products formed during the oxidative metabolism of arachidonic acid (fig. 2).[2-8] Activation of phospholipase A_2 in response to various stimuli results in the release of arachidonic acid from membrane phospholipids. The resulting free arachidonic acid is then converted by cyclo-oxygenase to form prostaglandins and thromboxane. Alternatively, it is converted by 5-lipoxygenase and the 5-lipoxygenase-activating protein (FLAP) to produce LTA_4 which is a com-

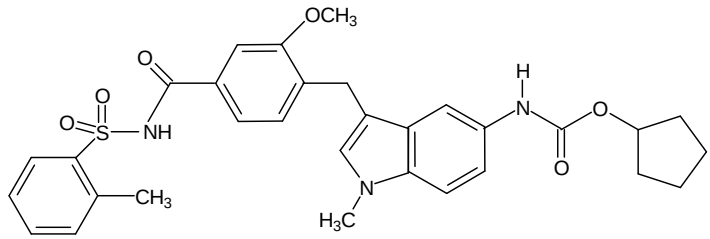

Fig. 1. Chemical structure of zafirlukast.

mon precursor of the leukotrienes LTB_4 and LTC_4 (fig. 2). LTC_4 undergoes further metabolism by γ-glutamyl-transpeptidase and a dipeptidase to form LTD_4 and LTE_4.[9]

In recent years, extensive data from *in vitro* and *in vivo* investigations have unequivocally implicated the cysteinyl leukotrienes in the pathogenesis of asthma. These biochemical mediators induce several pathophysiological effects relevant to asthma including:

- smooth muscle contraction leading to bronchoconstriction;[10-13]
- an increase in vascular permeability *in vivo*;[14]
- an increase in mucus production *in vitro*;[15]
- inflammatory cell infiltration into the lung *in vivo*.[16,17]

Leukotrienes may also contribute to bronchial hyper-responsiveness,[18-20] and increased levels of leukotrienes have been measured in the bronchoalveolar lavage fluid and urine of patients with spontaneous episodes of asthma or after antigen challenge.[21-24] The role of the cysteinyl leukotrienes in the pathogenesis of asthma has been recently reviewed in detail by several authors.[6-8,25,26]

Considerable heterogeneity exists among the leukotriene receptors identified in various animal species.[27] In human airways smooth muscle, current evidence suggests the presence of a $CysLT_1$ receptor which is activated by all 3 cysteinyl leukotrienes (LTC_4, LTD_4 and LTE_4) and the possible existence of a subgroup of this receptor which is activated by LTE_4 alone. An additional receptor, $CysLT_2$, may be located in human pulmonary vascular tissue.[2]

2. Pharmacodynamic Properties of Zafirlukast

2.1 *In Vitro* and *In Vivo* Studies in Animals

Zafirlukast is a selective and competitive inhibitor of LTD_4 and LTE_4. *In vitro*, zafirlukast antagonised the contractile activity of LTC_4, LTD_4 and LTE_4 in guinea-pig tracheal and pulmonary strips and in human bronchial rings.[28,29] However, zafirlukast failed to antagonise the contractile response of guinea-pig tracheal strips to aerosolised LTC_4 when the metabolism of LTC_4 to LTD_4 and LTE_4 was inhibited.[29] Zafirlukast competitively inhibited the binding of LTD_4 and LTE_4 to guinea-pig lung parenchymal membrane.[29] At concentrations 1000- to 10 000-fold greater than the apparent K_B (concentration of drug required to occupy 50% of receptors at equilibrium) for cysteinyl leukotriene antagonists, zafirlukast demonstrated virtually no affinity for a variety of other receptors, including α_1-, α_2-, β_1- and β_2-adrenoceptors and muscarinic receptors, located on isolated tissue.[29]

Dose-related antagonism of the pulmonary effects of LTC_4 and LTD_4 was observed in guinea-pigs pretreated with zafirlukast.[29] Administration of zafirlukast antagonised LTD_4-induced dyspnoea in conscious guinea-pigs and inhibited the effects of LTC_4 on airway conductance and dynamic lung compliance in the lungs of anaesthetised guinea-pigs. Zafirlukast 0.046 and 0.5 μmol/kg and 5.1 μmol/L, respectively, produced 50% inhibition of

LTD_4-induced dyspnoea after intravenous, oral and aerosol administration. Intravenous zafirlukast 1.0 μmol/kg also inhibited and reversed ovalbumin-induced bronchoconstriction in sensitised guinea-pigs.[29]

Prior administration of zafirlukast by aerosol (0.01 to 100 μmol/L) or the intraperitoneal route (0.03 to 3 μmol/kg) produced a concentration-dependent inhibition of the eosinophil chemotactic response to LTD_4 in guinea-pigs.[17] Similarly, aerosolised zafirlukast 30 μmol/L completely inhibited LTC_4- and LTE_4-induced eosinophil migration in guinea-pig lung. Intravenous zafirlukast 0.03 to 0.1 μmol/kg dose-dependently inhibited LTD_4-induced oedema in guinea-pig trachea.

2.2 Effects in Human Bronchial Challenge Studies

Considerable data are now available to suggest that zafirlukast is able to protect against bronchoconstriction induced by a range of challenges including LTD_4, platelet activating factor, allergen, exercise, cold air and sulphur dioxide (table I). Although the cysteinyl leukotrienes appear to be important in the pathogenesis of aspirin-sensitive asthma,[24] no studies to date have investigated the usefulness of zafirlukast in this setting.

2.2.1 Leukotriene D_4 Challenge

The bronchoconstrictor response to aerosolised LTD_4 was reduced for up to 24 hours in both pa-

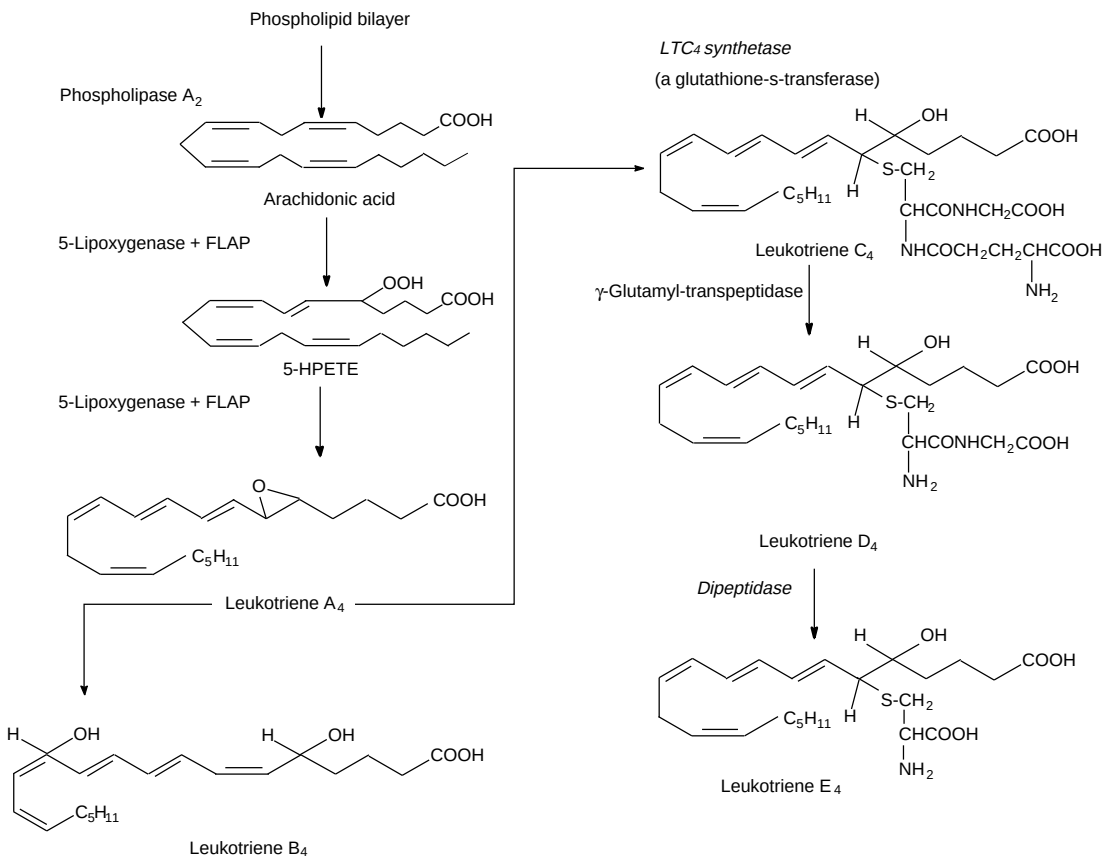

Fig. 2. Formation of leukotrienes via the arachidonic acid metabolic pathway. *Abbreviations*: FLAP = 5-lipoxygenase-activating protein; 5-HPETE = 5-hydroperoxy-eicosatetraenoic acid; LTC_4 = leukotriene C_4 (from Chanarin & Johnston.,[1] with permission).

Table I. Overview of double-blind crossover challenge studies comparing the protective effect of a single dose of zafirlukast (ZAF) and placebo (PL) against induced bronchoconstriction in patients with asthma (A) or healthy volunteers (HV)

Reference	No. of subjects (type)	Zafirlukast dosage (mg)	Time of administration prior to challenge (h)	Assessment criteria	Results
Leukotriene D_4					
Smith et al.[30]	30 (A)	ZAF 5, 10, 20, 40 or 100 PO	12	$PD_{20}FEV_1$	ZAF 10, 40 or 100 > PL
Smith et al.[31]a	6 (A)	ZAF 40 or 80 PO	24	$PD_{20}FEV_1$	ZAF 40 > PL ZAF 80 > PL
Smith et al.[32]	18 (HV)	ZAF 40 PO	2, 12, 24	$SGaw_{35}$	ZAF > PL at 2, 12 and 24h
Smith et al.[33]a	6 (A)[b]	ZAF 20 PO	2	$PD_{20}FEV_1$	ZAF > PL
Allergen					
Dahlén et al.[34]	10 (A)	ZAF 20 PO	2	$PD_{20}FEV_1$	ZAF > PL
Findlay et al.[35]	12 (A)	ZAF 40 PO	2	$PD_{20}FEV_1$	ZAF > PL
O'Shaughnessy et al.[36]	10 (A)	ZAF 1.6 INH	0.5	Maximum fall in FEV_1	ZAF[c] > PL
Taylor et al.[37]	8 (A)	ZAF 40 PO	2	FEV_1AUC	ZAF[d] > PL
Exercise					
Finnerty et al.[38]	8 (A)	ZAF 20 PO	2	Maximum fall in FEV_1, FEV_1AUC	ZAF > PL
Makker et al.[39]	9 (A)	ZAF 0.4 INH	0.5	Maximum fall in FEV_1, FEV_1AUC	ZAF > PL
Ostrom et al.[40]a	39(A)[e]	ZAF 5, 10, 20, 40 PO	4	Max fall in FEV_1, FEV_1AUC	ZAF 5, 20, 40 > PL ZAF 10 ≥ PL
Cold air					
Boulet et al.[41]a	10 (A)	ZAF 80 PO	0.5, 4, 24	$PD_{20}FEV_1RHE$, $PD_{20}FEV_1V_\varepsilon$	ZAF ≡ PL at 0.5 and 4h ZAF > PL at 24h
Glass et al.[42]a	18 (A)	ZAF 0.8 INH	0.5, 6, 24	$PD_{10,15,20}FEV_1RHE$, $PD_{10,15,20}FEV_1V_\varepsilon$	ZAF > PL at 0.5h ZAF ≥ PL at 6 and 24h
Israel et al.[43]a	24 (A)	ZAF 20 or 40 PO	2, 8	$PD_{10,15,20}FEV_1V_\varepsilon$	ZAF 20, 40 ≡ PL at 2h ZAF 20, 40 > PL at 8h
Richter et al.[44]a	19 (A)	ZAF 20 or 80 PO	3	$PD_{20}FEV_1V_\varepsilon$	ZAF 20 ≥PL ZAF 80 > PL
Sulphur dioxide					
Lazarus et al.[45]a	12 (A)	ZAF 20 PO	2, 10	PC_8SR_{aw}	ZAF > PL at 2h ZAF ≥ PL at 10h
Platelet activating factor					
Kidney et al.[46]	8 (HV)	ZAF 40 PO	2	Maximum fall in SGaw, SGawAUC	ZAF > PL

a Abstract.

b Patients were receiving treatment with inhaled corticosteroid therapy (median dose 800μg/day).

c ZAF significantly reduced the early phase response but did not have a significant effect on the late phase response *vs* PL.

d ZAF significantly reduced both the early and late phase responses *vs* PL.

e Patients were aged 6-14y.

Abbreviations and symbols: FEV_1 = forced expiratory volume in 1 second; FEV_1AUC = area under the curve of the percentage change in FEV_1 from baseline against time; INH = inhaled; PC_8SR_{aw} = 8 unit increase in specific airway resistance with a sulphur dioxide concentration ≤4 ppm; PD_xFEV_1 = concentration of challenge agent required to produce an *x*% decrease in FEV_1; PD_xFEV_1RHE = respiratory heat exchange that reduced FEV_1 by *x*%; $PD_xFEV_1V_\varepsilon$ = minute ventilation reducing FEV_1 by *x*%; PO = oral; SGaw = specific airways conductance; $SGaw_{35}$ = concentration of challenge agent required to decrease SGaw by 35%; SGawAUC = area under the curve of the time course of SGaw from baseline; > significantly greater efficacy *vs* placebo $p \leq 0.05$; ≥ trend towards greater efficacy *vs* placebo; ≡ similar efficacy *vs* placebo.

tients with asthma and healthy volunteers treated with single oral doses of zafirlukast 40 or 80mg (table I).[31,32]

In healthy volunteers, the extent of the bronchoprotective effect of zafirlukast was dependent upon the time of administration of the drug.[32] Administration of zafirlukast 40mg to healthy volunteers 2 hours prior to bronchial challenge resulted in a 117-fold increase in the concentration of LTD_4 required to reduce specific airway conductance by 35%; this compared with an increase of 9- and 5-fold when zafirlukast was administered 12 and 24 hours, respectively, prior to bronchial challenge. In patients with mild asthma, zafirlukast (5, 10, 20, 40 or 100mg) provided dose-dependent protection against LTD_4-induced bronchoconstriction when administered 12 hours prior to LTD_4 aerosol challenge.[30] A positive correlation between zafirlukast plasma concentration and the protective effect of the drug against LTD_4-induced bronchoconstriction has also been reported.[30,32]

In another study, single-dose administration of zafirlukast 20mg (2 hours prior to challenge) significantly attenuated LTD_4-induced bronchoconstriction in patients with asthma who were receiving treatment with inhaled corticosteroid therapy (median dose 800 μg/day).[33]

2.2.2 Allergen Challenge

Inhalation of allergen by susceptible individuals invokes an early bronchoconstrictive response induced by the release of preformed mediators, such as histamine, from IgE-triggered mast cells. Many patients also experience a late phase bronchoconstrictive response associated with tissue oedema, infiltration and recruitment of inflammatory leucocytes and an increase in airway hyperresponsiveness. The 2 types of response generally develop within 10 to 15 minutes and 3 to 6 hours after allergen challenge, respectively, and the late phase response may last for up to 24 hours.[47,48] Studies with leukotriene receptor antagonists and leukotriene synthesis inhibitors show that approximately 60 to 80% of the early phase and approximately 50 to 60% of the late phase bronchoconstrictive response to allergen challenge is leukotriene-dependent (reviewed by Holgate et al.[49,50]).

The protective effect of zafirlukast against the early phase response to allergen challenge has been demonstrated in several studies.[34-37,50,51] Compared with placebo, oral administration of zafirlukast 20mg to 10 patients with asthma 2 hours prior to allergen challenge produced a significant 2.5-fold increase in the concentration of allergen required to reduce the forced expiratory volume in 1 second (FEV_1) by 20% ($p = 0.01$). Zafirlukast also shortened the mean recovery time after immediate bronchoconstriction (defined as the time required for FEV_1 to return from its maximal decrease to within 90% of its prechallenge value) from 60 to 40 minutes compared with placebo ($p < 0.05$).[34] Successful inhibition of the allergen-induced early response has also been reported following administration of zafirlukast by inhalation.[36,51]

Preliminary data suggest that oral[35,37,50] but not inhaled zafirlukast[36] may attenuate the late phase response to allergen challenge. Oral administration of zafirlukast 40mg to 8 atopic patients 2 hours prior to allergen challenge significantly attenuated both early and late allergen-induced bronchoconstriction.[37] Zafirlukast produced a significant reduction in the mean area under the percentage change in FEV_1 versus time curve for the periods 0 to 2 hours and 2 to 6 hours after administration of the last dose of allergen.

In another study, pretreatment of patients with allergic asthma with both zafirlukast 80mg twice daily and the antihistamine loratadine 10mg twice daily for 1 week produced significantly greater inhibition of the late phase response (defined by the area under the FEV_1 versus time curve expressed as a percentage of the response during controlled bronchoprovocation testing) than either drug alone.[50] The late phase response was reduced by 55 and 40% following pretreatment with loratadine or zafirlukast, respectively, compared with a reduction of 74% following pretreatment with both drugs ($p < 0.05$).

The extent of the protection conferred by zafirlukast against bronchial hyper-responsiveness

requires further investigation. In one study, which reported a beneficial effect with zafirlukast,[37] the investigators chose a time point (6 hours) that was too soon after allergen challenge to reliably assess changes in bronchial hyper-responsiveness.[52] In another investigation, zafirlukast 20mg twice daily for 12 weeks did produce a significant (2.5-fold) reduction in baseline bronchial hyper-responsiveness to methacholine in patients with asthma [FEV_1-percentage predicted (FEV_1-PP) ≥ 55%] at week 2.[53] However, although bronchial hyper-responsiveness was still attenuated at week 10, the difference was no longer statistically significant. In a 2-week crossover comparison with inhaled fluticasone propionate (100μg twice daily), zafirlukast 20mg twice daily provided significantly less protection against histamine-induced bronchial hyperresponsiveness in patients with mild to moderate asthma.[54]

Examination of bronchial lavage fluid from zafirlukast-treated patients suggested that the drug may alter the inflammatory response to allergen challenge.[55,56] 48 hours after segmental antigen bronchoprovocation, basophil, mast cell, lymphocyte and histamine levels were significantly reduced in the bronchoalveolar lavage fluid of patients treated with zafirlukast 20 or 160mg twice daily for 7 days compared with placebo. A significant reduction in the number of eosinophils was also reported in patients treated with the higher dosage of zafirlukast (160mg twice daily).

2.2.3 Exercise and Cold Air Challenge

Exercise-induced asthma (EIA) is defined as an intermittent narrowing of the airways during or immediately after exercise. Frequent symptoms include wheezing, chest tightness, coughing and dyspnoea.[57,58] Several studies, mostly reported as abstracts (table I), have shown oral zafirlukast to be an effective inhibitor of EIA and cold air-induced bronchoconstriction (considered to closely mimic the airway effects of exercise) in patients with asthma. Protection against EIA and cold air challenge has also been reported with inhaled formulations of zafirlukast.[39,42]

Oral administration of zafirlukast 20mg 2 hours prior to exercise challenge significantly reduced the mean maximum percentage fall in FEV_1 compared with placebo (21.6 *vs* 36%; $p < 0.01$) in 8 patients with asthma, with the principal protective effect occurring after the first 5 to 30 minutes of exercise.[38] A significant attenuation of EIA was also reported 4 hours after single-dose oral administration of zafirlukast 5, 20 and 40mg to 39 children (aged 6 to 14 years).[40] Attenuation of EIA did not reach statistical significance with zafirlukast 10mg ($p = 0.056$).

In an evaluation of short term zafirlukast therapy, relatively more patients treated with zafirlukast 20 or 80mg twice daily for 2 weeks recovered to ≥95% of baseline FEV_1 ≤30 minutes after exercise compared with patients treated with sodium cromoglycate (cromolyn sodium) 10mg 4 times daily or placebo (73 to 87% *vs* 33 to 57%).[59]

Protection against cold air-induced bronchoconstriction has been reported after single-dose administration of zafirlukast 20, 40 or 80mg (table I).[41,43,44]

3. Pharmacokinetic Properties

Published pharmacokinetic data on the oral formulation of zafirlukast are limited; this section, therefore, mainly comprises data from unpublished studies.[60,61]

3.1 Absorption and Distribution

The pharmacokinetic profile of zafirlukast is best described using a 2-compartment model. Maximum plasma zafirlukast concentrations (C_{max}) [not specified] were achieved 3 hours after single-dose administration of zafirlukast 20 or 40mg to healthy volunteers (aged 18 to 40 years). Accumulation of zafirlukast was minimal during twice daily treatment (60 to 160 mg/day) for 10 days and systemic exposure was proportional to the dosage of zafirlukast over the range 20 to 80mg twice daily. The absolute bioavailability of zafirlukast is unknown; however, coadministration of zafirlukast with food high in protein or fat reduced the

mean bioavailability of the drug by approximately 40%.[60,61]

Zafirlukast is extensively plasma-protein bound; at plasma concentrations ranging from 0.25 to 10 mg/L, the drug was >99% bound to plasma proteins, predominantly to albumin.[60]

3.2 Metabolism and Elimination

Zafirlukast undergoes extensive hepatic metabolism in humans. The major biotransformation pathway is hydroxylation by the cytochrome P450 CYP2C9 isoenzyme.[62] Notably, *in vitro* comparison of LTD_4 antagonist activity showed zafirlukast metabolites in the plasma to be ≥90-fold less potent than the parent drug.[60] *In vitro*, zafirlukast inhibited the cytochrome P450 isoenzymes CYP2C9 and CYP3A at concentrations approaching those which are clinically relevant.[63]

In patients with asthma and healthy volunteers, the mean terminal elimination half-life of zafirlukast is approximately 10 hours. The drug is mainly eliminated in the faeces with urinary excretion accounting for <10% of an orally administered dose.[62] Zafirlukast is also excreted in breast milk; after administration of 40mg twice daily to healthy female volunteers, the mean steady-state concentration of zafirlukast in breast milk was 50 μg/L compared with 255 μg/L in plasma.[60]

Preliminary data suggest that the clearance of zafirlukast is reduced in patients with hepatic impairment; short term studies revealed a marked increase (50 to 60%) in the C_{max} and area under the plasma concentration-time curve (AUC) for zafirlukast in patients with stable alcoholic cirrhosis compared with healthy volunteers. However, to date, the pharmacokinetics of zafirlukast have not been evaluated in patients with hepatitis or in long term studies of patients with cirrhosis.[60]

A single-dose pharmacokinetic study in elderly patients with asthma (aged >66 years) and healthy volunteers (aged 19 to 35 years) demonstrated an increase in the normalised AUC and C_{max} and a decrease in the plasma clearance of zafirlukast with increasing age. Compared with younger adults, the C_{max} and AUC of zafirlukast were increased by 2-fold in elderly individuals.[61] However, there was no accumulation of the drug in elderly patients treated with 20mg twice daily for 10 days.[61]

3.3 Relationship Between Plasma Concentration and Clinical Effect

There was a slight positive correlation between the plasma trough concentration of zafirlukast and FEV_1 in patients (n = 276) with moderate to severe asthma treated with zafirlukast 5, 10 or 20mg twice daily for 4 weeks ($r = 0.18$; $p = 0.01$).[64] The trough plasma sample was collected 11 to 14 hours after treatment and FEV_1 was measured >3 hours after β-adrenoceptor agonist therapy. Conversely, higher zafirlukast concentrations correlated with a reduction in nocturnal awakenings ($r = -0.23$; $p = 0.002$) and asthma symptoms upon awakening in the morning ($r = -0.17$; $p = 0.02$) in this patient group.

3.4 Pharmacokinetic Drug Interactions

A summary of potential drug-drug interactions involving zafirlukast is provided in table II. The effects of zafirlukast on the pharmacokinetic properties of warfarin were investigated in 16 healthy volunteers in a crossover study.[65,66] Coadministration of zafirlukast (80mg twice daily for 10 days) and warfarin (25mg on day 5) resulted in a significant decrease in the clearance of *S*-warfarin and a clinically significant increase in prothrombin time. No clinically significant changes in the fraction of unbound *R*- or *S*-warfarin in the plasma were reported. Inhibition of the cytochrome P450 CYP2C9 isoenzyme system by zafirlukast is the proposed mechanism for this interaction. In an anecdotal report, an elderly patient concomitantly receiving warfarin 2mg daily for 9 months and zafirlukast 20mg twice daily (duration not specified) experienced excessive anticoagulation and gastrointestinal bleeding.[69] Close monitoring of prothrombin time and adjustment of the anticoagulant dosage are therefore recommended in patients receiving concomitant treatment with warfarin and zafirlukast.[60]

Table II. Summary of drug interaction studies evaluating the concomitant administration of zafirlukast (ZAF) and warfarin (WAR), terfenadine (TER), theophylline (THE), erythromycin (ERY), aspirin (ASP) or oral contraceptives (OC)

Drugs (dosage)	No. of subjects (type)	Effect
ZAF 80mg bid × 10 days + WAR 25mg SD[a]	16 (HV)	Significant ↑ in WAR AUC (+62%) and area under PT *vs* time curve (+8%) and a clinically significant ↑ in PT_{max} (+15%).[65] Significant ↓ (–38%) in *S*-WAR CL[66]
ZAF 160mg bid + TER 60mg bid[b]	8-16 (HV)	Significant ↓ in ZAF C_{max} (-61%) and ZAF AUC (–48%) on day 8. ZAF did not significantly alter TERC AUC, C_{max} or ECG parameters[67,68]
ZAF 40mg bid[c] + THE[d] 6mg/kg SD	13 (A)	Mean ZAF plasma concentration ↓ by ≈30%. No effect on THE plasma concentration[60]
ZAF 40mg SD + ERY 500mg tid × 5 days[c]	11 (A)	Mean ZAF plasma concentration ↓ by ≈40%[60]
ZAF 20mg bid + ASP 650mg qid	NR	Mean ZAF plasma concentration ↑ by ≈45%[60]
ZAF 40mg bid × 3wk + OC × 3wk	39 (HV)	No significant effect on EE plasma concentration or OC efficacy[60]

a WAR was administered on the 5th day of ZAF therapy.

b ZAF administered on days 1-16 and TER administered on days 8-16 or *vice versa*.

c Administered to steady-state.

d Oral liquid preparation.

Abbreviations and symbols: A = patients with asthma; AUC = area under the plasma concentration-time curve; bid = twice daily; C_{max} = maximum plasma concentration; CL = clearance; ECG = electrocardiographic; EE = ethinyl estradiol; HV = healthy volunteers; NR = not reported; od = once daily; PT = prothrombin time; PT_{max} = maximum prothrombin time; qid = 4 times daily; SD = single dose; TERC = terfenadine carboxylate; tid = 3 times daily; ↑ indicates an increase; ↓ indicates a decrease.

Terfenadine is a substrate for the cytochrome P450 isoenzyme CYP3A. In healthy volunteers, zafirlukast did not significantly alter the AUC of terfenadine carboxylate, the active metabolite of terfenadine. Furthermore, changes in electrocardiographic parameters, sometimes associated with increased plasma concentrations of terfenadine,[70] were not reported in this study; however, the C_{max} and AUC for zafirlukast were significantly reduced.[67,68]

No formal studies have been conducted to investigate drug-drug interactions between zafirlukast and other agents metabolised by the cytochrome P450 CYP2C9 (for example, tolbutamide, phenytoin and carbamazepine) or P450 CYP3A (for example, dihydropyridine calcium-channel antagonists, cyclosporin, cisapride and astemizole) isoenzyme systems. However, as zafirlukast has been shown to be an inhibitor of these enzyme systems *in vitro* (section 3.2), appropriate clinical monitoring should be undertaken if zafirlukast is coadministered with these drugs.

Other drug interaction studies reported a 30 to 40% reduction in plasma zafirlukast concentrations when the drug was coadministered with theophylline or erythromycin to patients with asthma. In contrast, the concomitant administration of aspirin increased plasma zafirlukast concentrations by approximately 45%. Limited data showed no significant reduction in contraceptive efficacy in healthy female volunteers who received concomitant oral zafirlukast (40mg twice daily) and oral contraceptive therapy over a 3-week period.[60]

4. Therapeutic Potential

The clinical efficacy of oral zafirlukast has been evaluated in patients (aged ≥12 years) with predominantly mild to moderate asthma recruited to large comparative double-blind trials. The majority of studies evaluated the efficacy of zafirlukast both objectively by measuring pulmonary function [FEV_1 and morning and evening peak expiratory flow (PEF)] and subjectively by assessing symptoms (using asthma symptom scores based on a 4-point scale) and recording the use of supplementary bronchodilator therapy (usually the short-acting inhaled β_2-adrenoceptor agonist salbutamol).

A range of oral zafirlukast dosages were evaluated, with 20mg twice daily being the most fre-

quently used. Most studies used placebo as the comparator agent. A small number of studies compared the efficacy of zafirlukast and other anti-asthma medications including sodium cromoglycate[71,72] and inhaled corticosteroids.[73] Recent investigations have also included an assessment of the potential steroid-sparing effect of zafirlukast.[74-78]

With the exception of 2 studies,[64,79] all investigations described in this section were reported as abstracts only at the time of this review.

4.1 Dose-Finding Studies

The results of 3 randomised double-blind placebo-controlled trials showed a dose-related improvement in pulmonary function and symptom control with zafirlukast.[64,80,81]

In a 6-week study in 266 patients with moderate to severe asthma (FEV_1-PP 40 to 75%), treatment with zafirlukast 20mg twice daily produced a greater improvement in symptom control (nocturnal awakenings, asthma symptoms upon awakening in the morning, daytime asthma score and use of rescue medication) than zafirlukast 10 or 5mg twice daily (table III); the percentage improvement from baseline ranged from 27 to 46%, 8 to 19% and 9 to 29%, respectively.[64] Zafirlukast 20mg twice daily also produced a significantly greater improvement in symptom control, FEV_1 and evening PEF at the 6-week study end-point than placebo ($p \leq 0.05$). However, only zafirlukast 5mg twice daily produced a significant improvement in morning PEF compared with placebo (fig. 3).

A significant increase in morning PEF ($p < 0.05$) and a significant decrease in the use of rescue medication ($p < 0.05$) was reported with increasing doses of zafirlukast (4, 10, 20, 40 or 80mg twice daily for 13 weeks) in patients with mostly mild to moderate asthma (FEV_1-PP ≥55%; n = 285).[80] Although not significant, higher doses of zafirlukast were also correlated with a greater reduction in morning asthma symptoms. Similarly, in a 6-week dose escalation study in which 124 patients with mild to moderate asthma were randomised to receive increasing doses of zafirlukast (doses were increased every 2 weeks from 5 to 20 to 40mg twice daily) or placebo, higher dosages of zafirlukast were associated with a small incremental benefit.[81]

4.2 Comparative Studies

4.2.1 Zafirlukast versus Placebo

The onset of action of zafirlukast 20mg twice daily was assessed during the first 2 weeks of a 13-week double-blind placebo-controlled trial.[85] Preliminary results from this study revealed significant improvements ($p < 0.05$) in daytime symptom scores, asthma symptoms upon awakening in the morning and morning PEF, and a significant reduction in the use of short-acting inhaled β_2-adrenoceptor agonist use, after 3 days of treatment with zafirlukast (n = 467) compared with placebo (n = 217). Evening PEF and the frequency of nocturnal awakenings did not differ significantly between the 2 treatment groups.

In a second study involving 198 patients with asthma (FEV_1-PP 50 to 75%), PEF was improved 2 hours after single-dose administration of zafirlukast 20mg (+37.9 L/min; not significant *vs* placebo) or 160mg (+45.3 L/min; $p < 0.05$ *vs* placebo).[86] This improvement in PEF was sustained during 2 weeks of treatment with zafirlukast 20mg or 160mg twice daily and was statistically significant versus placebo (+25.5 and +32.6 *vs* +5.6 L/min at week 2; $p < 0.05$).

The results of studies comparing the efficacy of zafirlukast 20mg twice daily and placebo over 6 to 13 weeks are summarised in table III.[79,83] These trials generally showed a significantly greater improvement in morning and evening PEF, FEV_1, symptom control and nocturnal awakenings and a significant reduction in the need for as-required short-acting inhaled β_2-adrenoceptor agonist therapy, with zafirlukast 20mg twice daily compared with placebo. In 1 study, which recruited patients with comorbid allergic rhinitis and asthma, symptoms of nasal congestion were also significantly improved during zafirlukast therapy.[84,87] Initial data suggest that patients with more severe asthma may benefit more from zafirlukast therapy than pa-

Table III. Summary of randomised, double-blind, parallel group comparative studies evaluating the efficacy of oral zafirlukast (ZAF) in patients with asthma

Reference	Asthma type (mean FEV_1-PP)	No. of pts	Treatment [mg] (duration [wk])	Relative efficacy					
				PEF	FEV_1	rescue medication	symptoms	nocturnal awakenings	overall (at study end-point)
Comparisons with placebo (PL)									
Howland et al.[82]a	Mild/moderate	54	ZAF 40 bid[b]	*am:* ZAF** > PL[c]		ZAF* > PL[c]	ZAF** > PL[c]	ZAF** > PL[c]	ZAF ≡ PL
	(NR)	52	PL	*pm:* ZAF** > PL[c]					
			(6)						
Fish et al.[79]	Mild/moderate	762	ZAF 20 bid	*am:* ZAF** > PL	ZAF* > PL	ZAF** > PL	ZAF** > PL	ZAF* > PL	
	(78.6)		PL	*pm*: ZAF ≡ PL					
			(13)						
Nathan et al.[83]a; Nayak et al.[84]a	Moderate	231	ZAF 20 bid	*am:* ZAF** > PL		ZAF** > PL	ZAF* > PL	ZAF** > PL	
	(66.4)	223	PL						
			(13)						
Spector et al.[64]	Moderate/severe	66	ZAF 5 bid	*am:* ZAF5* > PL	ZAF5 ≥ PL	ZAF5 ≥ PL	ZAF5 ≥ PL	ZAF5** > PL	
	(range 40-75)	67	ZAF 10 bid	ZAF10 ≥ PL	ZAF10 ≥ PL	ZAF10 ≥ PL	ZAF10 ≥ PL	ZAF10 ≥ PL	
		67	ZAF 20 bid	ZAF20 ≥ PL	ZAF20** > PL	ZAF20* > PL	ZAF20* > PL	ZAF20** > PL	
		66	PL	*pm:* ZAF5 ≥ PL					
			(6)	ZAF10 ≥ PL					
				ZAF20* > PL					
Comparisons with inhaled sodium cromoglycate (cromolyn sodium; SC)									
Holgate et al.[71]a	Mild	88	ZAF 20 bid	*am:* ZAF* > PL[e]		ZAF* > PL[e]	ZAF* > PL[e]		ZAF ≥ PL
	(82)	90	SC 40 od[d]						SC ≥ PL
		80	PL						
			(13)						
Nathan et al.[72]a	Mild/moderate	287	ZAF 20 bid						ZAF* > PL[g]
	(NR)		SC 1.6 qid[f]						SC* > PL[g]
			PL						ZAF ≡ SC[g]
			(13)						
Comparison with inhaled beclomethasone dipropionate (BDP)									
Laitinen et al.[73]a	Mild/moderate	162	ZAF 20 bid	*am:* BDP** > ZAF20	BDP** > ZAF20	BDP ≥ZAF20	BDP** > ZAF20	BDP ≥ZAF20	
	(79.6)	159	ZAF 80 bid	BDP ≥ ZAF80	BDP ≡ ZAF80	BDP ≥ZAF80	BDP* > ZAF80	BDP ≥ZAF80	
		160	BDP 0.2-0.25 bid	*pm:* BDP ≥ ZAF20	ZAF80* > ZAF20				
			(6)	BDP ≥ ZAF80					

a Abstract.
b Efficacy results for an additional 56 patients randomised to treatment with ZAF 2mg bid were not reported.
c Reported after 2wk of treatment.
d Dry powder inhalation.
e Reported for a number of individual treatment weeks (not specified) during the study treatment period.
f Aerosol inhalation.
g Efficacy assessed according to the percentage of patients who met ≥1 of the following criteria: 50% decrease in daytime symptoms, first morning symptoms or nocturnal awakenings without a 50% increase in short-acting β_2-adrenoceptor agonist use, or a 50% decrease in β_2-adrenoceptor agonist use without a 50% increase in daytime symptoms.

Abbreviations and symbols: bid = twice daily; FEV_1 = forced expiratory volume in 1 second; FEV_1-PP = FEV_1 percentage predicted; NR = not reported; od = once daily; *am* PEF = morning PEF; *pm* PEF = evening PEF; PEF = peak expiratory flow; qid = 4 times daily; > indicates significantly greater efficacy; ≥ indicates tendency towards greater efficacy; ≡ indicates similar efficacy; *p < 0.05, **p ≤ 0.01 *vs* comparator.

tients with less severe disease.[79,87] FEV_1 was improved by 15.9% in patients with more severe airflow obstruction (FEV_1-PP at baseline <65%) compared with 1.7% in patients with less severe disease (FEV_1-PP >80%) after treatment with zafirlukast 20mg twice daily for 13 weeks. The corresponding percentage improvements in morning PEF were 9.1 and 5.6%.[79]

In the largest comparative study in 762 patients with mild to moderate asthma (mean FEV_1-PP 78.6%), treatment with zafirlukast 20mg twice daily for 13 weeks improved morning PEF by 14 L/min ($p < 0.01$ *vs* placebo) and increased FEV_1 by 0.08L ($p < 0.05$ *vs* placebo).[79] FEV_1-PP at the end of treatment was 82.5 and 79.9%, respectively, among zafirlukast- and placebo-treated patients ($p < 0.01$).

Using the Asthma Quality of Life Questionnaire, Nathan et al.[83] reported favourable quality-of-life (QOL) benefits in patients treated with zafirlukast 20mg twice daily for 13 weeks. Significant improvements in the symptom and emotional function domains and in overall QOL score were reported with zafirlukast (n = 231) compared with placebo (n = 223) [$p \leq 0.01$]. The investigators also reported that these beneficial effects were associated with clinically relevant improvements in QOL (defined by ≥0.5 unit change from baseline).

Comparison of zafirlukast 40mg twice daily and placebo revealed no significant difference in pulmonary function or symptom control at a 6-week study end-point.[82] The investigators attributed this lack of difference to a confounding placebo effect. Morning and evening PEF, nocturnal awakenings, asthma symptoms upon awakening in the morning and use of rescue medication were significantly ($p < 0.05$) improved with zafirlukast compared with placebo after 2 weeks of treatment in this study (table III).

The effect of zafirlukast on the incidence of asthma exacerbations was evaluated in a recent meta-analysis of 5 double-blind placebo-controlled trials comparing treatment with zafirlukast (4 to 80mg twice daily) [n = 1129] or placebo (n = 547) for 13 weeks in patients with mild to moderate asthma.[88] The number of physician-reported asthma exacerbations leading to study withdrawal was significantly lower with zafirlukast than placebo [3.5 *vs* 6.5% of patients; p = 0.008; (odds ratio 0.51; 95% confidence interval 0.34 to 0.84)].

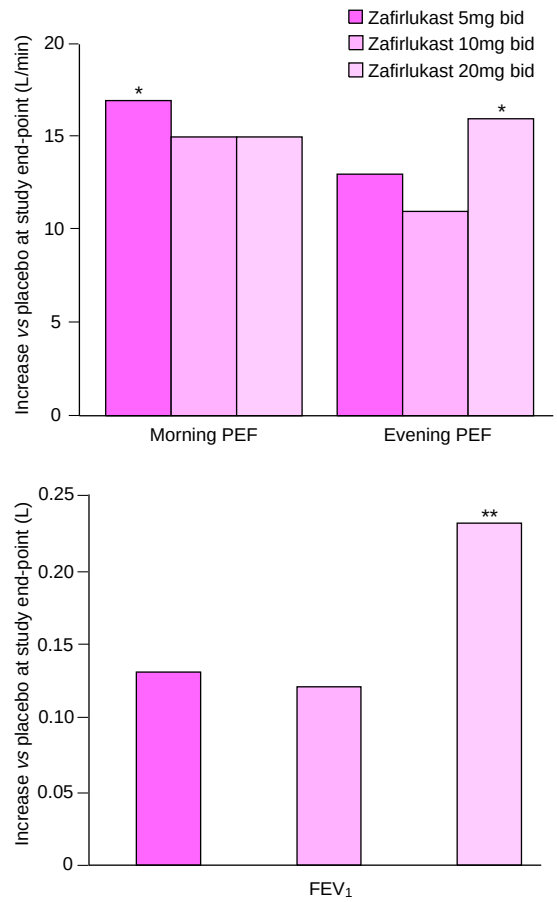

Fig. 3. Efficacy of zafirlukast in the treatment of moderate to severe persistent asthma [forced expiratory volume in 1 second (FEV_1) 40 to 75% of predicted value]. Improvement in peak expiratory flow (PEF) and FEV_1 at study end-point (6 weeks) compared with placebo (n = 66) for patients treated with zafirlukast 5 (n = 66), 10 (n = 67) or 20mg (n = 67) twice daily (bid).[64] *Symbols:* *$p \leq 0.05$ **$p \leq 0.01$ *vs* placebo.

4.2.2 Zafirlukast versus Sodium Cromoglycate

Limited data, provided by two 13-week studies, are available on the comparative efficacy of

zafirlukast and sodium cromoglycate (table III).[71,72]

One study recruited 287 patients with mild to moderate asthma (total daytime asthma scores ≥8 over 7 consecutive days).[72] Response to treatment was defined as a 50% reduction in daytime symptoms, asthma symptoms upon awakening or nocturnal awakenings without a 50% increase in short-acting inhaled β_2-adrenoceptor agonist use, or a 50% decrease in β_2-adrenoceptor agonist use without a 50% increase in daytime symptoms. Using these criteria, response to treatment was significantly greater in favour of zafirlukast 20mg twice daily and sodium cromoglycate aerosol inhalation (1.6mg 4 times daily) than with placebo (64 to 68% *vs* 46% of patients; $p < 0.05$). However, no significant difference was demonstrated between the 2 active treatment groups. In a subgroup analysis of 64 patients stratified for asthma severity (timing of stratification not specified), zafirlukast produced a greater increase in FEV_1 (+0.35L; statistical significance not provided) compared with sodium cromoglycate (+0.17L) or placebo (+0.04L) in patients with more severe asthma (FEV_1-PP < 65%).[89]

A second study involving 258 patients with mild to moderate asthma reported no overall significant difference in the efficacy of zafirlukast 20mg twice daily, sodium cromoglycate dry powder for inhalation (40mg daily) or placebo.[71] The mild nature of the asthma (mean FEV_1-PP 82% and asthma symptom score 0.68 to 0.80 on a scale of 0 to 3 at study entry) in patients recruited to this study, may have precluded a clear demonstration of the relative benefits of these 2 agents.

4.2.3 Zafirlukast versus Inhaled Corticosteroids

To date, only 1 study has compared the efficacy of zafirlukast and inhaled corticosteroid therapy in the treatment of asthma (table III).[73] In this study, patients with mild to moderate asthma (mean FEV_1-PP 79.6%) were randomised to treatment with zafirlukast 20mg twice daily (n = 162), zafirlukast 80mg twice daily (n = 159) or inhaled beclomethasone dipropionate 200 to 250μg twice daily for 6 weeks (n = 160). Beclomethasone produced a significantly ($p \leq 0.01$) greater increase in FEV_1 and morning PEF from baseline than zafirlukast 20mg twice daily and a significantly ($p < 0.05$) greater reduction in daytime asthma symptom score from baseline than zafirlukast either 20 or 80mg twice daily. Beclomethasone dipropionate was also associated with a trend towards a greater improvement in evening PEF, nocturnal awakenings, mornings with asthma symptoms and need for β_2-adrenoceptor agonist therapy. 30% and 41% of patients treated with zafirlukast 20 and 80mg twice daily, respectively, experienced a ≥10% improvement in morning PEF from baseline compared with 47% of patients treated with beclomethasone dipropionate.

4.3 Effect on Corticosteroid Dosage

The results of 2 multicentre double-blind studies investigating the potential steroid-sparing effect of oral zafirlukast 20mg twice daily do not permit a clear conclusion to be drawn regarding the ability of zafirlukast to facilitate a reduction in corticosteroid dosage in patients with asthma.[74,75] One study compared treatment with zafirlukast (n = 242) and placebo (n = 117) for 20 weeks in patients with mild stable asthma who were receiving inhaled corticosteroid therapy 400 to 750μg daily.[75] The second study compared treatment with zafirlukast (n = 175) and placebo (n = 87) for 12 weeks in patients with moderate stable asthma who had been receiving inhaled corticosteroid therapy 800 to 2000μg daily.[74]

During both investigations, the required dosage of inhaled corticosteroid therapy was reduced to a similar extent (60 to 85%) without loss of symptom control in both zafirlukast- and placebo-treated patients. However, the attainment of such large reductions in the inhaled corticosteroid dosage without loss of symptom control suggests that these patients were not receiving the lowest effective dose of inhaled corticosteroids at study entry, thus confounding the results.

One study reported a steroid-sparing effect in patients with moderate asthma (FEV_1-PP 60 to 80%) treated with zafirlukast 20mg daily for 12

weeks.[77] However, the study report provided only limited efficacy data and only 9 patients were recruited.

Concomitant high-dose zafirlukast therapy (80mg twice daily) for 6 weeks significantly improved asthma control in 368 patients with moderate or severe persistent asthma (FEV_1-PP 50 to 75%) who were symptomatic despite treatment with high-dose inhaled corticosteroid therapy (beclomethasone dipropionate ≥1200 μg/day or equivalent).[76,78] Zafirlukast produced a significantly greater improvement in morning PEF relative to baseline than placebo (18.7 *vs* 1.5 L/min; $p < 0.001$). Improvements in secondary efficacy parameters (evening PEF, FEV_1, daytime asthma score, use of short-acting inhaled β_2-adrenoceptor agonist medication and mornings with asthma symptoms) were also significantly greater with zafirlukast. Moreover, zafirlukast recipients experienced fewer asthma exacerbations which required additional treatment (8 *vs* 15% of patients) and required fewer days off work due to respiratory illness (250 *vs* 310 days lost among zafirlukast and placebo recipients, respectively).

4.4 Patient Preference and Compliance

An assessment of patient preference for treatment with oral zafirlukast (20mg twice daily) or inhaled beclomethasone dipropionate therapy (0.2 to 0.25mg twice daily) for 4 weeks revealed a 2 to 1 preference in favour of zafirlukast in a nonblind crossover study (n = 152).[90] This was despite a higher incidence of adverse events with zafirlukast than with beclomethasone therapy in this study (further details not provided). In addition, more patients found zafirlukast easier to use (66 *vs* 20%).

Assessment of patient compliance with zafirlukast, using an electronic tracking cap device, revealed an overall compliance rate of 81%, with 74% of patients achieving at least 80% compliance.[61,91] Adherence to the daily regimen (number of days on which two 20mg zafirlukast tablets were taken ≥8 hours apart) was 64%. A retrospective comparison showed the rate of compliance with twice-daily zafirlukast therapy to be approximately twice that with inhaled corticosteroid therapy (as a dry powder administered twice daily).

5. Pharmacoeconomic Considerations

With the increase in use of anti-inflammatory medications as recommended by current treatment guidelines[92,93] and the introduction of new drug treatments, drug costs for the management of asthma have continued to rise. This has led to heightened interest in pharmacoeconomic research to evaluate whether this potential increase in cost is offset by cost savings in other areas and a reduction in asthma morbidity.

Data for the first pharmacoeconomic study on zafirlukast[94] originated from a 13-week multicentre double-blind trial comparing the efficacy of zafirlukast 20mg twice daily with placebo in 762 patients with mild to moderate asthma receiving as-required short-acting β_2-adrenoceptor agonist therapy.[79] All patients were aged ≥12 years, had an FEV_1-PP ≥55% and were symptomatic (defined as a cumulative 7-day asthma symptom score ≥8). Clinical effectiveness and resource consumption for zafirlukast therapy were assessed in a 13-week subgroup analysis of 146 patients enrolled in this trial. Clinical effectiveness was measured using patient assessment of the number of days per month without asthma symptoms, limitation of activity, β_2-adrenoceptor agonist use, sleep disturbance and episodes of asthma. Resource consumption was evaluated according to the use of healthcare services and resources (frequency and type of unscheduled healthcare contacts, use of β_2-adrenoceptor agonist agents and non-asthma medication) and absenteeism from school or work.

In addition to greater clinical efficacy (table IV), zafirlukast had a significant effect on the use of healthcare resources compared with placebo. Patients treated with zafirlukast experienced a 55% reduction in both the number of healthcare contacts and absenteeism from school or work, and a non-significant 17 and 19% reduction in the use of inhaled β_2-adrenoceptor agonists and non-asthma medication, respectively, (table IV). However, the significantly lower mean FEV_1-PP at baseline

Table IV. Clinical efficacy and resource consumption for patients treated with zafirlukast 20mg twice daily (n = 103) or placebo (n = 43) in a subgroup analysis of a 13wk randomised[a] double-blind study[94]

	Zafirlukast	Placebo	Comparison with placebo	
			mean increase (%)[bc]	estimated rate reduction (%)[d]
Time spent in specific health states (mean no. days/month)				
Without symptoms	7.0	3.7	89*	
Without inhaled β_2-adrenoceptor agonist use	11.3	6.0	89**	
Without limitations	NR	NR	7	
Nights without sleep disturbance	NR	NR	3	
Episode-free days[e]	10.1	5.1	98**	
Resource consumption (rate per 100 patients/month)				
Healthcare contacts	18.5	40.7		55**
Absenteeism from school or work	15.6	35.0		55*
Use of inhaled β_2-agonists	47.5	57.1		17
Use of non-asthma medications	70.4	87.4		19

a Patients were randomised in a 2 : 1 ratio to zafirlukast and placebo, respectively.

b Corrected for baseline differences in percentage predicted forced expiratory volume in 1 second and measures of clinical effectiveness.

c Defined as (value for zafirlukast group minus value for placebo group) divided by value for placebo group.

d Defined as (value for placebo group minus value for zafirlukast group) divided by value for placebo group.

e Defined as the number of days without an asthma attack, β_2-adrenoceptor agonist use, sleep disturbance due to asthma or adverse events.

Abbreviation and symbols: NR = not reported; *p < 0.05, **p < 0.01 *vs* placebo.

among the zafirlukast-recipients (74.2 *vs* 83.7% in the placebo group; p = 0.002) may have been responsible for the greater treatment effects seen in this group, as patients with more severe asthma are likely to benefit more from treatment. The usefulness of these results in determining the effect of zafirlukast on disease outcome and costs are further limited, as several major expenses associated with asthma, including death and hospitalisation, were not incurred during the study because of the small number of patients recruited and the short study duration. Furthermore, this study did not include an analysis of the potentially high costs incurred as a result of treatment failure.

The cost impact of treatment failure in this setting has been assessed using data from a meta-analysis of 5 clinical trials. This meta-analysis demonstrated a significant reduction in the incidence of asthma exacerbations leading to treatment withdrawal in patients treated with zafirlukast compared with placebo for 13 weeks (3.5 *vs* 6.6%; p = 0.008).[88] Although direct and indirect costs incurred by the patients were not considered, calculations based on the number of asthma exacerbations per 1000 patients per year showed that the costs incurred by placebo-treated patients were almost twice those calculated for the zafirlukast treatment group (£48 000 *vs* £26 000; 1995 costs).[95] Well designed pharmacoeconomic studies which compare zafirlukast with other anti-asthma drugs are required to fully quantitate the effect of zafirlukast on disease outcome in economic terms.

6. Tolerability

This section is primarily based on data from 5188 patients treated with zafirlukast (generally 20mg twice daily) in controlled clinical trials of up to 20 weeks duration.[61] 1120 of these patients went on to receive zafirlukast 20mg twice daily in longer term trials (duration ≥21 weeks) and 172 of these received the drug for >2 years. 380 and 316 patients, respectively, received zafirlukast 40mg and 80mg twice daily in studies of >6 months duration.

The most frequent adverse events associated with short term zafirlukast therapy (≤20 weeks) were pharyngitis (16%), headache (12%) and aggravation reaction (a COSTART term used to define worsening of any pre-existing condition, e.g. asthma) [8%].[61] Other adverse events including infection, rhinitis, flu syndrome, nausea and cough developed in 3 to 4% of patients. Notably, the incidence and profile of adverse events did not differ significantly between zafirlukast- and placebo-treated patients (table V). Treatment withdrawal due to exacerbation of asthma was necessary in 1.3 and 2.4% of zafirlukast- and placebo-treated patients, respectively; withdrawals for all other non-serious adverse events were necessary in 2.6 and 3.2% of patients.

A similar profile of adverse events was reported during long term zafirlukast therapy (21 weeks to >2 years; n = 1120).[61] Over this longer period, pharyngitis (46%), aggravation reaction (28%), headache (16%), infection (16%), flu syndrome (10%) and rhinitis (8%) were the most frequent adverse events. Other adverse events occurred with an incidence of ≤6% (table V).

Serious adverse events, the most frequent of which were aggravation reaction, accidental injury and asthma (defined as increased bronchoconstriction), were reported in 1.3% of patients treated with short term zafirlukast therapy compared with 1.0% of placebo recipients. Aggravation reaction (1.5%) and infection (0.8%) were the most frequent serious adverse events during long term zafirlukast therapy.

During both short and long term treatment, higher doses of zafirlukast (40 or 80mg twice daily) were not generally associated with a higher incidence of adverse events. However, infrequent asymptomatic elevations in serum liver enzymes have been associated with zafirlukast 80mg twice daily.[61] Although the levels returned to normal after cessation of therapy, the administration of zafirlukast at doses exceeding 40mg twice daily is not recommended.

The incidence of adverse events among elderly patients treated with zafirlukast was similar to that of the general population, with the exception of infection.[61] The risk of infection was increased in elderly patients treated with zafirlukast; however, except for 1 case of appendicitis, these infections did not necessitate the cessation of zafirlukast therapy.

No deaths, hospitalisations or serious adverse events were reported among 276 evaluable patients with mild to moderate asthma randomised to treatment with zafirlukast (5, 10, or 20mg twice daily) [n = 206] or placebo (n = 70) for 6 weeks in a multicentre double-blind trial.[64] The majority of adverse events were mild or transient and occurred with a similar frequency in both the zafirlukast and

Table V. Tolerability profile of zafirlukast presented as the incidence of adverse events (%). Data were taken from a large database comprising a total of 5188 patients treated with zafirlukast in controlled clinical studies[61]a

Adverse event	Short term therapy[b]		Long term therapy[c]
	zafirlukast (n = 5188)	placebo (n = 2573)	zafirlukast (n = 1120)
Pharyngitis	16	16	46
Headache	12	11	16
Aggravation reaction[d]	8	10	28
Infection	4	4	16
Rhinitis	3	4	8
Flu syndrome	3	3	10
Nausea	3	2	4
Cough	3	3	6
Pain	NR	NR	6
Bronchitis	NR	NR	6
Accidental injury	NR	NR	5
Back pain	NR	NR	5
Diarrhoea	NR	NR	4
Abdominal pain	NR	NR	3
Gastroenteritis	NR	NR	3
Rash	NR	NR	3

a Data were measured from graphs and rounded to the nearest 1%. Only adverse events which developed in ≥3% of patients were recorded.

b Patients were treated with zafirlukast (generally 20mg twice daily) for ≤20wk.

c Patients were treated with zafirlukast 20mg twice daily for 21wk to >2y.

d A COSTART term for the worsening of any pre-existing condition e.g. asthma.

Abbreviation: NR = not reported.

placebo treatment groups (53 *vs* 63% of patients). The most frequent adverse events associated with zafirlukast therapy were pharyngitis (16 *vs* 23% in the placebo treatment group), headache (14 *vs* 11%), rhinitis (6 *vs* 1%) and gastritis (2 *vs* 6%). There was some variation between the incidence of adverse events associated with the 3 zafirlukast dosage regimens; the incidence of pharyngitis was greatest with zafirlukast 20mg twice daily (20 *vs* 13 to 15%), whereas headache was reported more frequently with the lower zafirlukast dosages (7 *vs* 16 to 18%). During the study, 1 patient treated with zafirlukast 10mg twice daily was withdrawn because of fever and weakness and 2 patients who received placebo were withdrawn from treatment because of an exacerbation of asthma or abnormal serum biochemistry results.

Other randomised double-blind studies evaluating treatment with zafirlukast for 6 or 13 weeks reported the drug to be well tolerated.[71-73,79,82,83]

Postmarketing surveillance studies have recently highlighted a small number of cases of Churg-Strauss syndrome, a rare and potentially fatal eosinophilic vasculitis, among patients treated with zafirlukast.[96] This syndrome has been diagnosed in 6 patients with severe asthma in whom oral corticosteroid therapy was being withdrawn or discontinued during treatment with zafirlukast.

7. Dosage and Administration

Zafirlukast is indicated for the treatment and prophylaxis of persistent asthma. For adults and children aged ≥12 years, the recommended dosage schedule for zafirlukast is one 20mg tablet administered twice daily at regular intervals.[60] Because of potential reductions in the bioavailability of zafirlukast, the drug should not be administered with food (see section 3.1). Treatment with zafirlukast should be continued during symptom-free periods and, although not recommended for the management of acute asthma symptoms, zafirlukast can be continued during episodes of acute asthma.

No dosage guidelines are currently available for the use of zafirlukast in paediatric patients (aged <12 years).

Zafirlukast is excreted in breast milk and therefore should not be used by women who are breastfeeding. Furthermore, zafirlukast should not be used during pregnancy, as comprehensive well controlled trials have not been conducted in this patient group.

There are no specific dosage recommendations for the elderly. Although the clearance of zafirlukast was reduced in patients aged >66 years (section 3.2), no increase in the overall incidence of adverse events or patient withdrawals due to adverse events was reported in clinical trials involving elderly patients treated with zafirlukast 20mg twice daily (duration not specified).[60]

Further investigations are required to determine the pharmacokinetics and tolerability of zafirlukast in patients with hepatic impairment; a reduction in the clearance of zafirlukast has been reported in patients with stable alcoholic cirrhosis (section 3.2), suggesting the need for specific dosage guidelines for this patient group. Elevated liver enzyme levels may develop on rare occasions in patients treated with zafirlukast. Medical attention should be sought immediately and liver function tests performed if a patient experiences symptoms of liver dysfunction such as right upper quadrant abdominal pain, nausea, fatigue, pruritus or jaundice.[97]

As Churg-Strauss syndrome has been reported in 6 patients who were being tapered or withdrawn from oral corticosteroid therapy while receiving treatment with zafirlukast (see section 6), such patients should be closely monitored.[96]

No dosage adjustments are necessary in patients with renal impairment.

8. Potential Place of Zafirlukast in the Management of Asthma

Asthma is a chronic inflammatory disease of the airways characterised by recurrent episodes of wheezing, chest tightness, dyspnoea, coughing and nocturnal awakenings. These symptoms are usually associated with widespread but variable airflow

limitation and an increase in bronchial hyperresponsiveness to a variety of physical, physiological, chemical and biological stimuli.[98]

The goals of effective asthma management should include the attainment of minimal or no symptoms, a decrease in the number of acute asthma attacks, a reduction in requirements for short-acting inhaled β_2-adrenoceptor agonist therapy, near normal lung function and a greater ability to participate in normal physical activities. In addition to the pharmacological management of asthma, a comprehensive treatment approach should also include patient education[99] and avoidance of known allergens such as house dust mites, animal dander and tobacco smoke.[100]

The recently updated UK[92] and US guidelines[93] for the management and treatment of persistent asthma recommend a stepwise approach for the pharmacological treatment of this disease. The selection of treatment is based on the severity of the asthma being treated, with the number of medications and the dose and/or frequency of their administration increasing with the severity of the disease.[92,93] Of particular note in these updated guidelines is the increase in emphasis on the early use of anti-inflammatory medications to gain initial control of the disease, even in patients with persistent but mild asthma. Currently, corticosteroids remain the most effective and frequently used anti-inflammatory agents available,[93] the anti-inflammatory response to sodium cromoglycate and nedocromil sodium being less predictable.

Following the discovery of their importance in the aetiology of asthma, the leukotrienes have become a significant target for the development of new agents for the treatment of this disease. Two approaches to the blockade of leukotriene synthesis have been used in the drug development process, namely the development of 5-lipoxygenase inhibitors and leukotriene receptor antagonists.

In preliminary clinical efficacy studies, the oral leukotriene receptor antagonist zafirlukast produced a modest improvement in lung function and symptom control and reduced the need for short-acting inhaled β_2-adrenoceptor agonist therapy in patients with mild to moderate asthma.

Although not included in current UK asthma guidelines, zafirlukast has been incorporated in the recently updated US guidelines.[93] These guidelines suggest that zafirlukast may be considered as an alternative treatment option to low dose inhaled corticosteroid therapy, sodium cromoglycate or nedocromil sodium for the treatment of mild persistent asthma in patients aged ≥12 years.[93] Despite these recommendations, further clinical studies are still required to identify patients who would most benefit from zafirlukast and to more clearly define the role of this drug among existing antiasthma medications in current treatment guidelines. In particular, studies are required to evaluate the efficacy of zafirlukast in patients with severe asthma and in children aged <12 years, and to determine the role of zafirlukast in the attenuation of the underlying inflammatory response in asthma. Although zafirlukast has been reported to inhibit cellular infiltration into the airways after allergen challenge, the extent of the protection conferred by zafirlukast against bronchial hyper-responsiveness is currently unclear.

High dosages of zafirlukast (80mg twice daily), which are outside recommended treatment guidelines, appear to allow tapering of corticosteroid dosage; however, confounding data from 2 studies preclude any clear conclusions regarding the potential steroid-sparing effect of zafirlukast at recommended dosages (20mg twice daily). Furthermore, patients who require tapering of their oral corticosteroid dosage during treatment with zafirlukast should be closely monitored as Churg-Strauss syndrome has been reported in 6 zafirlukast-treated patients in association with discontinuation of oral corticosteroid prophylaxis.

Although inhaled antiasthma medications facilitate the use of lower dosages compared with oral medications, thereby reducing systemic adverse effects, their use is often complicated by reduced compliance due to poor inhaler technique.[101,102] Therefore, an important advantage of zafirlukast is its availability as an oral formulation, which should

promote improved patient compliance and more predictable drug bioavailability compared with currently available inhaled medications. However, patients receiving concomitant treatment with other oral medications such as warfarin will require careful monitoring because of the potential for drug interactions with zafirlukast. Although zafirlukast is administered orally, available data suggest that it is generally well tolerated. Rare cases of elevated liver enzymes have been reported with high dosages of the drug (80mg twice daily).

Thus, preliminary data suggest that zafirlukast is a potentially useful alternative therapeutic option for the prophylaxis and treatment of persistent mild to moderate asthma in patients aged ≥12 years. As an oral medication, zafirlukast may be particularly useful in patients with poor compliance due to incorrect inhaler technique. It is expected that ongoing and future comparative studies with established antiasthma medications will enable zafirlukast to be definitively positioned within revised national and international asthma management guidelines.

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