ADIS DRUG EVALUATION

Drugs 2001; 61 (2): 285-315
0012-6667/01/0002-0285/$27.50/0

Zafirlukast

An Update of its Pharmacology and Therapeutic Efficacy in Asthma

Christopher J. Dunn and *Karen L. Goa*

Adis International Limited, Auckland, New Zealand

Various sections of the manuscript reviewed by:

P. Barnes, Department of Thoracic Medicine, Imperial College School of Medicine at the National Heart and Lung Institute, London, England; ***P. Black***, Faculty of Medicine, University of Auckland Medical School, Auckland, New Zealand; ***A.P. Sampson***, Division of Respiratory Cell and Molecular Biology, Southampton University School of Medicine, Southampton, England; ***J.P. Kemp***, Allergy and Asthma Medical Group and Research Center, San Diego, California, USA; ***E.G. Weinberg***, Allergy Clinic, Red Cross War Memorial Children's Hospital, Rondebosch, South Africa.

Data Selection

Sources: Medical literature published in any language since 1998 on Zafirlukast, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International, Auckland, New Zealand). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: Medline search terms were 'zafirlukast' or 'ICI 204219' and 'asthma'. EMBASE search terms were 'zafirlukast' or 'ICI 204219' and 'asthma'. AdisBase search terms were 'zafirlukast' and 'asthma'. Searches were last updated 5th February 2001.

Selection: Studies in patients with asthma who received zafirlukast. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Zafirlukast, asthma, leukotriene antagonists, pharmacodynamics, pharmacokinetics, therapeutic use, pharmacoeconomics, tolerability, dosage and administration, review.

Contents

Summary

Abstract

Zafirlukast is a selective and competitive orally administered inhibitor of the cysteinyl leukotrienes LTC_4, LTD_4 and LTE_4. The drug is indicated for the prophylaxis and treatment of chronic asthma, and has been developed in response to mounting evidence indicating the importance of the cysteinyl leukotrienes in the pathogenesis of this disorder.

The efficacy of zafirlukast 20mg twice daily has been shown in double-blind placebo-controlled studies of up to 13 weeks' duration in patients aged ≥12 years. Zafirlukast was consistently superior to placebo in improving objective measures of lung function and subjective measures such as symptom scores and use of as-required bronchodilator therapy. This dosage is also as effective when added to low-dosage inhaled corticosteroid therapy as doubling of corticosteroid dosages. Recent studies indicate superior efficacy over zafirlukast of twice-daily inhaled fluticasone propionate 88μg or salmeterol 42μg, although zafirlukast was nevertheless associated with clinical improvement. Data also show zafirlukast 40mg to be of similar efficacy to pranlukast 225mg (both twice daily).

Overall, preliminary pharmacoeconomic data suggest that healthcare costs are reduced by zafirlukast therapy, although superior cost effectiveness has been reported with inhaled fluticasone propionate, and further studies are needed. Data are available to show improvements in patient-rated quality of life, and preference for and high rates of compliance with zafirlukast.

In clinical trials, zafirlukast has shown an adverse event profile similar to that of placebo. Isolated reports of hepatic dysfunction in a small number of individuals receiving the drug have been received, and recommendations for monitoring of patients are in place. Although no causal relationship has been established between zafirlukast and Churg-Strauss Syndrome, patients undergoing corticosteroid dosage reductions require careful surveillance.

Conclusions: zafirlukast is an effective and well tolerated agent for preventive monotherapy in mild to moderate persistent asthma. Emerging data indicate benefit of the drug when added to low-dosage inhaled corticosteroids and show that it may be a viable alternative to inhaled adjunctive treatments and increased corticosteroid dosages in some patients. Although inhaled fluticasone propionate and salmeterol have been associated with greater clinical improvement than zafirlukast in clinical studies, compliance considerations and the confirmed clinical efficacy relative to placebo of the drug denote zafirlukast as an effective alternative in treatment programmes based on individualised therapy. As experience with zafirlukast accumulates, it is expected that the drug will be positioned more definitively in national and international treatment guidelines.

Pharmacological Profile

Zafirlukast is a selective and competitive inhibitor of the cysteinyl leukotrienes LTC_4, LTD_4 and LTE_4. In humans, the drug prevents bronchoconstriction induced by LTD_4, allergens, exercise, cold air, sulphur dioxide or platelet activating factor. Zafirlukast has also been shown to have a beneficial effect on airway inflamma-

tion induced by LTE_4, and to attenuate late-phase bronchoconstrictive responses to allergenic challenge. The effect of the drug on bronchial hyper-responsiveness has not been fully clarified, although limited data suggest a smaller effect of zafirlukast than inhaled fluticasone propionate in this respect.

Zafirlukast exhibits 2-compartment pharmacokinetic characteristics. Peak plasma concentrations are reached within 3 hours, and steady-state conditions are attained after 3 days of twice-daily oral administration. Coadministration with food reduces the rate and extent of absorption of the drug. Zafirlukast is approximately 99% bound to plasma proteins.

The mean plasma elimination half-life of zafirlukast ranged from 8 to 16 hours in pharmacokinetic studies, and the drug is metabolised extensively in the liver by the cytochrome P450 (CYP) system. Elimination of zafirlukast, chiefly as metabolites, takes place predominantly via the faecal route.

Inhibition by zafirlukast of the hepatic microsomal enzymes CYP2C9 and CYP3A gives rise to the potential for interactions with other drugs metabolised via these routes. Coadministration of zafirlukast with warfarin may result in increased prothrombin times, and careful monitoring with possible adjustment of warfarin dosages is required in patients so affected. Plasma concentrations of zafirlukast have been reduced in patients also receiving theophylline or erythromycin, and increased with coadministration of aspirin. Increases in plasma theophylline concentrations have not been reported in studies in patients who also received zafirlukast, although there have been isolated reports of increased serum/plasma concentrations of theophylline (occasionally with signs of theophylline toxicity) in patients on long term therapy who have had zafirlukast added to their medication. There have been no significant interactions reported with single doses of azithromycin or clarithromycin. Zafirlukast does not appear to affect oral contraceptive efficacy.

Therapeutic Use

The therapeutic efficacy of zafirlukast 20mg twice daily orally has been shown in a series of randomised and double-blind comparisons with placebo of up to 13 weeks' duration. Zafirlukast was consistently superior to placebo in improving objective measures of lung function [forced expiratory flow in 1 second (FEV_1) and morning and evening peak expiratory flow (PEF)] and subjective measures such as symptom scores and use of as-required bronchodilator therapy in patients with mild to moderate asthma. The drug has also shown efficacy in patients with severe persistent asthma, and data are available to show maintenance of benefit with long term use.

Three double-blind placebo-controlled studies of 4, 6 and 10 weeks' duration have been carried out in a total of 1193 children aged from 5 to 11 or 12 years with mild to moderate asthma. Improved asthma control was seen consistently with zafirlukast 10mg twice daily across these studies, not all of which are fully published.

According to preliminary reports, the addition of zafirlukast to low-dosage inhaled beclomethasone dipropionate therapy was at least as effective as doubling of corticosteroid dosages in 1 double-blind study and equivalent in another. In 1 study (n = 394), mean morning PEFs were increased from baseline over 13 weeks by 21, 25 and 13 L/min with zafirlukast 40 and 80mg twice daily and doubled dosages of beclomethasone dipropionate, respectively. Improvements of at least 10% in mean morning PEF were reported in 36% of patients treated with zafirlukast 20 or 80mg twice daily and in 38% of those on doubled corticosteroid dosages in the other trial (n = 440). At a dosage of 80mg twice daily, zafirlukast has also

been shown to improve asthma control when added to existing high-dosage inhaled corticosteroid therapy.

A series of randomised and double-blind 6- or 12-week studies (only one of which has been fully published to date) involving at least 100 or 200 patients in each treatment group has recently indicated inhaled fluticasone propionate 88μg twice daily to be more effective (in terms of pulmonary function, symptomatic improvement, β_2-agonist usage and frequency of nocturnal awakening) than zafirlukast 20mg twice daily in the control of mild to moderate asthma. In most studies, patients had been managed previously with inhaled short-acting β_2-agonist therapy. Nevertheless, in 2 studies in which placebo controls were included, strong trends towards improved lung function were noted in patients receiving zafirlukast. Mean percentages of symptom-free days were increased to a significantly greater extent with fluticasone propionate than with zafirlukast, but improvements with zafirlukast were nevertheless superior to those seen with placebo.

β_2-agonist usage and nocturnal awakenings were statistically significantly reduced relative to placebo by zafirlukast in 1 placebo-controlled trial. In the other such study, the mean percentage of days on which β_2-agonist therapy was not needed was increased to a greater extent with fluticasone propionate than with zafirlukast ($p < 0.05$), but significant increases ($p < 0.05$) relative to placebo were nevertheless seen with both active treatments (37.5% with zafirlukast and 48.9% with fluticasone propionate).

Significantly greater improvements with inhaled salmeterol 42μg twice daily than with zafirlukast 20mg twice daily were reported in 2 randomised double-blind 4-week studies in patients with moderate asthma, over 80% of whom were also receiving inhaled corticosteroid therapy. In 1 study, mean morning and evening PEFs were increased from baseline by 3.5 and 2.5%, respectively, with zafirlukast, and by 8 and 5.6% with salmeterol (between-group differences were statistically significant). The difference between groups at 4 weeks for mean FEV_1 was not significant, however, and statistically significant increases from baseline were reported with both treatments. Salmeterol recipients reported significantly greater improvement relative to baseline in patient-rated symptom scores than did patients receiving zafirlukast. There was no significant difference between groups in reduction of mean frequency of nocturnal awakening, however.

Overall, data from a double-blind 6-week study in 298 Japanese patients with mild to moderate asthma show zafirlukast 40mg twice daily to be of similar efficacy in terms of global efficacy ratings and mean morning and evening PEFs to pranlukast 225mg twice daily. The rate of marked or moderate improvement was shown to be statistically significantly greater with zafirlukast than with pranlukast by 1 statistical method (Dunnett-Gent 1-sided test), but not by another (Wilcoxon 2-sample test). Nonsignificant trends towards greater increases from baseline in mean morning and evening PEFs were observed with zafirlukast.

A nonblind pharmacoepidemiological study has been carried out in the practice setting in 3759 patients with mild to moderate or severe asthma who received zafirlukast 20mg twice daily for 4 weeks. The extent of improvement in pulmonary function decreased with increasing age, but zafirlukast was associated with overall clinical improvement in patients of all ages. Adolescents showed the greatest improvements in all measures of efficacy (PEF and FEV_1, β_2-agonist use, symptom scores, nocturnal awakenings and mornings with asthma).

Pharmacoeconomic, Quality-of-Life and Compliance Considerations

Cost analyses based on results of clinical studies have shown significant reductions in the use of healthcare resources relative to placebo in patients receiving zafirlukast. According to a meta-analysis of 5 placebo-controlled trials, costs associated with asthma exacerbations per 1000 patients per year were £26 000 and £48 000 (1995 values) for zafirlukast and placebo, respectively.

Recent cost and cost-effectiveness analyses have been based on results of double-blind clinical studies comparing zafirlukast with inhaled fluticasone propionate, and have consistently shown lower costs from a third party payer's perspective with corticosteroid treatment. One report showed daily direct costs per successfully treated patient to be $US4.64 for zafirlukast and $US2.76 (1998 values) for fluticasone propionate; these values increased to $US6.02 and $US3.81 when indirect costs (based on missed days of work) were included. A study in 451 patients yielded cost-effectiveness ratios of $US428.64 and $US157.67 per sickness-free day per patient per month for zafirlukast and fluticasone dipropionate, respectively (year of costing not stated).

Results of retrospective US analyses of medical claims are inconclusive. One study showed a 21% increase from baseline in the total annual cost of asthma care over 21 months in 392 patients receiving zafirlukast, whereas 857 individuals receiving fluticasone propionate showed a 22% decrease ($p < 0.0001$ between groups). In an analysis of managed care claims from 780 patients, however, outpatient visits, inpatient stays, emergency department visits and prescriptions for inhaled salbutamol were all significantly reduced ($p < 0.002$) over 3 months by the addition of zafirlukast to existing inhaled corticosteroid therapy.

There is some disagreement in the literature over the effect on quality of life of zafirlukast treatment, although data are available to show improvement in patients treated with the drug. No clinically meaningful change with zafirlukast 20mg twice daily over 12 weeks in quality of life according to the Asthma Quality-of-Life Questionnaire (AQLQ) was suggested in a comparison with fluticasone propionate 88μg or salmeterol 42μg twice daily. However, these findings are at variance with data showing improved quality of life after 13 weeks' treatment with zafirlukast 20mg twice daily in patients with moderate asthma. Twice-daily therapy with zafirlukast has also been shown to be associated with greater improvements in quality of life than increased dosages of inhaled corticosteroids in a 52-week UK assessment.

Data are also available to show high rates of compliance with zafirlukast therapy, with an approximate 2 to 1 preference by patients for oral zafirlukast over inhaled treatment.

Tolerability

Pooled data from 5188 patients treated with zafirlukast in clinical trials showed pharyngitis (incidence of 16%), headache (12%) and aggravation reaction (a COSTART term used to define worsening of any pre-existing condition) [8%] to be the major adverse events reported with short term therapy (≤20 weeks). Other adverse events, reported in 3 to 4% of patients, included infection, rhinitis, influenza syndrome, nausea and cough. All were reported with incidences similar to those with placebo.

According to more recent US tolerability data based on 6090 healthy volunteers and patients with asthma, only headache was reported with an incidence above 10% (12.9% with zafirlukast and 11.7% with placebo) in a listing of adverse events reported at rates higher than those with placebo in at least 1% of zafirlukast recipients. UK prescribing information highlights headache (inci-

dence of 9.9 *vs* 9% with placebo) and GI disturbance (nausea 2.6 *vs* 2.2%; vomiting 1.2 *vs* 1%; diarrhoea 2.3 *vs* 1.8%; and abdominal pain 1.6 *vs* 1.2%) as the predominant adverse events reported in comparisons of zafirlukast with placebo.

Comparative clinical studies have shown no clinically significant differences between zafirlukast and pranlukast or inhaled fluticasone propionate or salmeterol in adverse event profiles.

Raised serum levels of liver enzymes have been occasionally reported in patients receiving zafirlukast, but these usually return to normal or near-normal after withdrawal of treatment. There have been isolated reports of hepatic dysfunction in a small number of patients, and recommendations have been made to address this issue.

Zafirlukast 10mg twice daily had a tolerability profile similar to placebo in studies in 411 children aged 5 to 11 years, with pharyngitis being reported most commonly (9.3 and 13.6%, respectively, of zafirlukast and placebo recipients). Treatment-related adverse events were reported in 4.2, 7.4 and 8.1%, respectively, of adolescent, adult and elderly patients receiving zafirlukast in a pharmacoepidemiological study in 3759 individuals. Relative to other patient groups, headache, abdominal pain, diarrhoea and nausea were most frequent, and infection and sinusitis least common, in elderly patients.

Churg-Strauss Syndrome, a form of vasculitis, has been noted in patients receiving zafirlukast. The majority of reports have been in patients in whom oral corticosteroid dosages were being reduced, and it is thought that the syndrome is seen chiefly in patients with an underlying eosinophilic disorder, masked by corticosteroid treatment, that becomes clinically apparent when corticosteroid dosages are reduced following the addition of zafirlukast therapy. No direct causal relationship has been established between Churg-Strauss Syndrome and the leukotriene receptor antagonists.

Dosage and Administration

Zafirlukast is administered orally as one 20mg tablet twice daily at regular intervals for the prophylaxis and treatment of persistent asthma in patients aged 12 years and over. As food may reduce the bioavailability of zafirlukast, the drug should be taken at least 1 hour before or 2 hours after meals.

There are no specific dosage guidelines for the use of zafirlukast in the elderly, but a dosage of 10mg twice daily is recommended for children aged 7 to 11 years in some countries, including the US, and the drug is contraindicated in children aged under 12 years in the UK. Prescribing guidelines in the latter country also state that zafirlukast should not be given to patients with hepatic impairment or cirrhosis. US guidelines state that dosage adjustments are not required in patients with renal impairment, but zafirlukast is contraindicated in the UK in patients with moderately or severely impaired renal function.

The recognition of asthma as a chronic inflammatory disorder, concern over the limitations of established therapies and identification of the important role played by the leukotrienes in the pathogenesis of asthma have led to the development of a class of new agents, the leukotriene receptor antagonists, of which zafirlukast (fig. 1) is a member. The pharmacology and therapeutic potential of zafirlukast were first reviewed in *Drugs* in 1998,[1] and the present article re-examines the role of this agent in the light of research carried out and clinical experience gained since that time.

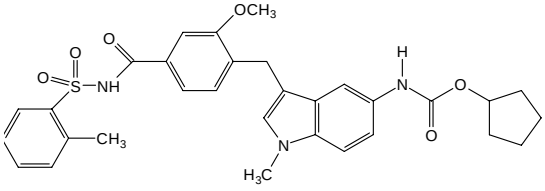

Fig. 1. Structural formula of zafirlukast.

1. Physiological Role of the Leukotrienes

The leukotrienes are lipoxygenase products formed by the oxidative metabolism of arachidonic acid, a 20-carbon fatty acid. The discovery of this group of compounds dates back over 60 years to studies on snake venom that revealed a substance that caused sustained contractions of airway smooth muscle.[2] The pattern of this contractile response differed from that seen with histamine, and the newly discovered substance was named slow-reacting substance of anaphylaxis (SRS-A). SRS-A was later discovered in lung tissue from individuals with asthma.[3]

The compounds making up SRS-A are now known to be the inflammatory mediators leukotriene C_4 (LTC_4), D_4 (LTD_4) and E_4 (LTE_4), also known as the cysteinyl leukotrienes (reviewed by Adkins and Brogden[1]). This group of compounds is one of 2 leukotriene classes, the other of which consists of the non-peptide leukotrienes A_4 (LTA_4) and B_4 (LTB_4). Their precursor, arachidonic acid, becomes available after cleavage from cell membrane phospholipids by phospholipase A_2,[4,5] and is then acted upon by 5-lipoxygenase after presentation by 5–lipoxygenase-activating protein (FLAP) [both of which are located in the nuclear envelope[6]] to form 5-hydroperoxyeicosatetraenoic acid[7,8] (fig. 2). This is in turn converted to LTA_4, an unstable compound that is converted rapidly to the dihydroxyleukotriene LTB_4 in neutrophils, or to the cysteinyl leukotriene LTC_4 in eosinophils, mast cells and alveolar macrophages.[9,10] After formation, LTC_4 is transported into the extracellular space where LTD_4 is formed by the loss of a glutamic acid moiety.[11,12] Subsequent cleavage by extracellular dipeptidases leads to the formation of LTE_4.

The leukotrienes exert their physiological effects by binding to specific receptors. Two cysteinyl leukotriene receptor subtypes, $CysLT_1$ and $CysLT_2$, have been identified pharmacologically in humans,[13] and have been characterised more recently after cloning in *Xenopus laevis* oocytes and/or the human embryonic kidney cell line HEK-693.[14,15] Most of the actions of the cysteinyl leukotrienes are mediated by the $CysLT_1$ receptor, which is found in the smooth muscle of airways and is activated by all 3 compounds (LTC_4, LTD_4 and LTE_4). The effects produced include smooth muscle contraction leading to bronchoconstriction,[16-19] increased vascular permeability[20] and mucus production,[21] and inflammatory cell infiltration into the lungs.[22,23] In humans, the $CysLT_2$ receptor mediates constriction of pulmonary vascular smooth muscle, although this process is less well understood than those mediated by the $CysLT_1$ receptor.[24] A receptor that is acted upon by LTB_4 and that predominantly mediates chemotaxis [the B leukotriene (BLT) receptor] has also been identified.[25]

2. Pharmacological Profile

2.1 Pharmacodynamics

As reported previously by Adkins and Brogden,[1] zafirlukast is a selective and competitive inhibitor of LTC_4, LTD_4 and LTE_4. Preclinical studies in guinea-pigs showed the drug to inhibit the binding of LTD_4 and LTE_4 to parenchymal lung membrane tissue,[26] to antagonise LTD_4-induced dyspnoea[26] and to attenuate leukotriene-induced eosinophil responses[23] in a dose- or concentration-dependent manner. Zafirlukast also inhibited and reversed ovalbumin-induced bronchoconstriction in sensitised animals, and dose-dependently inhibited LTD_4-induced tracheal oedema.[26]

Extensive human data are available to show the ability of zafirlukast to confer protection against a

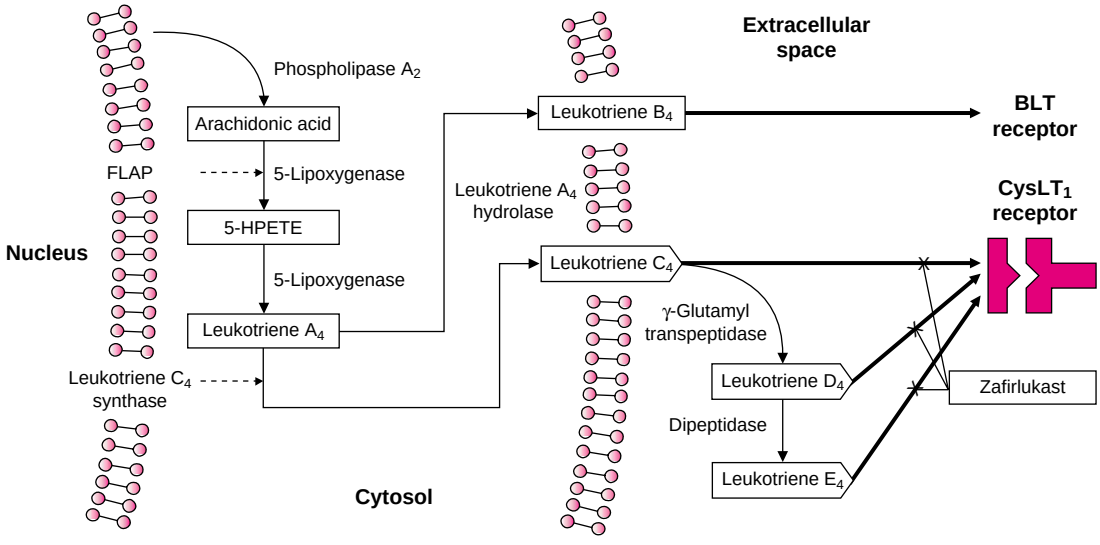

Fig. 2. Biochemical formation and receptor interactions of the leukotrienes. The precursor, arachidonic acid, is cleaved from the phospholipid bilayer by cytosolic phospholipase A_2 as shown. Leukotrienes B_4 and C_4 are carried through the cell membrane into the extracellular space by membrane transporters. Note blockade of access of leukotrienes C_4, D_4 and E_4 to the cysteinyl leukotriene receptor $CysLT_1$ by zafirlukast. **BLT** = B leukotriene; **5-HPETE** = 5-hydroperoxyeicosatetraenoic acid; **FLAP** = 5-lipoxygenase-activating protein.

variety of challenges that induce bronchoconstriction. Previously reviewed results[1] from double-blind, placebo-controlled crossover studies involving 6 to 39 participants have shown the efficacy of single doses of the drug in the prevention of bronchoconstriction induced by LTD_4,[27-30] allergens,[31-34] exercise,[35-37] cold air,[38-41] sulphur dioxide[42] or platelet activating factor.[43] Most of these studies were carried out in patients with asthma and involved assessments based on forced expiratory volume in 1 second (FEV_1). Zafirlukast was administered orally in most trials, and although doses ranged from 5 to 100mg, 20 or 40mg was used most frequently. Treatment was given from 0.5 to 24 hours before the challenge, with an interval of 2 to 8 hours being most common.

Since publication of the last review of zafirlukast in *Drugs*, preliminary data have become available from a double-blind study to confirm the beneficial effect of the drug on airways inflammation induced by LTE_4.[44] After initial screening to determine the dose of LTE_4 required to reduce FEV_1 by 15% (PD_{15}), 6 weeks' oral therapy with zafirlukast 80mg twice daily was associated with substantial reductions relative to placebo in eosinophil and neutrophil counts in bronchial biopsies taken both before and after repeat LTE_4 (PD_{15}) challenge in a total of 19 adults with mild asthma (fig. 3).

Data reported in the previous review,[1] which showed the protective effect of zafirlukast against the early response to allergenic challenge have been supported by 2 recent and similarly designed randomised and double-blind crossover studies in a total of 36 patients with cat-induced asthma.[45,46] In both trials, patients received zafirlukast 20mg twice daily or placebo orally for 1 week, and were exposed to allergenic material at the end of each treatment period by being placed in a sealed room with 2 cats. Overall decreases in median FEV_1 relative to baseline were significantly smaller after zafirlukast than after placebo treatment [26.5 *vs* 33.12% ($p = 0.02$)[45] and 15 *vs* 25% ($p = 0.019$)[46]]. In one of the studies (for which a fully published report was available),[45] median FEV_1 reductions

were significantly smaller with zafirlukast 15 and 30 minutes after the start of the challenge, but not at 45 and 60 minutes. It should be noted that the median challenge duration was significantly longer with zafirlukast than with placebo after adjustment for differences in levels of allergenic exposure (risk ratio 0.37; p = 0.0223).

Many patients also experience a late bronchoconstrictive response to allergenic challenge that is associated with tissue oedema, infiltration and recruitment of inflammatory leukocytes and increased bronchial hyper-responsiveness.[47,48] This response develops 3 to 6 hours after challenge and may last for up to 24 hours. Previously reported preliminary data indicated attenuation of the late-phase response by zafirlukast given orally,[32,34,49] but no further studies of this effect have been published to date.

The full extent of the effect of zafirlukast on bronchial hyper-responsiveness remains to be clarified. Most recent data are from a double-blind crossover comparison with inhaled fluticasone propionate in 30 patients with mild to moderate asthma.[50] Patients received zafirlukast 20mg orally or fluticasone propionate 100μg by inhalation twice daily for 2 weeks each, with a 2- to 4-week washout period between treatments. Mean concentrations of nebulised histamine required to cause a 20% reduction in FEV_1 (PD_{20}) were 1.61 and 0.99 g/L after fluticasone propionate and zafirlukast treatment, respectively (p = 0.037 between treatments), which indicated a greater effect with the corticosteroid. Mean baseline (pretreatment) PD_{20} values ranged from 0.57 to 0.58 g/L.

Zafirlukast exhibited bronchoprotective and anti-inflammatory effects with improved peak expiratory flow (PEF) when added to inhaled corticosteroid therapy in a recent study in 24 patients with the glycine-16 β_2-adrenoceptor genotype (which is known to predispose to β_2-agonist desensitisation and is present in around 40% of individuals with asthma).[51] Patients were randomised to single-blind crossover treatment with placebo, zafirlukast 20mg twice daily orally or formoterol 120μg twice daily by inhalation. Mean

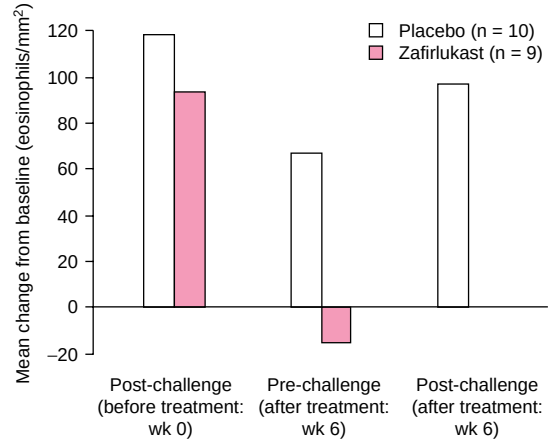

Fig. 3. Effect of zafirlukast on eosinophil counts in bronchial biopsies after leukotriene E_4 (LTE_4) challenge. After screening to determine the dose of LTE_4 inducing a 15% reduction in forced expiratory volume in 1 second (PD_{15}), 19 patients with mild asthma were randomised to double-blind treatment with zafirlukast 80mg or placebo twice daily orally for 6 weeks.[44] Fibreoptic bronchoscopy was carried out and biopsies taken before and 4 to 6 hours after LTE_4 PD_{15} challenge before and after treatment.

methacholine PD_{20} values were increased 1.5-fold with zafirlukast and 1.9-fold with formoterol relative to placebo (both $p < 0.05$). Zafirlukast, but not formoterol, was associated with significant ($p < 0.05$ *vs* placebo) suppression of mean exhaled levels of nitric oxide, a marker of bronchial inflammation. However, in contrast to inhaled fluticasone propionate, 4 weeks' treatment with zafirlukast 20mg twice daily had no beneficial effect on levels of exhaled nitric oxide in a recent double-blind crossover study in 8 patients already receiving inhaled β_2-adrenoceptor agonist therapy.[52]

2.2 Pharmacokinetics

The pharmacokinetic profile of orally administered zafirlukast has been described in detail previously by Adkins and Brogden;[1] the following is a brief summary based on updated information.[53-55]

Zafirlukast exhibits 2-compartment pharmacokinetic characteristics after oral administration. After

rapid GI absorption, peak plasma concentrations of the drug are attained typically within 3 hours. The absolute bioavailability of zafirlukast has not been determined, although coadministration with food generally reduces the rate and extent of absorption. Whether this effect is clinically significant is not known, but patients are nevertheless advised not to take the drug with food (section 6). Steady-state plasma concentrations of the drug are reached within 3 days with twice-daily administration, are proportional to dosage and are predictable from single-dose data. Zafirlukast is approximately 99% bound to plasma proteins (chiefly albumin) over the plasma concentration range 0.25 to 10 mg/L.

Systemic exposure to zafirlukast as shown by mean areas under plasma drug concentration versus time curves (AUCs) is greater in children than in adults. Accumulation in plasma after multiple doses is similar in children and adults, however. Plasma clearance of zafirlukast appears to decrease with advancing age. Peak plasma concentrations and AUC values in elderly men and women (aged up to 78 years) have been shown to be 2 to 3 times greater than those in younger patients.

Zafirlukast is metabolised extensively in the liver, and plasma concentrations of the drug decline in a biphasic fashion after oral administration. The mean elimination half-life in pharmacokinetic studies ranged from 8 to 16 hours. *In vitro* studies indicate that hydroxylation by the cytochrome P450 (CYP) isoenzyme CYP2C9 is the major route of biotransformation of zafirlukast, and that the drug inhibits both this and the CYP3A4 isoenzyme (section 2.3). The metabolites of zafirlukast in plasma are 90 times less potent *in vitro* in terms of leukotriene antagonism than the parent compound. Elimination primarily involves these metabolites and takes place predominantly via the faecal route, with urinary excretion accounting for less than 10% of an oral dose.

Peak plasma drug concentrations and AUC values are increased by 50 to 60% relative to those in healthy individuals in patients with stable alcoholic hepatic cirrhosis who receive zafirlukast. There are no data, however, from studies in patients with hepatitis or from long term trials in patients with cirrhosis, and recommendations vary between countries. Limited data suggest that the pharmacokinetics of zafirlukast are not altered, and that dosage adjustments are therefore not required, in patients with mild renal impairment, but recommendations again differ as to whether the drug should be used in patients with more severe disease (see section 6).

2.3 Pharmacokinetic Drug Interactions

Because zafirlukast inhibits the hepatic microsomal enzymes CYP2C9 and CYP3A, concurrent use of other drugs metabolised by these enzymes may result in altered clearances and plasma drug concentrations. As reported previously,[1] concomitant administration of zafirlukast and warfarin may result in increased plasma concentrations of *S*-warfarin and clinically significantly increased prothrombin times. Monitoring and adjustment of warfarin dosages where necessary are therefore recommended in patients receiving zafirlukast at the same time as warfarin.[53]

Other previously reviewed studies showed 30 to 40% reductions in plasma concentrations of zafirlukast when the drug was coadministered with theophylline or erythromycin in patients with asthma, and the concomitant administration of aspirin increased plasma concentrations of zafirlukast by approximately 45%.[1] Subsequent data indicate no significant effect of zafirlukast on plasma theophylline concentrations after single doses of the latter.[53,56] Increased serum/plasma concentrations of theophylline (sometimes accompanied by signs of theophylline toxicity) have been reported rarely in patients on long term therapy who have had zafirlukast added to their medication.[53,57] The mechanism behind this effect is not known, but an idiosyncratic reaction has been postulated.[56] A randomised crossover study in 12 healthy volunteers showed no evidence of any clinically significant interaction between zafirlukast 20mg twice daily and single 500mg doses of azithromycin or clarithromycin.[58]

Zafirlukast 40mg twice daily orally was not associated with any clinically significant effect on

Table I. National Heart, Lung, and Blood Institute/WHO classification of asthma severity.[62] Note that the presence of 1 feature in a category is sufficient to place a patient in that category

Mild intermittent	Intermittent symptoms (less than once weekly) and nocturnal symptoms rare (less than twice monthly). Exacerbations brief, with normal lung function between exacerbations. PEF or FEV_1 ≥80% predicted; variability in PEF <20%
Mild persistent	Symptoms at least once weekly, but less than once daily. Nocturnal symptoms more than twice monthly. Exacerbations may affect activity and sleep. PEF or FEV_1 ≥80% predicted; variability in PEF 20 to 30%
Moderate persistent	Symptoms daily; nocturnal symptoms present on more than 1 night each week. Daily use of short-acting inhaled β_2-agonists. Exacerbations affect activity and sleep. PEF or FEV_1 60 to 80% predicted; variability in PEF >30%
Severe persistent	Continuous symptoms limit physical activity, with frequent nocturnal symptoms and exacerbations. PEF or FEV_1 ≤60% predicted; variability in PEF >30%

FEV_1 = forced expiratory volume in 1 second; **PEF** = peak expiratory flow.

plasma ethinylestradiol concentrations or contraceptive efficacy in a 3-week study in 39 healthy women receiving a fixed-dosage estrogen/progestogen oral contraceptive regimen.[1,53]

As with all drugs that affect these hepatic enzyme systems, it is recommended that appropriate care be exercised when zafirlukast is coadministered with any drugs likely to inhibit CYP3A or CYP2C9.[53]

3. Therapeutic Use

At the time of the previous review,[1] the efficacy of zafirlukast 20mg twice daily over placebo had been shown in large double-blind parallel-group studies predominantly in patients aged 12 years and over with mild to moderate asthma (the drug was given orally in all studies discussed). Efficacy relative to placebo has also been demonstrated in patients with moderate to severe asthma[59-61] (a generally accepted asthma severity classification is given in table I[62]).

Since the publication of the last review, the efficacy of zafirlukast relative to placebo has been confirmed, and data pertaining to long term treatment have been published. Studies have also assessed the efficacy of zafirlukast relative to placebo in younger patients, and the drug has been compared with other anti-asthmatic therapies, most notably inhaled fluticasone propionate and the long-acting β_2-adrenoceptor agonist salmeterol. Zafirlukast has also been investigated as an alternative to increased dosages of inhaled corticosteroids, and as add-on therapy in patients receiving high dosages of these agents. A comparison with one other leukotriene antagonist, pranlukast, has also been carried out.

Changes in pulmonary function were measured chiefly in terms of PEF and FEV_1 across these studies. Symptoms and use of as-required inhaled bronchodilator therapy were also widely monitored. Randomised and double-blind study designs were commonly employed, although the results of many of the studies conducted since the last review are available in preliminary abstract form only (see following subsections for details).

As might be expected for an agent that modulates the actions of mediators of inflammation, case reports are available in the literature to suggest benefit of zafirlukast in a number of other conditions. These include eczema,[63,64] chronic urticaria,[65,66] sinusitis[67-69] and chronic nasal polyps.[70,71] However, results of a small randomised, double-blind and placebo-controlled comparison of zafirlukast with intranasal beclomethasone dipropionate do not support the use of zafirlukast in seasonal allergic rhinitis,[72] and the potential place, if any, of the drug in the management of these other conditions remains debatable and will not be discussed further in this article.

3.1 Comparisons with Placebo

Previously reported comparisons of zafirlukast with placebo were of 6 or 13 weeks' duration and involved between 106 and 762 patients treated previously with a short-acting inhaled β_2-agonist with or without theophylline. The efficacy of zafirlukast was assessed objectively by measuring pulmonary function (FEV_1 and morning and evening PEF), and subjectively by symptom assessment and by recording the use of as-required bronchodilator therapy [usually in the form of the inhaled short-acting β_2-adrenoceptor agonist salbutamol (albuterol)]. Studies consistently showed significantly greater improvements in these end-points with zafirlukast than with placebo.[1] Frequencies of nocturnal awakening were also consistently reduced to a greater extent in zafirlukast than in placebo recipients.

In the largest of these trials (n = 762),[73] in which patients were randomised after a single-blind run-in period of 7 to 14 days, treatment with zafirlukast 20mg twice daily for 13 weeks improved mean morning PEF by 13.6 L/min ($p < 0.01$) and increased mean FEV_1 by 0.08L ($p < 0.05$) relative to placebo. Mean weekly frequencies of nocturnal awakening were 2.05 and 2.52 after 13 weeks in the zafirlukast and placebo groups, respectively ($p < 0.05$) [awakenings decreased from baseline by 19.8 and 4.3%]. Trends towards reductions in daytime asthma symptom scores, mornings with asthma and β_2-agonist use, and increased morning PEF, were evident in zafirlukast recipients after 2 days.[73] These findings are concordant with those of another group of investigators,[74] who reported clinical improvement relative to placebo after only 3 days of therapy.

Patients with severe asthma at baseline (FEV_1 <65% predicted) derived greater benefit from zafirlukast treatment than did patients with less severe disease (FEV_1 >80% predicted) [note that classification of severity of disease by percentage of predicted FEV_1 is based on expected normal values according to recommendations by Crapo et al.[75] or Polgar and Promadhat[76]].[73] In addition, retrospective analyses of subsets of patients who participated in 13-week randomised double-blind studies have indicated greater benefit of zafirlukast in moderate asthma than in mild disease,[77] and have shown efficacy of the drug as monotherapy in patients with severe persistent asthma.[78] In 1 analysis (involving a total of 1484 patients previously managed with inhaled short-acting β_2-agonist therapy), incremental increases in benefit of zafirlukast 20mg twice daily were noted in subgroups with high levels of inhaled β_2-agonist use (>8 puffs/day), PEF variability (≥20%) and airflow obstruction (FEV_1 : forced vital capacity ratio <0.7) at baseline.[77]

Data from a meta-analysis of 5 randomised and double-blind 13-week studies indicated that the risk of an asthma exacerbation requiring oral corticosteroid treatment was approximately halved (odds ratio 0.53; $p = 0.01$) relative to placebo (n = 692) in patients receiving zafirlukast 20mg twice daily (n = 972).[79]

Preliminary data from a 6-week multicentre, double-blind and placebo-controlled Japanese study[80] concur with the findings reported in the previous review. Patients aged 16 years or over with mild to moderate asthma were recruited, of whom 243 completed the trial. Of these patients, 161 (66%) were receiving concurrent therapy with inhaled or oral corticosteroids. Mean morning PEF was increased by 21 to 26 L/min after treatment with zafirlukast 10, 20 or 40mg twice daily; the corresponding increase in the placebo group was 3 L/min.

3.2 Long Term Efficacy

Long term efficacy of zafirlukast 20mg twice daily has been shown in a nonblind extension[81] of a large double-blind study[73] (section 3.1). Of an original cohort of 762 patients, 443 (of whom 310 had previously received zafirlukast and 133 placebo during the 13-week double-blind phase) entered the nonblind extension phase in which all patients received active treatment. Data are available for the first 39 weeks to show sustained therapeutic benefit of zafirlukast, with significant improvements ($p \leq 0.01$) after 3 weeks relative to the start

of the nonblind extension period in mean, percentage predicted and personal best FEV_1 in patients who had previously received placebo.

Analysis of combined results for all patients (previous treatment with zafirlukast or placebo) showed a statistically significant mean increase from baseline (the start of the double-blind phase) in FEV_1 over the 52-week period covering the double-blind and extension phases of 4.7% ($p < 0.001$). Similarly, mean percentage predicted and percentage personal best FEV_1 values increased by 5.1 and 6, respectively (both $p < 0.001$).

3.3 Studies in Children

Preliminary results are available for 3 randomised, double-blind and placebo-controlled studies in children aged 5 to 11[82] or 12[83,84] years. Children with mild to moderate asthma (mean FEV_1 at baseline ranging from 72 to 77.8% predicted) were recruited, and dosages ranging from 5 to 40mg twice daily were given for 4 to 10 weeks after a single-blind run-in period of 7 to 14 days. Fully published combined results from 2 studies of 4 and 6 weeks' duration in a total of 714 children previously treated with short-acting inhaled β_2-agonists showed improvements relative to placebo from baseline in spirometric and patient-reported parameters with zafirlukast 5 or 10mg twice daily, with no additional clinical benefit being evident at higher dosages.[85] Onset of action was particularly rapid in this age group, with statistically significant improvements relative to placebo in morning and evening PEF, peak flow variability and β_2-agonist usage being noted by the end of day 1.

Pooled data analysis showed statistically significant improvements versus placebo in all efficacy outcomes except asthma episode score and nocturnal awakenings in children receiving zafirlukast 10mg twice daily.[85] Least squares mean treatment differences versus placebo were 2.55 for the mean change from baseline in percentage predicted FEV_1 ($p = 0.043$), 3.8 for the mean percentage change in FEV_1 ($p = 0.04$) and 5.09 for the mean percentage change in morning PEF ($p = 0.003$). Frequency of nocturnal awakening was significantly reduced ($p = 0.009$ *vs* placebo) in the subset of children with at least 1 awakening per week at baseline (78 zafirlukast 10mg and 86 placebo recipients) at this dosage level.

Both the above studies were designed with 52-week nonblind extensions during which patients received zafirlukast 10 ($n = 179$)[83] or 20mg ($n = 321$)[84] twice daily. Statistically significant ($p < 0.001$) improvements from baseline were reported at the end of these treatment periods for PEF,[83,84] FEV_1,[84] forced vital capacity,[84] peak flow variability,[83] symptoms[83] and β_2-agonist use[83] (no further details given in the abstracts available).

Improved asthma control was reported over 10 weeks with zafirlukast 10mg twice daily in the third study,[82] in which a total of 479 children, of whom 98 were already receiving inhaled corticosteroid therapy, were randomised to active treatment or placebo. Overall mean morning PEF was increased from baseline by 17 and 10 L/min in the zafirlukast and placebo groups, respectively ($p < 0.01$ between groups). Corresponding increases for patients also receiving inhaled corticosteroids were 18 and 3.5 L/min ($p < 0.05$). Mean frequencies of nocturnal awakening and β_2-agonist use were also statistically significantly reduced relative to placebo in the overall study population and in patients receiving inhaled corticosteroids. For children with night-time awakening in the run-in period, zafirlukast ($n = 22$) and placebo ($n = 19$) were associated with decreases of 1.4 and 0.5 awakenings per week, respectively ($p < 0.05$).

3.4 Comparisons with Increased Dosages of Inhaled Corticosteroids

Anti-inflammatory therapy with inhaled corticosteroids is a key feature of the pharmacological management of persistent asthma. Patients who remain symptomatic on low dosages of these agents are conventionally prescribed higher dosages to obtain ongoing control of their condition.[86] However, preliminary data from recent randomised and double-blind studies in patients aged 12 years and over have shown that the addition of zafirlukast to

low-dosage inhaled corticosteroid therapy may be an alternative to this approach.[87,88]

In 394 patients with asthma not satisfactorily controlled by low dosages of inhaled beclomethasone dipropionate (mean dosage 336 μg/ day), the addition of zafirlukast 40 or 80mg twice daily (n.b. dosages higher than those currently recommended) was at least as effective as the doubling of corticosteroid dosages.[87] Mean morning PEF was increased from baseline over 13 weeks by 21, 25 and 13 L/min in the zafirlukast 40 and 80mg and doubled corticosteroid groups, respectively. Significant improvements in daytime asthma symptom scores (mean improvements of 16% in the zafirlukast 40mg and doubled corticosteroid groups and 23% in the zafirlukast 80mg group), nocturnal awakening, mornings with asthma symptoms, β_2-agonist usage and FEV_1 were also reported in all 3 groups. Diurnal variability in mean PEF was reduced to a greater extent in patients receiving zafirlukast (by 16 and 24% relative to baseline in the 40 and 80mg groups, respectively) than in those receiving doubled dosages of inhaled corticosteroids (5% reduction from baseline; $p < 0.05$ *vs* zafirlukast 80mg twice daily). Of patients in the zafirlukast 40 and 80mg groups, 29 and 33%, respectively, showed improvements of at least 10% in PEF; this was compared with 22% of those in the doubled corticosteroid group.

Other investigators randomised 440 patients previously on inhaled beclomethasone dipropionate 400 to 500 μg/day to additional zafirlukast 20 or 80mg twice daily or doubled corticosteroid dosages for 12 weeks,[88] and noted similar results across treatment groups. Improvements of at least 10% in mean morning PEF were reported in 36% of patients in both zafirlukast groups, and in 38% of those randomised to an increased corticosteroid dosage. Incidences of asthma exacerbations were 26, 20 and 25% in the zafirlukast 20 and 80mg and doubled corticosteroid groups, respectively. It should be noted that preliminary details only are available for both of these studies, and the severity of asthma at baseline in participating patients was not reported.

At the time of the last review of zafirlukast in *Drugs*,[1] 2 multicentre, double-blind and placebo-controlled studies had been performed to assess the potential steroid-sparing effect of zafirlukast 20mg twice daily in patients receiving inhaled corticosteroids.[89,90] In both studies, one of which involved 359 patients with mild stable asthma and a study duration of 20 weeks,[89] and the other 262 patients with moderate asthma who were studied over 12 weeks,[90] dosages of inhaled corticosteroids were reduced by 60 to 85% with no loss of symptom control. However, the extent of the reductions reported indicates that patients were not receiving the lowest effective corticosteroid dosages at study entry, and any conclusions that can be drawn are therefore limited.

3.4.1 Addition to High-Dosage Corticosteroid Therapy

Zafirlukast has been shown to improve pulmonary function and symptoms, and to reduce the risk of exacerbation of asthma, when added at a dosage of 80mg twice daily to high-dosage inhaled corticosteroid treatment. In a double-blind multicentre study, 368 patients with chronic asthma requiring treatment with at least 1.2mg of inhaled beclomethasone dipropionate daily or an equivalent dosage of budesonide dipropionate or fluticasone propionate were randomised to additional treatment with zafirlukast (n = 180) or placebo (n = 188) for 6 weeks.[91]

The primary study end-point of mean morning PEF was increased from baseline by 18.7 L/min with zafirlukast and by 1.5 L/min with placebo after 6 weeks. The least squares mean treatment difference of 17.5 L/min was statistically significant ($p < 0.001$). Least squares mean differences between treatments were also statistically significant for mean evening PEF (16.2 L/min; $p = 0.002$), FEV_1 (0.12L; $p = 0.014$), daytime asthma symptom score (–0.28; $p < 0.001$), patient-reported β_2-agonist usage (–0.93 puffs/day; $p = 0.007$) and β_2–agonist-free days per month (2.38; $p = 0.021$). The between-treatment differences for mornings with asthma and number of symptom-free days per month did not attain statistical significance, how-

Table II. Randomised, double-blind parallel-group studies comparing zafirlukast 20mg twice daily orally (ZAF) with inhaled fluticasone propionate 88μg twice daily (FP) in patients with mild to moderate asthma

Reference	FEV_1 (L) [% predicted] at baseline	Treatment regimen and duration (no. of patients)	Mean changes from baseline at end-point				
			PEF (am, pm; L/min)	FEV_1 (L)	β_2-agonist usage	symptom scores	nocturnal awakenings (no./night)
Bleecker et al.[94]	Mean 67.5	ZAF × 12wk (220)	↑11.68, ↑10.50	↑0.2	↓1.45 puffs/day	↓0.19	↓0.15
		FP × 12wk (231)	↑49.94***, ↑38.91***	↑0.42***	↓2.39 puffs/day***	↓0.46***	↓0.28***
Busse et al.[93] Rickard et al.[97] Storms et al.[98] (abstract)	Range 50-80	ZAF × 12wk[a]	↑15.2, ↑12.8	↑0.33	↓45.3%	↓0.36	
		FP × 12wk[a]	↑46.7**, ↑33.3**	↑0.57**	↓61%	↓0.65*	
		PL × 12wk[a]	↑7.3, ↑4.8	↑0.21	↓25.6%	↓0.43	
Dvorin et al.[95] (abstract)	Range 60-85	ZAF × 6wk (210)	↑3.11[b]	↑0.03	↑0.27 puffs/day		
		FP × 6wk (215)	↑17.78*[b]	↑0.22*	↓0.66 puffs/day*		
Kalberg et al.[96] (abstract)	Mean 67-68	ZAF × 12wk (219)	↑16.7, ↑17.1	↑0.32	↓2 puffs/day†	↓0.39	↓0.27†
		FP × 12wk (214)	↑40.8***, ↑32.1***	↑0.5***	↓2.7 puffs/day***	↓0.65***	↓0.35**
		PL × 12wk (229)	↑8.8, ↑11.5	↑0.25	↓1.4 puffs/day	↓0.47	↓0.19

a Total number of patients randomised = 338.

b Morning value.

FEV_1 = forced expiratory volume in 1 second; **PEF** = peak expiratory flow; **PL** = placebo; * $p < 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$ *vs* comparator(s); † $p \leq 0.05$ *vs* PL; ↑ indicates an increase from baseline; ↓ indicates a decrease from baseline.

ever. Zafirlukast therapy was associated with a reduction relative to placebo in the risk of a first exacerbation of asthma of any severity (odds ratio 0.61; $p = 0.046$), and there was a 44% reduction approaching statistical significance ($p = 0.053$ *vs* placebo) with zafirlukast in frequency of exacerbations.

3.5 Comparisons with Inhaled Fluticasone Propionate

Fluticasone propionate is well established as an inhaled corticosteroid therapy for severe asthma, and has more recently been shown to be effective in patients with mild to moderate disease when used at dosages of up to 500μg daily (reviewed by Jarvis and Faulds[92]). The drug is known to be well tolerated and at least as effective as high dosages of other inhaled corticosteroids in maintenance therapy in mild to moderate asthma,[92] and this has led to its widespread clinical use and to comparisons with other treatments (including the leukotriene antagonists).

Results from a number of 6- or 12-week studies comparing zafirlukast with inhaled fluticasone propionate in mild to moderate asthma have become available since 1998. Although preliminary details only are currently available for most of these studies (table II), all were carried out in a randomised and double-blind fashion, and involved over 100[93] or 200[94-96] patients in each treatment group. Two trials also included placebo groups.[93,96] An 8- to 14-day run-in period was stated to have been used in the study for which full details are available.[94] In 1 trial, patients were transferred to study medication from inhaled corticosteroid therapy (beclomethasone dipropionate 168 to 336 μg/day or triamcinolone acetonide 400 to 800 μg/day)[95] [table II]; in all other trials, pa-

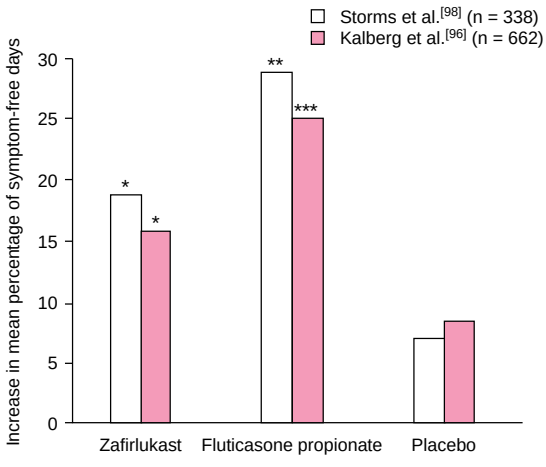

Fig. 4. Effect of zafirlukast or fluticasone propionate on percentage of symptom-free days experienced. Patients with moderate asthma previously managed with inhaled short-acting β_2-adrenoceptor agonist therapy were randomised by Storms et al.[98] and Kalberg et al.[96] in double-blind placebo-controlled studies to treatment with oral zafirlukast 20mg twice daily, inhaled fluticasone propionate 88μg twice daily or placebo for 12 weeks. Results are shown as changes relative to baseline at study end-point. * $p \leq 0.05$ *vs* placebo; ** $p < 0.05$ *vs* placebo and zafirlukast; *** $p \leq 0.01$ *vs* placebo and zafirlukast.

tients had previously been managed with inhaled short-acting β_2-agonist therapy only.

Across all studies, fluticasone propionate 88μg twice daily by inhalation produced significantly greater improvements from baseline over 6 or 12 weeks in lung function as shown by mean PEF and FEV_1 than did zafirlukast 20mg twice daily (table II). Fluticasone propionate treatment was also associated with greater symptomatic improvement,[94,96,98] less use of inhaled short-acting β_2-adrenoceptor agonist therapy[94-96,98] and fewer nocturnal awakenings.[94,96]

In the single study for which full details are available,[94] symptoms were recorded as chest tightness, wheeze, shortness of breath and cough, and were assessed before relief with salbutamol and rated on a 6-point scale. Mean percentages of symptom-free days were increased from baseline over 12 weeks by factors of approximately 3 and 4 in the zafirlukast and fluticasone propionate groups, respectively ($p < 0.001$ between groups). Mean forced vital capacity was also reported, and was increased relative to baseline by 0.15L (4.2%) with zafirlukast and by 0.36L (9.9%) with fluticasone propionate ($p < 0.001$ between treatments). Exacerbations of asthma were reported by 4 and 6% of patients in the fluticasone propionate and zafirlukast groups, respectively; the difference between groups was not statistically significant.

Strong trends towards improved lung function were seen in patients receiving zafirlukast in the studies in which a placebo group was included.[93,96] In addition, although mean percentages of symptom-free days were increased to a significantly greater extent with fluticasone propionate than with zafirlukast, improvements with zafirlukast were superior to those seen with placebo (fig. 4).[96,98]

β_2-Agonist usage and nocturnal awakenings were both statistically significantly reduced relative to placebo by zafirlukast treatment in 1 placebo-controlled trial (table II).[96] In the other trial,[98] the mean percentage of days on which β_2-agonist rescue medication was not needed was increased from baseline to a greater extent with fluticasone propionate than with zafirlukast (increases of 37.5% with zafirlukast and 48.9% with fluticasone propionate; $p < 0.05$ between treatments), although both active treatments conferred significantly greater improvement than did placebo ($p < 0.05$).

In a further study, reported as an abstract, 294 patients not previously treated with inhaled corticosteroids were randomised to double-blind therapy with either zafirlukast 20mg or inhaled fluticasone propionate 88μg twice daily for 4 weeks.[99] At the end of this period, mean morning PEF and percentage of symptom-free days were increased, and use of inhaled salbutamol reduced, to a significantly ($p \leq 0.025$) greater extent with fluticasone propionate than with zafirlukast. All patients then received nonblind treatment with fluticasone propionate for 4 weeks: patients previously treated with zafirlukast showed significantly increased mean morning

Table III. Randomised, double-blind, parallel-group 4-week studies comparing zafirlukast 20mg twice daily orally (ZAF) with inhaled salmeterol 42μg twice daily (SAL) in patients with moderate asthma

Reference	Mean FEV_1 (L) [% predicted] at baseline	Treatment (no. of patients)	Mean changes from baseline at end-point				
			PEF (am, pm; L/min)	FEV_1 (L)	β_2-agonist usage (puffs/day)	symptom scores	nocturnal awakenings (no./night)
Busse et al.[104]	67	ZAF (145)	↑13, ↑9.9	↑0.22	↓0.93	↓0.23	↓0.1
		SAL (144)	↑29.6***, ↑21.8*	↑0.28	↓1.5**	↓0.43***	↓0.2
Kalberg & Rickard[105] (abstract)	66	ZAF[a]	↑13.2, ↑9.1	Difference between groups NS at wk 4[b]	↓1.1	↓15%	
		SAL[a]	↑29.4***, ↑21.8**		↓1.9**	↓36%***	

a Total number of patients randomised = 301.

b Results not given.

FEV_1 = forced expiratory flow in 1 second; **PEF** = peak expiratory flow; **NS** = not statistically significant; * $p < 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$ *vs* ZAF; ↑ indicates an increase from baseline; ↓ indicates a decrease from baseline.

PEF and reduced need for inhaled salbutamol ($p \leq 0.001$) relative to baseline values taken at the end of the double-blind phase.

3.6 Comparisons with Inhaled Salmeterol

Salmeterol is a long-acting selective inhaled β_2-adrenoceptor agonist indicated for maintenance therapy of adults and children with asthma. Although the drug can be used alone, most treatment guidelines direct that salmeterol should be used as adjunctive therapy in patients with symptoms not adequately controlled by regular use of inhaled corticosteroids, and not as a replacement for the latter[100-102] (see also the review by Adkins and McTavish[103]).

Zafirlukast has been investigated as an alternative to salmeterol therapy in 2 randomised, double-blind multicentre studies, both of which recruited patients aged 12 years or over with moderate persistent asthma (FEV_1 50 to 80% predicted).[104,105] Of these individuals, over 80% in each trial were receiving inhaled corticosteroid therapy (to which was added study medication). Both studies were of 4 weeks' duration and compared zafirlukast 20mg with inhaled salmeterol 42μg twice daily (table III). In the single trial for which full details are available,[104] criteria for enrolment included a requirement for an increase of at least 12% in FEV_1 within 30 minutes of salbutamol inhalation, and a 7- to 14-day run-in period was used.

Both studies showed significantly greater improvements in asthma control with salmeterol than with zafirlukast (table III). In the fully published study,[104] mean morning and evening PEFs were increased from baseline by 3.5 and 2.5%, respectively, with zafirlukast, and by 8 ($p = 0.001$ between treatments) and 5.6% ($p = 0.019$) with salmeterol. There were significant increases from baseline in mean FEV_1 values in both treatment groups at week 1 and week 4. At the end of week 1, the increase in the salmeterol group was significantly greater than that in zafirlukast recipients (0.29 *vs* 0.19L; $p = 0.023$); however, the between-group difference at week 4 was not significant (table III). Exacerbations of asthma were reported by similar proportions of patients in each group (5% with salmeterol and 6% with zafirlukast).

Patients treated with salmeterol reported significantly greater improvements over 4 weeks relative to baseline in all patient-rated symptom scores than did those receiving zafirlukast.[104] Mean scores for chest tightness, shortness of breath and wheezing decreased by 37, 37 and 35%, respectively, with salmeterol, whereas reductions of 20, 18 and 16% were reported in zafirlukast recipients. Mean

patient-rated sleep symptoms decreased by 46% from baseline with salmeterol and by 22% with zafirlukast ($p < 0.001$), although there was no significant difference between groups in reduction of mean frequency of nocturnal awakening (table III).[104]

Retrospective analysis of combined data from the subset of 429 patients who received unchanged dosages of inhaled corticosteroid for at least 30 days before and during these 2 studies showed significantly greater improvements with salmeterol than with zafirlukast in PEF (33 *vs* 14 L/min; $p < 0.001$), percentage of symptom-free days (24 *vs* 11%; $p < 0.001$), composite symptom scores (–0.45 *vs* –0.25; $p = 0.014$) and salbutamol usage (–1.98 *vs* –1.12 puffs/day; $p = 0.001$).[106]

3.7 Comparison with Pranlukast

Zafirlukast has been compared with one other leukotriene receptor antagonist, pranlukast, in a randomised, double-blind and multicentre study involving 298 Japanese patients with mild to moderate asthma (Japanese Society of Allergology criteria).[107] Overall, the 2 drugs appeared to be of similar efficacy over the 6-week study period at the dosages given [40mg twice daily for zafirlukast (n = 153) and 225mg twice daily for pranlukast (n = 145)]. Patients were aged 16 years or over, and approximately 80% were receiving concurrent inhaled and/or oral corticosteroids (≤1.2 mg/day beclomethasone dipropionate or equivalent). Bronchodilator therapy was also permitted.

The primary end-point was the final global improvement rating after 6 weeks, an assessment based on symptomatic improvement (7-point scale ranging from marked improvement to marked worsening), pulmonary function test results, use of concurrent medication, and investigator and patient impressions. Rates of marked or moderate improvement were 57 and 48.6% for the zafirlukast and pranlukast groups, respectively. Statistical significance in favour of zafirlukast was suggested by the application of a 1-sided Dunnett-Gent test to the 95% confidence interval for the difference between treatments (–5.7 to 22.6%; $p = 0.003$), but not by the use of a Wilcoxon 2-sample test ($p = 0.122$).

Mean morning PEF (secondary end-point) increased from 328.4 to 352.5 L/min with zafirlukast and from 334.3 to 347.3 L/min with pranlukast. Mean evening PEFs increased from 348.8 to 369 L/min and from 347.3 to 358.8 L/min with zafirlukast and pranlukast, respectively. All changes from baseline were statistically significant ($p < 0.01$). Differences between treatments did not attain statistical significance, although there was a consistent trend towards greater improvement in mean PEF in patients receiving zafirlukast.

3.8 Pharmacoepidemiological Data

The clinical efficacy of zafirlukast 20mg twice daily over 4 weeks has been evaluated recently in a large nonblind multicentre study in 3759 patients with mild to moderate or severe asthma.[108] This trial was carried out to assess the effects of zafirlukast on a heterogeneous patient population in the practice setting, and involved a large enough number of individuals for the investigators to compare drug effects between different age groups.

Patients were aged 12 years or more, and were required to have FEV_1 between 45 and 85% predicted after abstinence of at least 4 hours from β_2-agonist use. There were no restrictions on con- current asthma medications, but patients were required to be nonsmokers. Baseline values for PEF, FEV_1, asthma symptoms (4-point scale), nocturnal awakenings and β_2-agonist usage were recorded during a 3-day run-in period, after which all patients received zafirlukast therapy for 4 weeks.

Of the patients enrolled, 3120 (83%) completed 4 weeks of zafirlukast treatment, and 3207 (85.3%) were evaluable for efficacy. Adolescents aged 12 to 17 years accounted for 263 patients, adults aged 18 to 65 years for 2602, and elderly individuals (aged 66 years and over) for 321. A further 21 patients in the evaluable population were of unknown age.

After 4 weeks of zafirlukast therapy, least squares mean changes from baseline were statistically significant for all measures (morning and evening PEF and FEV_1) in adolescents and adults

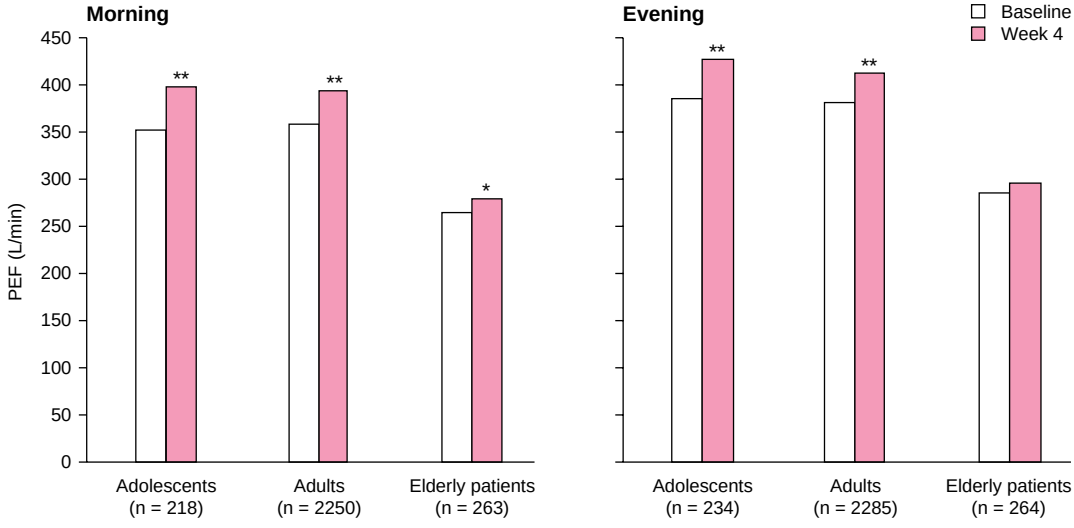

Fig. 5. Effect of 4 weeks' treatment with zafirlukast 20mg twice daily on peak expiratory flow (PEF) in patients in different age groups. Patients with mild to moderate or severe asthma were categorised as adolescents (aged 12 to 17 years), adults (aged 18 to 65 years) and elderly individuals (aged 66 years and over) in a large multicentre nonblind study.[108] Least squares mean changes from baseline in morning and evening PEF over 4 weeks are shown, together with numbers of evaluable patients. * $p < 0.01$ between baseline and week 4; ** $p < 0.01$ between baseline and week 4, and for adolescents and adults *vs* elderly patients.

and for morning PEF in elderly patients; the extent of improvement decreased with increasing age (fig. 5). There were also significant ($p < 0.01$) improvements from baseline in all age groups for β_2-agonist use (respective reductions of 38.3, 24.8 and 9.5% in adolescents, adults and the elderly), asthma symptom scores (reductions of 39.7, 30.1 and 23.3%), nocturnal awakenings (reductions of 62, 46.3 and 46%) and mornings with asthma (reductions of 65.3, 37.3 and 38.3%). Overall, zafirlukast was associated with clinical improvement in all patient groups.[108]

4. Pharmacoeconomic, Quality-of-Life and Compliance Considerations

4.1 Pharmacoeconomic Analyses

As with many other medical conditions, the introduction of new therapies for asthma has been accompanied by concern over rising treatment costs and interest in pharmacoeconomic research to determine whether these potential cost increases are offset by reductions in morbidity and mortality and by cost savings in other areas.

Data reported in previous reviews[1,86] have shown reductions in the use of healthcare resources and reduced absenteeism relative to placebo in patients receiving zafirlukast. The first pharmacoeconomic study of zafirlukast[109] was based on results from 146 patients participating in a 13-week multicentre double-blind trial that compared a dosage of 20mg twice daily with placebo in a total of 762 patients aged 12 years and over with mild to moderate asthma controlled by short-acting inhaled β_2-agonist therapy (see also section 3.1).[73] Resource consumption was evaluated in terms of use of healthcare services (frequency and type of unscheduled healthcare contacts, use of β_2-agonists and non-asthma medication) and absence from work or school.

Relative to placebo (n = 43), zafirlukast recipients (n = 103) showed statistically significant 55%

reductions in the number of healthcare contacts ($p = 0.007$) and levels of absenteeism from school or work ($p = 0.04$); there were also nonsignificant 17 and 19% reductions in the use of inhaled β_2-agonists and non-asthma medications, respectively. The conclusions that might be drawn from these results are limited, however, by the significantly lower mean percentage of predicted FEV_1 recorded in zafirlukast than in placebo recipients at baseline (74.2 *vs* 83.7%; $p = 0.002$). This may have been responsible for the greater treatment effects seen in the active treatment group, as patients with more severe asthma are likely to benefit more from treatment. In addition, the number of patients recruited and the study duration were not sufficient to show effects on several major sources of cost, such as rates of death or hospitalisation, and the study did not include an analysis of the potentially high costs of treatment failure.

The cost of treatment failure has been estimated, however, in a meta-analysis of 5 placebo-controlled trials, according to which zafirlukast treatment was associated with an approximate halving of costs associated with asthma exacerbations.[110] The incidence of asthma exacerbations leading to treatment withdrawal in patients treated for 13 weeks was 3.5% with zafirlukast and 6.6% with placebo ($p = 0.008$). Although direct and indirect costs incurred by patients were not considered, calculations based on the number of asthma exacerbations per 1000 patients per year showed respective costs for zafirlukast and placebo recipients to be £26 000 and £48 000 (1995 values).

Attention has recently been focused on cost and cost-effectiveness analyses (all available in abstract form only) based on results of double-blind clinical trials comparing zafirlukast 20mg with inhaled fluticasone propionate 88μg twice daily (see also section 3.5). The results of a US cost analysis undertaken from a third party payer's perspective with data from 2 placebo-controlled studies in patients previously managed with low-dosage inhaled corticosteroids showed daily mean treatment costs of $US2.30 and $US1.66 for zafirlukast and fluticasone propionate, respectively (year of costing not stated).[111] Costs accounted for included those for drugs (average wholesale price), emergency room visits, unscheduled physician visits, drug-related adverse events, oral corticosteroids and inhaled salbutamol. Cost-effectiveness ratios were higher for zafirlukast than for fluticasone propionate for each 10% improvement in FEV_1 ($US9.89 *vs* $US4.67) and 0.5-point improvement in asthma quality-of-life scores ($US6.54 *vs* $US3.18). Costs per sickness-free day were $US5.71 and $US3.35 for zafirlukast and fluticasone propionate, respectively. This preliminary report did not clearly identify the clinical studies or the numbers of patients involved, however.

Three US cost-effectiveness analyses based on results of placebo-controlled double-blind comparisons of zafirlukast 20mg twice daily with fluticasone propionate 88μg twice daily by inhalation in patients previously treated with inhaled short-acting β_2-agonists are also available.[112-114] One of these reports, which accounted for direct costs (as in the study discussed above[111]) and indirect costs in terms of missed days of work, showed daily direct costs per successfully treated patient to be $US4.64 for zafirlukast and $US2.76 (1998 values) for fluticasone propionate; these values increased to $US6.02 and $US3.81 when indirect costs were included.[112] Patient numbers were not reported.

Another analysis, which included 329 patients from a single study, showed cost-effectiveness ratios of $US12.08 and $US6.62 per sickness-free day for zafirlukast and fluticasone propionate, respectively.[113] Direct costs (study drugs, emergency room visits, hospitalisations, unscheduled physician visits, treatment of adverse events and use of rescue medication) only were included for the year 1998. Corresponding values with inclusion of indirect costs were $US14.15 and $US8.86. In addition, analysis of data from a study in 451 patients yielded cost-effectiveness ratios of $US428.64 and $US157.67 per sickness-free day per patient per month for zafirlukast and fluticasone dipropionate, respectively (year of costing not stated).[114] Sensitivity analyses were used in

all studies, although details were not given in the preliminary reports available. Drug costs were based on average wholesale prices.

A recent retrospective US analysis of pharmacy and medical claims from 392 patients starting treatment with zafirlukast and 857 given fluticasone propionate who were followed for 21 months indicated a 21% increase from baseline in the total annual cost of asthma care in patients receiving zafirlukast, whereas those receiving fluticasone propionate showed a 22% decrease ($p < 0.0001$ between groups).[115] All patients were followed for a 9-month pre-baseline washout period during which no claims were made for inhaled corticosteroid or leukotriene antagonist therapy, and costs were calculated on the basis of utilisation rates, asthma costs and total healthcare costs (adjusted for age, gender and pre-baseline utilisation rates and costs).

These results, however, do not concur with other findings based on US managed care claims from 780 patients aged over 12 years who were followed for 3 months before and 3 months after starting treatment with zafirlukast.[116] Of these patients, 72% were already receiving treatment with inhaled corticosteroids. The addition of zafirlukast to existing therapy was associated with reduced healthcare utilisation which was deemed likely to translate into reductions in direct healthcare costs. Within 3 months of starting zafirlukast, outpatient visits, inpatient stays, emergency department visits and prescriptions for inhaled salbutamol were all significantly reduced relative to the previous 3 months ($p < 0.002$).

4.2 Quality of Life

Recent analyses (one based on a retrospective analysis of 845 patients from 6 US clinical trials,[117] and another on 329 patients enrolled in a single study[118]) of results of double-blind placebo-controlled studies where zafirlukast 20mg was compared with fluticasone propionate 88μg or salmeterol 42μg twice daily have suggested no clinically meaningful improvement with zafirlukast over 12 weeks in quality of life according to the Asthma Quality-of-Life Questionnaire (AQLQ).[117,118] However, these findings (which are available in preliminary abstract form only) are at variance with previously reported data[86] showing improved quality of life after 13 weeks' treatment with zafirlukast 20mg twice daily in patients with moderate asthma.[60,119] Improvements in objective and subjective measures of severity of asthma were associated with significant improvement in the symptoms and emotional function domains and the overall score on the AQLQ. In the 1 fully published study,[60] proportions of patients experiencing clinically meaningful improvements in quality of life (defined as a change of 0.5 units or more from baseline) were significantly greater with zafirlukast than with placebo for all 4 specified domains (activities, symptoms, emotions and environmental; $p \leq 0.037$) and for the overall quality-of-life score (56 *vs* 46%; $p = 0.021$).

Zafirlukast has also been shown to confer greater improvements in quality of life than increased dosages of inhaled corticosteroids. British patients receiving inhaled beclomethasone dipropionate 400 to 500 μg/day were randomised to 12 weeks' double-blind treatment with zafirlukast 20 or 80mg twice daily or doubled dosages of beclomethasone dipropionate, with an optional 40-week extension (see also section 3.4[88]).[120] The 52-week quality-of-life assessment was completed by 58 patients receiving zafirlukast 20mg twice daily and by 62 receiving doubled corticosteroid dosages. Quality-of-life scores on the St George's Respiratory Questionnaire were reduced (indicating improvement) from 30.5 to 19.3 in patients in the zafirlukast group and from 32.4 to 24.1 in corticosteroid recipients. The difference between these 2 groups was stated to be statistically and clinically significant.

4.3 Compliance and Patient Preference

Concerns over compliance with inhaled therapies and the ability of patients to obtain maximum therapeutic benefit through their correct use raises the issue of potential benefits that may be associ-

ated with the use of orally administered asthma treatments.

Data are available to show a preference by patients for oral therapy with zafirlukast over treatment with inhalers. Results from a nonblind crossover study in 152 patients revealed a 2 to 1 preference over 4 weeks for zafirlukast 20mg over inhaled beclomethasone dipropionate (both given twice daily), despite a higher incidence of adverse effects with zafirlukast (further details not available).[121] More patients found zafirlukast easier to use than inhaled therapy (66 *vs* 20%).

A median compliance rate of 89% (mean 80%) was shown in a study in which an electronic device that records removal and replacement of tablet bottle caps was used to monitor 12 weeks' treatment with zafirlukast 20mg twice daily in 47 patients.[122] The median rate of adherence to the prescribed regimen (the number of days on which two 20mg zafirlukast tablets were taken at least 8 hours apart) was 71% (mean 64%).

Advantages of zafirlukast in terms of compliance and patient preference have also been shown in a study in adolescent patients with chronic asthma managed with inhaled short-acting β_2-agonists and corticosteroids.[123] In this nonblind crossover trial carried out in 4 countries, patients aged 12 to 17 years received zafirlukast 20mg or beclomethasone dipropionate 100 or 200μg by aerosol inhalation twice daily, each for 4 weeks. Questionnaire answers showed that 70% of 113 respondents preferred zafirlukast and 27% preferred inhaled corticosteroid therapy; the remainder had no preference. Zafirlukast tablets and beclomethasone dipropionate inhalers were rated as 'very easy' to use by 65 and 30%, respectively, of respondents. Most interesting is the observation that only 29% of 122 patients who were assessed for inhaler technique were using their inhalers correctly at study entry.

5. Tolerability

Previously reported data from 5188 patients treated with zafirlukast (predominantly 20mg twice daily) in clinical trials indicated the most frequently reported adverse events associated with short term therapy (≤20 weeks) to be pharyngitis (incidence of 16%), headache (12%) and aggravation reaction (a COSTART term used to define worsening of any pre-existing condition, e.g. asthma) [8%].[1] Other adverse events, reported in 3 to 4% of patients, included infection, rhinitis, influenza syndrome, nausea and cough. Adverse event profiles and incidences were similar to the above in 2573 patients receiving placebo and in 1120 patients receiving long term (21 weeks to 2 years) zafirlukast therapy. Treatment withdrawal due to exacerbation of asthma was reported in 1.3% of patients treated with zafirlukast and 2.4% of placebo recipients.

More recent adverse event figures from a US database (reported in prescribing information[55]) involving 4058 healthy volunteers and patients treated with zafirlukast and 2032 placebo recipients are similar to those reported previously. Of events reported at rates higher than those with placebo in at least 1% of zafirlukast recipients, only headache was noted with an incidence above 10% (12.9 and 11.7% in patients receiving zafirlukast and placebo, respectively). All other adverse events were seen in fewer than 4% of patients (fig. 6). Of the patients who had received zafirlukast and were included in this database, 1723 had asthma and were recruited to clinical trials of at least 13 weeks' duration. A total of 671 patients received zafirlukast for at least 1 year.

UK prescribing information highlights headache (incidence of 9.9 *vs* 9% with placebo) and GI disturbance (nausea 2.6 *vs* 2.2%; vomiting 1.2 *vs* 1%; diarrhoea 2.3 *vs* 1.8%; and abdominal pain 1.6 *vs* 1.2%) as the adverse events most frequently reported in comparisons of zafirlukast with placebo.[54]

Comparisons of zafirlukast with pranlukast (section 3.7), inhaled fluticasone propionate (section 3.5) or inhaled salmeterol (section 3.6) have shown no clinically relevant differences between treatments in adverse event profiles.

Elevations in serum levels of liver enzymes have been observed in small numbers of patients

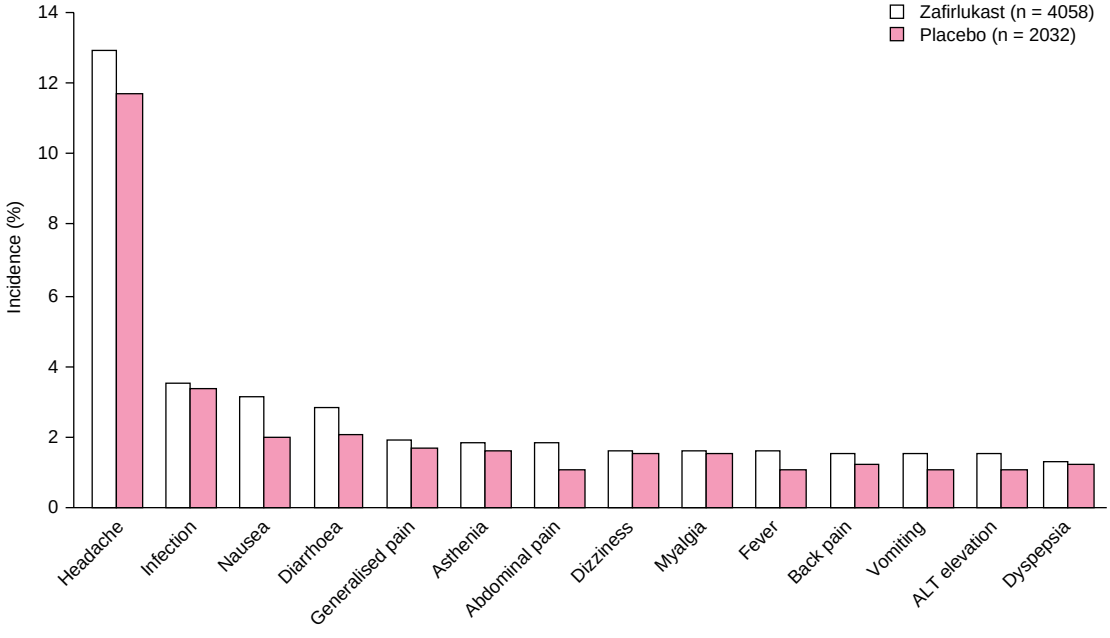

Fig. 6. Tolerability of zafirlukast. Events reported at higher rates than with placebo by ≥1% of zafirlukast recipients (aged ≥12 years) as shown in a US database (data from healthy volunteers and patients with asthma).[55] Of patients receiving active treatment, 1723 had asthma and were enrolled in clinical studies of at least 13 weeks' duration, and 222 were aged between 12 and 18 years.

receiving zafirlukast, usually in individuals receiving dosages above those normally recommended (see section 6). Patients remained asymptomatic, and levels returned to normal after cessation of zafirlukast therapy. Rare cases of symptomatic hepatitis and hyperbilirubinaemia have been linked to zafirlukast treatment at recommended dosages. In most patients, enzyme levels returned to normal or near-normal after withdrawal of treatment.[54,55] Severe hepatitis has recently been reported in 3 middle-aged female patients who received zafirlukast 20mg twice daily for 2 to 6 months.[124] The first patient recovered spontaneously, the second developed subfulminant hepatic failure and required transplantation, and the third responded to treatment with corticosteroids. Histological changes consistent with a drug reaction were observed in 2 of these individuals, and the authors recommended appropriate monitoring in patients receiving zafirlukast.[124]

In clinical studies, an increased incidence of infection relative to placebo has been noted in zafirlukast recipients aged over 55 years.[54,55] These infections were mostly mild to moderate in intensity, predominantly affected the respiratory tract, increased in incidence with zafirlukast dosage and were associated with concurrent use of inhaled corticosteroids. The clinical significance of these observations remains unclear, however.

Integrated data from 2 studies of 4 and 6 weeks' duration in children aged 5 to 11 years (section 3.3) showed a tolerability profile for zafirlukast 10mg twice daily (n = 205) similar to that with placebo (n = 206).[85] Pharyngitis was the most commonly reported adverse event (9.3 and 13.6% of children receiving zafirlukast and placebo, respectively).

In the pharmacoepidemiological study in 3759 patients discussed in section 3.8, adverse events were noted in 11.5% of adolescents, 17.5% of adults and 18.8% of elderly patients after treatment with zafirlukast 20mg twice daily for 4 weeks. These were considered to be treatment-related in 4.2, 7.4 and 8.1% of cases, respectively. Relative to other age groups, elderly individuals were found to have the highest incidences of headache, abdominal pain, diarrhoea and nausea, but the lowest incidences of infection and sinusitis.

The safety of zafirlukast in pregnancy in humans has not been established, although results of animal studies have not shown any apparent effects of the drug on fertility or on fetal development.[54]

Churg-Strauss Syndrome, a form of vasculitis characterised by the presence of at least 4 of (i) asthma, (ii) eosinophilia, (iii) pulmonary infiltration, (iv) polyneuropathy, (v) sinusitis, and (vi) presence of extravascular eosinophils, has been linked in a number of isolated cases to zafirlukast use (reviewed by Gozalo Reques and Estrada Rodriguez[125]). The majority of reports have been in patients in whom oral corticosteroid dosages were being reduced, and although the condition has been described in 2 zafirlukast recipients who were not receiving corticosteroids,[126] symptoms have recurred in patients undergoing repeated attempts to withdraw corticosteroid therapy 1 year after stopping zafirlukast.[127]

Analysis of all reported cases has led to the suggestion that the syndrome develops primarily in patients with an underlying eosinophilic disorder that is masked by corticosteroid treatment and that becomes clinically apparent when corticosteroid dosages are reduced following the addition of a new asthma therapy (i.e. zafirlukast).[128,129] Debate on this issue continues in the literature,[126,127,130-135] and physicians are advised to monitor patients for the signs and symptoms of Churg-Strauss Syndrome, particularly in patients with mild to moderate asthma in whom corticosteroid therapy is being gradually withdrawn.[54,55,128] Nevertheless, recent review of collated adverse event reports pertaining to zafirlukast and another leukotriene receptor antagonist, montelukast, supports the suggestion of no causal relationship between Churg-Strauss Syndrome and this group of agents.[136]

6. Dosage and Administration

Zafirlukast is administered orally as one 20mg tablet twice daily at regular intervals for the prophylaxis and treatment of persistent asthma in patients aged 12 years and over.[53-55] A dosage of 10mg twice daily is recommended for children aged 7 to 11 years in some countries, including the US,[55] but the drug is contraindicated in children aged below 12 years in the UK.[54] As food may reduce the bioavailability of zafirlukast, the drug should be taken at least 1 hour before or 2 hours after meals. Patients should be advised not to use the drug for acute attacks of asthma.

Although the clearance of zafirlukast is reduced in elderly patients (section 2.2), there are no specific dosage guidelines for the use of zafirlukast in this age group. The clearance of zafirlukast is also reduced in patients with alcoholic cirrhosis of the liver (section 2.2), and further investigations are needed to clarify the pharmacokinetics and tolerability of zafirlukast in patients with hepatic dysfunction. UK prescribing guidelines state that the drug should not be used in patients with hepatic impairment or cirrhosis, although there is no such formal recommendation in the US. Most recent recommendations take account of adverse reaction reports over the past 3 years and state that zafirlukast therapy should be withdrawn in cases of suspected liver dysfunction.[137] According to US guidelines,[55] dosage adjustments are not required in patients with renal impairment; however, the drug is contraindicated in the UK in patients with moderately or severely impaired renal function.[54]

Zafirlukast is excreted in breast milk and is not recommended for use in nursing mothers.[54,55]

7. Place of Zafirlukast in the Management of Asthma

The leukotriene receptor antagonists zafirlukast, montelukast and pranlukast represent the first novel group of drugs for the treatment of asthma to

be introduced for over 20 years, and the use of these agents in the management of persistent asthma is supported by the results of placebo-controlled clinical studies. It is clear that zafirlukast produces bronchodilation, inhibits responses to allergenic and other challenges (including exercise and cold air in susceptible individuals) and improves pulmonary function. The drug has also been shown to reduce symptom severity, to improve objective measures of lung function, to reduce the need for short-acting inhaled β_2-agonist therapy and to reduce the incidence of exacerbation of asthma in controlled clinical studies. At the time of the last review in *Drugs*,[1] the data available showed zafirlukast to be a potentially useful therapeutic option for the prophylaxis and treatment of mild to moderate asthma in patients aged 12 years and over. These conclusions remain valid, but the more recent data reviewed in the present evaluation permit further comment and some refinement of this broad recommendation.

Current treatment guidelines divide asthma into degrees of severity, and these are used as the starting points for treatment recommendations (reviewed by Kemp[138]). However, asthma is a complex condition, and the large number of variables to be considered for each patient points to a need to individualise therapy. The availability of the leukotriene receptor antagonists increases the ability of physicians to do this.

Current US consensus guidelines suggest that leukotriene receptor antagonists be viewed as an alternative to inhaled corticosteroids in patients with mild persistent asthma, although corticosteroids remain the most effective and frequently used anti-inflammatory agents available.[100] Preliminary abstracts reporting recent clinical trials (section 3.5) have shown that inhaled fluticasone propionate is superior to zafirlukast in the improvement of lung function and relief of symptoms in patients with mild to moderate asthma. It should also be noted, however, that these trials did demonstrate improvement with zafirlukast (most notably in studies in which a placebo control group was included), and this highlights the need to consider (i) other factors that may contribute to the overall benefit of treatment and (ii) the aims of therapy (particularly in patients with mild asthma).

Zafirlukast has been shown to be effective in patients with mild to moderate asthma, and offers the additional advantage of oral administration. This enables patients to avoid the difficulties inherent in mastering the correct use of inhalers. Such considerations are likely to be particularly relevant in children and the elderly, and clinical efficacy of zafirlukast has been shown in both these patient groups (sections 3.3 and 3.8). The extent of improvement in lung function with zafirlukast treatment was lower in elderly than in younger patients[108] (section 3.8), but this observation must be interpreted in light of special considerations relevant to this age group (i.e. the nonspecific presentation of elderly patients with asthma, the likely presence of other pulmonary or cardiovascular conditions, and age-related factors affecting response to treatment overall[139]). Furthermore, patient compliance with oral therapy is known to be superior to that with inhalers,[140] and data are available to show high rates of compliance with and preference for zafirlukast treatment (section 4.3).

Similar considerations apply to patients in whom zafirlukast might be used as an alternative to treatments such as the long-acting β_2-agonist salmeterol. Although this drug was more effective in 4-week studies than zafirlukast (section 3.6), salmeterol is usually used in conjunction with inhaled corticosteroid therapy, and preliminary data (section 3.4) indicate zafirlukast 20mg twice daily to be as effective as increased dosages of inhaled corticosteroids in patients not adequately controlled by low dosages of these drugs (superiority of zafirlukast over doubled dosages of corticosteroids was also shown, but only when dosages higher than those recommended were used). Furthermore, although improvements in lung function and symptoms with salmeterol have been sustained for up to 46 weeks in placebo-controlled studies,[141-144] some authors have reported attenuation of initial protection against bronchoconstriction induced by

exercise[145] or methacholine challenge,[146,147] and reduced response over time to inhaled salbutamol,[148,149] in patients receiving salmeterol. The duration (4 weeks) of the comparisons of zafirlukast with this drug may therefore have been insufficient to show the full relative efficacy of the leukotriene antagonist. Furthermore, the requirement for sensitivity of patients to inhaled β_2-agonists at baseline (as stated in one of the 2 studies[104]) may have predisposed the study population to a more favourable response to salmeterol than might be expected in the general asthmatic population.

It is important to note when considering the relative merits of zafirlukast and inhaled therapies that clinical studies are carried out under controlled conditions, and usually follow patients (in whom inhaler technique has been carefully explained and verified) for limited periods only. Long term surveillance of large numbers of patients in 'real world' practice settings is needed to clarify and quantify benefits (not least in terms of efficacy) that accrue from ease of use and improved compliance in patients receiving zafirlukast.

To date, zafirlukast has been compared in a single clinical trial with one other leukotriene receptor antagonist only (section 3.7). Although this comparison showed zafirlukast and pranlukast to be of similar overall efficacy, with some data suggesting superiority of the former drug, patients received zafirlukast 40mg twice daily rather than the generally recommended dosage of 20mg twice daily (as used in other clinical studies). Further studies are therefore needed to demonstrate any differences between zafirlukast and other drugs of the same class.

Since the last review, data have started to emerge to show sustained efficacy of zafirlukast therapy over periods beyond those covered by previous clinical trials (sections 3.2 and 3.3). Additional long term studies and clinical experience with the drug are required to confirm these findings. The role of zafirlukast in the attenuation of the underlying inflammatory response in asthma also remains to be determined.

As with much recent clinical data, most of the available pharmacoeconomic analyses of zafirlukast are available in preliminary form only, and it is therefore difficult to assess the value of these studies and to formulate firm conclusions on their basis. Early data based on results of trials comparing zafirlukast with placebo suggested benefit of the drug in terms of reduced healthcare resource consumption and reduced cost of management of exacerbations of asthma (section 4.1). More recent data suggest greater cost effectiveness of inhaled fluticasone propionate in patients with persistent asthma. However, these pharmacoeconomic studies were based on retrospective analysis of and attachment of healthcare costs to the results of randomised clinical trials. Furthermore, the findings of analyses of managed care and medical/pharmacy claims are inconclusive at present (section 4.1). Clearly, prospectively designed and specific pharmacoeconomic studies, preferably carried out over prolonged periods in the practice setting (to take full account of such factors as medication compliance and quality of life), are required to indicate the true effect of zafirlukast on overall healthcare costs and patients' well-being. Furthermore, although current data are not consistent, quality-of-life analyses have shown improvements in patients receiving zafirlukast (section 4.2).

Zafirlukast is well tolerated by most patients. In particular, despite earlier concerns, no direct link has been shown between the drug and Churg-Strauss Syndrome (section 5). Hepatic enzyme changes have been reported occasionally, but are not clinically significant in the majority of patients in whom they are seen. Isolated reports of hepatitis in a very small number of individuals have been received (section 5), and recommendations for patient monitoring and treatment withdrawal if necessary are in place. Patients receiving concomitant treatment with medications such as warfarin require monitoring because of the potential for drug interactions (section 2.3); further studies are required to clarify the clinical significance of other potential interactions.

Data from clinical studies of up to 12 weeks' duration have shown no clinically significant differences in terms of adverse events between zafirlukast and inhaled fluticasone propionate or salmeterol. Corticosteroids are associated with lower incidences of dosage-related adverse effects when administered via inhalation rather than systemically, particularly when used at the low dosages usually required in patients with mild to moderate asthma, but these effects (most notably adrenal suppression and impairment of bone metabolism) nevertheless need to be borne in mind in patients receiving prolonged therapy (see review by Lipworth[150]). Use of inhaled corticosteroids is also associated with oropharyngeal adverse effects in some patients (e.g. dysphonia, pharyngitis and oral candidiasis).[92] Despite the greater efficacy of inhaled fluticasone propionate in clinical trials (section 3.5) and the need for more data on the possible steroid-sparing effects of zafirlukast (section 3.4), these tolerability considerations, together with compliance concerns, may make zafirlukast a preferred option in some patients.

In conclusion, zafirlukast is a useful and well tolerated therapeutic option, suitable for preventive monotherapy (with as-required short-acting β_2-agonists), in the management of mild to moderate persistent asthma. Emerging data indicate that the drug is likely to prove beneficial when added to low-dosage inhaled corticosteroids and that it may be a viable alternative to inhaled adjunctive treatments (notably long-acting β_2-agonists) and increased corticosteroid dosages in some patients. Although inhaled fluticasone propionate and salmeterol have been associated with greater clinical improvement than zafirlukast in clinical studies, compliance considerations and the confirmed clinical efficacy relative to placebo of the drug denote zafirlukast as an effective alternative in treatment programmes based on individualised therapy. As experience with zafirlukast accumulates, it is expected that the drug will be positioned more definitively in national and international treatment guidelines.

References

1. Adkins JC, Brogden RN. Zafirlukast: a review of its pharmacology and therapeutic potential in the management of asthma. Drugs 1998 Jan; 55: 121-44
2. Feldberg W, Kellaway CH. Liberation of histamine and formation of lysocithin-like substances by cobra venom. J Physiol (Lond) 1938; 94: 187-91
3. Brocklehurst W. The release of histamine and formation of a slow-reacting substance (SRS-A) during anaphylactic shock. J Physiol (Lond) 1960; 151: 416-35
4. Dennis EA, Rhee SG, Billah MM, et al. Role of phospholipase in generating lipid second messengers in signal transduction. FASEB J 1991; 5: 2068-77
5. Murakami M, Nakatani Y, Atsumi G, et al. Regulatory functions of phospholipase A_2. Crit Rev Immunol 1997; 17: 225-83
6. Woods JW, Evans JF, Ethier D, et al. 5-Lipoxygenase and 5-lipoxygenase-activating protein are localized in the nuclear envelope of activated human leucocytes. J Exp Med 1993; 178 (6): 1935-46
7. Dixon RA, Diehl RE, Opas E, et al. Requirement of a 5-lipoxygenase-activating protein for leukotriene synthesis. Nature 1990; 343: 282-4
8. Coffey MJ, Wilcoxon SE, Peters-Golden M. Increases in 5-lipoxygenase activating protein expression account for enhanced capacity for 5-lipoxygenase metabolism that accompanies differentiation of peripheral blood monocytes into alveolar macrophages. Am J Resp Cell Mol Biol 1994; 11: 153-8
9. Lam BK, Penrose JF, Freeman GJ, et al. Expression cloning of a cDNA for human leukotriene C_4 synthase, an integral membrane protein conjugating reduced glutathione to leukotriene A_4. Proc Natl Acad Sci U S A 1994; 91: 7663-7
10. Wetterholm A, Medina JF, Radmark O, et al. Recombinant mouse leukotriene A4 hydrolase: a zinc metalloenzyme with dual enzymatic activities. Biochim Biophys Acta 1991; 1080: 96-102
11. Lam BK, Owen Jr WF, Austen KF, et al. The identification of a distinct export step following the biosynthesis of leukotriene C_4 by human eosinophils. J Biol Chem 1989; 264: 12885-9
12. Loe DW, Almquist KC, Deeley RG, et al. Multidrug resistance protein (MRP)-mediated transport of leukotriene C_4 and chemotherapeutic agents in membrane vesicles: demonstration of glutathione-dependent vincristine transport. J Biol Chem 1996; 271: 9675-82
13. Coleman RA, Eglen RM, Jones RL, et al. Prostanoid and leukotriene receptors: a progress report from the IUPHAR working parties on classification and nomenclature. Adv Prostaglandin Thromboxane Leukot Res 1995; 23: 283-5
14. Heise CE, O'Dowd BF, Figueroa DJ, et al. Characterization of the human cysteinyl leukotriene 2 receptor. J Biol Chem 2000; 275 (39): 30531-6
15. Sarau HM, Ames RS, Chambers J, et al. Identification, molecular cloning, expression, and characterization of a cysteinyl leukotriene receptor. Mol Pharmacol 1999; 56 (3): 657-63
16. Dahlén S-E, Hedqvist P, Hammarström S, et al. Leukotrienes are potent constrictors of human bronchi. Nature 1980 Dec; 288: 484-6
17. Weiss J, Drazen JM, Coles N. Bronchoconstrictor effects of leukotriene C in humans. Science 1982 Apr; 216: 196-8
18. Griffin M, Weiss J, Leitch AG, et al. Effects of leukotriene D on the airways in asthma. N Engl J Med 1983 Feb; 308: 436-9

19. Barnes NC, Piper PJ, Costello JF. Comparative effects of inhaled leukotriene C_4, leukotriene D_4, and histamine in normal human subjects. Thorax 1984; 39: 500-4
20. Joris I, Majno G, Corey EJ, et al. The mechanism of vascular leakage induced by leukotriene E_4. Endothelial contraction. Am J Pathol 1987 Jan; 126: 19-24
21. Marom Z, Shelhamer JH, Bach MK, et al. Slow-reacting substances, leukotrienes C_4 and D_4 increase the release of mucus from human airways *in vitro*. Am Rev Respir Dis 1982; 126: 449-51
22. Laitinen LA, Laitinen A, Haahtela T, et al. Leukotriene E_4 and granulocytic infiltration into asthmatic airways. Lancet 1993 Apr; 341: 989-90
23. Krell RD, Dehaas CJ, Lengel DJ, et al. Preclinical exploration of the potential antiinflammatory properties of the peptide leukotriene antagonist ICI 204,219 (Accolate™). Ann NY Acad Sci 1994; 744: 289-98
24. Chung KF. Leukotriene receptor antagonists and biosynthesis inhibitors: potential breakthrough in asthma therapy. Eur Respir J 1995 Jul; 8: 1203-13
25. Yokomizo T, Izumi T, Chang K, et al. A G-protein-coupled receptor for leukotriene B4 that mediates chemotaxis. Nature 1997; 387: 620-4
26. Krell RD, Aharony D, Buckner CK, et al. The preclinical pharmacology of ICI 204,219: a peptide leukotriene antagonist. Am Rev Respir Dis 1990 Apr; 141: 978-87
27. Smith LJ, Glass M, Minkwitz MC. Inhibition of leukotriene D_4-induced bronchoconstriction in subjects with asthma: a concentration-effect study of ICI 204,219. Clin Pharmacol Ther 1993 Oct; 54: 430-6
28. Smith LJ, Glass M, Miller CJ. Effect of oral zafirlukast on leukotriene D_4 (LTD_4)-induced bronchoconstriction in patients with asthma [abstract]. Eur Respir J 1995 Sep; 8 Suppl. 19: 48s
29. Smith LJ, Geller S, Ebright L, et al. Inhibition of leukotriene D_4-induced bronchoconstriction in normal subjects by the oral LTD_4 receptor antagonist ICI 204,219. Am Rev Respir Dis 1990 Apr; 141: 988-92
30. Smith LJ, Hanby LA, Simonson MS, et al. Effect of zafirlukast on leukotriene D_4 (LTD_4)-induced bronchoconstriction in asthmatic patients receiving inhaled corticosteroids [abstract]. Eur Respir J 1997 Sep; 10 Suppl. 25: 437s
31. Dahlén B, Zetterström O, Björck T, et al. The leukotriene-antagonist ICI-204,219 inhibits the early airway reaction to cumulative bronchial challenge with allergen in atopic asthmatics. Eur Respir J 1994 Feb; 7: 324-31
32. Findlay SR, Barden JM, Easley CB, et al. Effect of the oral leukotriene antagonist, ICI 204,219, on antigen-induced bronchoconstriction in subjects with asthma. J Allergy Clin Immunol 1992 May; 89: 1040-5
33. O'Shaughnessy KM, Taylor IK, O'Connor B, et al. Potent leukotriene D_4 receptor antagonist ICI 204,219 given by the inhaled route inhibits the early but not the late phase of allergen-induced bronchoconstriction. Am Rev Respir Dis 1993 Jun; 147 (Pt 1): 1431-5
34. Taylor IK, O'Shaughnessy KM, Fuller RW, et al. Effect of cysteinyl-leukotriene receptor antagonist ICI 204.219 on allergen-induced bronchoconstriction and airway hyperreactivity in atopic subjects. Lancet 1991 Mar 23; 337: 690-4
35. Finnerty JP, Wood-Baker R, Thomson H, et al. Role of leukotrienes in exercise-induced asthma. Inhibitory effect of ICI 204219, a potent leukotriene D_4 receptor antagonist. Am Rev Respir Dis 1992 Apr; 145: 746-9
36. Makker HK, Lau LC, Thomson HW, et al. The protective effect of inhaled leukotriene D_4 receptor antagonist ICI 204,219 against exercise-induced asthma. Am Rev Respir Dis 1993 Jun; 147 (Pt 1): 1413-8
37. Pearlman DS, Ostrom NK, Bronsky EA, et al. The leukotriene D_4-receptor antagonist zafirlukast attenuates exercise-induced bronchoconstriction in children. J Pediatr 1999 Mar; 134: 273-9
38. Boulet LP, Bai TR, Miller CJ, et al. Effects of zafirlukast on cold-air-induced bronchoconstriction in patients with asthma [abstract no. 1732]. Eur Respir J 1996; 9 Suppl. 23: 272s
39. Glass M, Snader LA, Israel E, et al. Effect of the inhaled LTD_4-receptor antagonist, ICI 204,219, on cold-air-induced bronchoconstriction in patients with asthma [abstract]. J Allergy Clin Immunol 1993; 93 (Pt 2): 295
40. Israel E, Lavins BJ, Miller CJ, et al. Effect of zafirlukast (20 and 40mg) on cold-air-induced bronchoconstriction in patients with bronchial asthma [abstract no. P0381]. Eur Respir J 1996; 9 Suppl. 23: 51s
41. Richter K, Jörres RA, Magnussen H. Efficacy and duration of action of the antileukotriene zafirlukast on cold air-induced bronchoconstriction. Eur Respir J 2000 Apr; 15: 693-9
42. Lazarus SC, Lavins BJ, Wong HH, et al. Effect of Accolate™ (zafirlukast) on sulfur dioxide (SO2)-induced bronchoconstriction in patients with mild to moderate asthma [abstract]. Allergy 1995; 50 Suppl. 26: 26
43. Kidney JC, Ridge SM, Chung KF, et al. Inhibition of platelet-activating factor-induced bronchoconstriction by the leukotriene D_4 receptor antagonist ICI 204,219. Am Rev Respir Dis 1993 Jan; 147: 215-7
44. Laitinen LA, Laitinen A, Lindqvist A, et al. Effect of zafirlukast (Accolate™) on leukotriene E_4 (LTE_4) induced airway inflammation in asthma [abstract]. Am J Respir Crit Care Med 1999 Mar; 159 Suppl. (Pt 2): A642
45. Phipatanakul W, Eggleston PA, Conover-Walker MK, et al. A randomized, double-blind, placebo-controlled trial of the effect of zafirlukast on upper and lower respiratory responses to cat challenge. J Allergy Clin Immunol 2000 Apr; 105: 704-10
46. Corren J, Spector S, Fuller L, et al. Effect of zafirlukast (Accolate®) on pulmonary responses to natural cat allergen exposure [abstract]. J Allergy Clin Immunol 1999 Jan; 103: S134
47. Diaz P, Gonzalez MC, Galleguillos FR, et al. Leukocytes and mediators in bronchoalveolar lavage during allergen-induced late-phase asthmatic reactions. Am Rev Respir Dis 1989; 139: 1383-9
48. Djukanovic R, Roche WR, Wilson JW, et al. Mucosal inflammation in asthma. Am Rev Respir Dis 1990; 142: 434-57
49. Roquet A, Dahlén B, Kumlin M, et al. Combined antagonism of leukotrienes and histamine produces predominant inhibition of allergen-induced early and late phase airway obstruction in asthmatics. Am J Respir Crit Care Med 1997; 155: 1856-63
50. Westbroek J, Pasma HR. Effects of 2 weeks of treatment with fluticasone propionate 100 mcg b.d. by comparison with zafirlukast 20 mg b.d. on bronchial hyper-responsiveness in patients with mild to moderate asthma. Respir Med 2000 Feb; 94: 112-8
51. Dempsey OJ, Wilson AM, Aziz I, et al. Effects of adding in a leukotriene antagonist or a long acting β_2-agonist in asthmatic patients possessing the glycine-16 β_2-adrenoceptor genotype [abstract]. Thorax 1999 Dec; 54 Suppl. 3: A65
52. Lanz MA, Eisenlohr CP, Toledo Y, et al. Effect of low dose inhaled fluticasone propionate (FP) and oral zafirlukast (ZK) on exhaled nitric oxide (ENO) in Hispanic asthmatics [abstract]. J Allergy Clin Immunol 2000 Jan; 104 (1 Pt 2): S11

53. Zafirlukast. In: McEvoy GK, editor. AHFS drug information 2000. Bethesda, MD: American Society of Health-System Pharmacists, 2000: 3466-70
54. Accolate. In: Walker G, editor. ABPI data sheet compendium and summaries of product characteristics 1999-2000. London: Datapharm Publications Ltd, 1999: 1776-7
55. Accolate (zafirlukast) tablets. Professional information brochure [online]. Zeneca Pharmaceuticals. Wilmington, Delaware, 2000. Available from: URL: http://www.astrazenecaus.com/pi/AC1244.pdf [Accessed 2000 Dec 14]
56. Carlson GF, Suttle AB, Ruckle JL, et al. Lack of interaction between zafirlukast and theophylline in children [abstract]. Ann Allergy Asthma Immunol 2000 Jan; 84: 157
57. Stelzle RC, Katial RK, Bonner MW, et al. An alarming drug interaction between zafirlukast and theophylline [abstract]. Ann Allergy Asthma Immunol 1998 Jan; 80: 135
58. Garey KW, Peloquin CA, Godo PG, et al. Lack of effect of zafirlukast on the pharmacokinetics of azithromycin, clarithromycin, and 14-hydroxyclarithromycin in healthy volunteers. Antimicrob Agents Chemother 1999 May; 43: 1152-5
59. Spector SL, Smith LJ, Glass M, et al. Effects of 6 weeks of therapy with oral doses of ICI 204,219, a leukotriene D_4 receptor antagonist, in subjects with bronchial asthma. Am J Respir Crit Care Med 1994 Sep; 150: 618-23
60. Nathan RA, Bernstein JA, Bielory L, et al. Zafirlukast improves asthma symptoms and quality of life in patients with moderate reversible airflow obstruction. J Allergy Clin Immunol 1998 Dec; 102 (6 Pt 1): 935-42
61. Minkwitz MC, Bonuccelli CB, Warren MS. Zafirlukast (Accolate®) response in severe persistent asthma [abstract]. Am J Respir Crit Care Med 1998; 157 (3): A410
62. National Institutes of Health. Global initiative for asthma. Global strategy for asthma management and prevention. NHLBI/WHO workshop report. Bethesda, MD: National Heart, Lung, and Blood Institute, 1995 Jan. Publication no. 95-3659
63. López AL, López G, Orozco S, et al. Zafirlukast in a case of severe eczema with hyper-IgE [abstract]. Ann Allergy Asthma Immunol 1999 Jan; 82: 82
64. MacDowell-Carneiro AL, Hurtado RC, Bellanti JA. Improvement of atopic eczema with a leukotriene inhibitor: a new therapeutic use? [abstract]. Ann Allergy Asthma Immunol 1998 Jan; 80: 119
65. Chu TJ, Warren MS. Zafirlukast (Accolate) in the treatment of chronic idiopathic urticaria - a case series [abstract]. J Allergy Clin Immunol 1998 Jan; 101 (1 Pt 2): S155
66. Spector S, Tan RA. Antileukotrienes in chronic urticaria [letter]. J Allergy Clin Immunol 1998 Apr; 101 (4 Pt 1): 572
67. Kukhta AL, Bratton DL, Chan KH, et al. Leukotriene pathway modifiers: are they the newest line of therapy for chronic sinusitis?: case reports [abstract]. J Allergy Clin Immunol 1998 Jan; 101: S252
68. Micheletto C, Tognella S, Trevisan F, et al. Nasal function is improved by zafirlukast (20mg bid x 4wks) in ASA-sensitive rhinitis [abstract]. Am J Respir Crit Care Med 2000 Mar; 161 (Pt 2 Suppl.): A323
69. Ovcharenko SI, Tchitchkova NV, Ovchinnikov JM. The first successful experience of applying zafirlukast in patients with allergic rhinosinusitis and mild-to-moderate asthma in Russia [abstract no. P3336]. Annual Congress of the European Respiratory Society; 1999 Oct 9-13; Madrid
70. Cohn JR, Keane WM, Branton CF. Resolution of chronic nasal polyps by zafirlukast [abstract]. Ann Allergy Asthma Immunol 1999 Jan; 82: 110
71. Cohn JR, Keane WM, Branton CF. Treatment of refractory nasal polyps with leukotriene inhibitors/antagonists [abstract]. J Allergy Clin Immunol 1999 Jan; 103: S256
72. Pullerits T, Praks L, Skoogh B-E, et al. Randomized placebo-controlled study comparing a leukotriene receptor antagonist and a nasal glucocorticoid in seasonal allergic rhinitis. Am J Respir Crit Care Med 1999 Jun; 159: 1814-8
73. Fish JE, Kemp JP, Lockey RF, et al. Zafirlukast for symptomatic mild-to-moderate asthma: a 13-week multicenter study. Clin Ther 1997; 19 (4): 675-90
74. Kemp JP, Glass M, Minkwitz MC. Onset of action of the leukotriene-receptor antagonist, zafirlukast, in patients with asthma [abstract]. Eur Respir J 1995 Sep; 8 Suppl. 19: 288s
75. Crapo RO, Morris AH, Gardner RM. Reference spirometric values using techniques and equipment that meets ATS recommendations. Am Rev Respir Dis 1981; 123: 659-64
76. Polgar G, Promadhat V, editors. Pulmonary function testing in children: techniques and standards. Philadelphia (PA): W.B. Saunders, 1971
77. Tashkin DP, Nathan RA, Howland WC, et al. An evaluation of zafirlukast in the treatment of asthma with exploratory subset analyses. J Allergy Clin Immunol 1999 Feb; 103 (2 Pt 1): 246-54
78. Kemp JP, Minkwitz MC, Bonuccelli CM, et al. Therapeutic effect of zafirlukast as monotherapy in steroid-naive patients with severe persistent asthma. Chest 1999 Feb; 115: 336-42
79. Barnes NC, Miller CJ. Effect of leukotriene receptor antagonist therapy on the risk of asthma exacerbations in patients with mild to moderate asthma: an integrated analysis of zafirlukast trials. Thorax 2000 Jun; 55: 478-83
80. Miyamoto T. Efficacy and safety of zafirlukast (Accolate™) in asthmatic patients treated with and without corticosteroids. Accolate™ Clinical Trial Committee [abstract]. Am J Respir Crit Care Med 1999 Mar; 159 (Pt 2 Suppl.): A640
81. Grossman J, Smith LJ, Wilson AM, et al. Long-term safety and efficacy of zafirlukast in the treatment of asthma: interim results of an open-label extension trial. Ann Allergy Asthma Immunol 1999 Apr; 82: 361-9
82. Finn Jr AF, Banuccelli CM, Traxler BM, et al. Zafirlukast improves asthma control in children treated with and without inhaled corticosteroids [abstract]. Pediatr Res 2000 Apr; 47 (4 Pt 2 Suppl.): 16A
83. Lampl KL, Dixon SJ, Bonuccelli CM. Long-term safety and efficacy of zafirlukast (Accolate) in pediatric patients with mild-to-moderate asthma [abstract]. Am J Respir Crit Care Med 1999 Mar; 159 (Pt 2 Suppl.): A138
84. Kerwin EM, Jeppson JD, Pearlman DS, et al. Long-term safety and effectiveness of zafirlukast in school-aged children with asthma [abstract]. Pediatr Res 2000 Apr; 47 (4 Pt 2 Suppl.): 18A
85. Pearlman DS, Lampl KL, Dowling Jr PJ, et al. Effectiveness and tolerability of zafirlukast for the treatment of asthma in children. Clin Ther 2000; 22 (6): 732-47
86. Jarvis B, Adkins JC. Management of asthma. The potential role of zafirlukast. Dis Manage Health Outcomes 1998; 4 (6): 337-53
87. Nayak AS, Anderson PJ, Charous BL, et al. Addition of zafirlukast compared with a doubled dosage of inhaled corticosteroids in asthmatic patients with symptoms on inhaled corticosteroids [abstract]. Eur Respir J 1998 Sep; 12 Suppl. 28: 361s
88. Ringdal N, White M, Harris A. Addition of zafirlukast (Accolate™) compared with a double-dose of inhaled corticosteroids in patients with reversible airways obstruction symptomatic on inhaled corticosteroids [abstract]. Am J Respir Crit Care Med 1999 Mar; 159 (Pt 2 Suppl.): A639

89. Laitinen LA, Zetterström O, Holgate ST, et al. Effects of Accolate™ (zafirlukast; 20 mg bd) in permitting reduced therapy with inhaled steroids: a multicenter trial in patients with doses of inhaled steroid optimised between 800 and 2000 mcg per day [abstract]. Allergy 1995; 50 Suppl. 26: 320
90. Bateman ED, Holgate ST, Binks SM, et al. A multicentre study to assess the steroid-sparing potential of Accolate™ (zafirlukast; 20 mg BD) [abstract]. Allergy 1995; 50 Suppl. 26: 320
91. Virchow Jr JC, Prasse A, Naya I, et al. Zafirlukast improves asthma control in patients receiving high-dose inhaled corticosteroids. Am J Respir Crit Care Med 2000 Aug; 162: 578-85
92. Jarvis B, Faulds D. Inhaled fluticasone propionate: a review of its therapeutic efficacy at dosages ≤500 μg/day in adults and adolescents with mild to moderate asthma. Drugs 1999 May; 57: 769-803
93. Busse W, Srebro SH, Edwards L, et al. Low-dose inhaled fluticasone propionate versus oral zafirlukast in asthma patients [abstract]. Am J Respir Crit Care Med 1999 Mar; 159 (Pt 2 Suppl.): A628
94. Bleecker ER, Welch MJ, Weinstein SF, et al. Low-dose inhaled fluticasone propionate versus oral zafirlukast in the treatment of persistent asthma. J Allergy Clin Immunol 2000 Jun; 105 (Pt 1): 1123-9
95. Dvorin DJ, Pepsin PJ, Srebro S, et al. Switching asthma patients from low dose inhaled corticosteroids to low dose fluticasone or zafirlukast [abstract]. J Allergy Clin Immunol 2000; 105 (1 Pt 2): S260
96. Kalberg CJ, Johnson MJ, Srebro SH, et al. Fluticasone propionate compared to zafirlukast in the treatment of persistent asthma [abstract]. Thorax 1998 Dec; 53 Suppl. 4: A16
97. Rickard K, Srebro SH, Edwards L, et al. Inhaled fluticasone propionate versus oral zafirlukast in asthma patients [abstract no. P841]. Annual Congress of the European Respiratory Society; 1999 Oct 9-13; Madrid
98. Storms W, Srebro SH, Edwards L, et al. Better asthma symptom control with low-dose inhaled fluticasone propionate than with oral zafirlukast [abstract]. Am J Respir Crit Care Med 1999 Mar; 159 (Pt 2 Suppl.): A628
99. Bleecker E, Kalberg C, Edwards L, et al. Low-dose fluticasone versus zafirlukast in patients with persistent asthma [abstract]. Am J Respir Crit Care Med 1999 Mar; 159 (Pt 2 Suppl.): A630
100. National Institutes of Health. National Asthma Education and Prevention Program. Highlights of the expert panel report 2: guidelines for the diagnosis and management of asthma. Bethesda, MD: National Heart, Lung, and Blood Institute, 1997 Apr. Publication no. 97-4051
101. Warner JO, Naspitz CK, Cropp GJA. Third international pediatric consensus statement on the management of childhood asthma. Pediatr Pulmonol 1998 Jan; 25: 1-17
102. Boulet L-P, Becker A, Berube D, et al. Summary of recommendations from the Canadian Asthma Consensus Report, 1999. Can Med Assoc J 1999; 161 (11) Suppl. I: S1-S61
103. Adkins JC, McTavish D. Salmeterol: a review of its pharmacological properties and clinical efficacy in the management of children with asthma. Drugs 1997 Aug; 54: 331-54
104. Busse W, Nelson H, Wolfe J, et al. Comparison of inhaled salmeterol and oral zafirlukast in patients with asthma. J Allergy Clin Immunol 1999 Jun; 103: 1075-80
105. Kalberg CJ, Rickard KA. A comparison of salmeterol and zafirlukast in patients with persistent asthma [abstract]. Thorax 1998 Dec; 53 Suppl. 4: A17
106. Kalberg CJ, Yancey S, Emmett AH, et al. A comparison of salmeterol versus zafirlukast in patients using inhaled corticosteroids [abstract]. J Allergy Clin Immunol 1999 Jan; 103 (1 Pt 2): S229
107. Miyamoto T, Kabe J, Nakajima S, et al. Phase III comparative study of ICI 204,219 (zafirlukast, Accolate), a cysteinyl-leukotriene (LT) receptor antagonist, in adult patients with bronchial asthma: double-blind comparative study with pranlukast hydrate. Rinsho Iyaku 2000; 16 (8): 1181 (125)-216 (160)
108. Korenblat PE, Kemp JP, Scherger JE, et al. Effect of age on response to zafirlukast in patients with asthma in the Accolate Clinical Experience and Pharmacoepidemiology Trial (ACCEPT). Ann Allergy Asthma Immunol 2000 Feb; 84: 217-25
109. Suissa S, Dennis R, Ernst P, et al. Effectiveness of the leukotriene receptor antagonist zafirlukast for mild-to-moderate asthma: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 1997 Feb 1; 126: 177-83
110. Klim JB, Brown J, Syrett N, et al. Cost impact of reducing exacerbations of asthma in multi-national clinical trials with zafirlukast [abstract no. P0382]. Eur Respir J 1996; 9 Suppl. 23: 52s
111. Stanford R, Carranza-Rosenweig J, Bowers B, et al. Cost effectiveness of inhaled fluticasone versus zafirlukast in patients switched from low dose inhaled corticosteroids [abstract]. Chest 1999 Oct; 116 Suppl. 2: 247S
112. Carranza Rosenzweig J, Bowers B, Edwards L, et al. A cost effectiveness analysis of inhaled fluticasone propionate (Flovent) versus zafirlukast (Accolate) in the treatment of patients with persistent asthma [abstract]. Am J Respir Crit Care Med 1999 Mar; 159 (Pt 2 Suppl.): A760
113. Carranza-Rosenzweig JR, Bowers BW, Stanford RH, et al. Cost-efficacy analysis of an inhaled corticosteroid versus a leukotriene receptor antagonist [abstract]. Value Health 1999 May-Jun; 2: 132-3
114. Menendez R, Carranza-Rosenzweig R, Stanford R, et al. Cost-efficacy of an inhaled corticosteroid, fluticasone propionate, and an oral leukotriene modifier, zafirlukast, in patients wtih persistent asthma [abstract]. J Allergy Clin Immunol 2000; 104 (1 Pt 2): S13
115. Brondum J, Stanford R, Yancey S, et al. Patients on inhaled fluticasone 44 & 110 μg demonstrate significant reductions in both asthma and total health care costs while zafirlukast increases costs [abstract]. J Allergy Clin Immunol 2000 Jan; 105: S284
116. Silverman S, Wang Y, Klingman S, et al. Retrospective outcomes analysis of the effects of zafirlukast therapy in the management of patients with asthma in the US [abstract]. Value Health 1999 Sep-Oct; 2: 406-7
117. Howard K, Bowers B, Edwards L, et al. The impact of single-agent controller therapies on asthma-related quality of life [abstract]. Am J Respir Crit Care Med 2000 Mar; 161 Suppl. (Pt 2): A788
118. Bowers B, Johnson M, Edwards L, et al. The impact of fluticasone propionate and zafirlukast on patient quality of life [abstract]. Am J Respir Crit Care Med 1999 Mar; 159 Suppl. (Pt 2): A761
119. Kylstra JW, Sweitzer DE, Miller CJ, et al. Zafirlukast (Accolate®) in moderate asthma: patient-reported outcomes and peripheral eosinophil data from a 13-week trial [abstract]. Am J Respir Crit Care Med 1998; 157 (3): A410
120. Jones PW, Silverman S, Naya I, et al. Greater improvements in quality of life (QoL) over 12 months with zafirlukast 20mg BD plus low dose steroids vs double-dose steroids in patients with greater QoL impairment [abstract no. P2289]. Annual

Congress of the European Respiratory Society; 1999 Oct 9-13; Madrid
121. Ringdal N, Whitney JG, Summerton L. A comparison of patient preference for treatment with oral zafirlukast or inhaled beclomethasone [abstract]. Eur Respir J 1997; 10 Suppl. 25: 437s
122. Chung KF, Naya I. Compliance with an oral asthma medication: a pilot study using an electronic monitoring device. Respir Med 2000; 94 (9): 852-8
123. Weinberg EG, Naya I. Treatment preferences of adolescent patients with asthma. Pediatr Allergy Immunol 2000; 11 (1): 49-55
124. Reinus JF, Persky S, Burkiewicz JS, et al. Severe liver injury after treatment with the leukotriene receptor antagonist zafirlukast. Ann Intern Med 2000; 133 (12): 964-8
125. Gozalo Reques F, Estrada Rodriguez JL. Tolerability of leukotriene modifiers in asthma: a review of clinical experience. BioDrugs 1999; 11 (6): 385-94
126. Green RL, Vayonis AG. Churg-Strauss syndrome after zafirlukast in two patients not receiving systemic steroid treatment [letter]. Lancet 1999 Feb 27; 353: 725-6
127. Wechsler ME, Drazen JM. Zafirlukast and Churg-Strauss syndrome. Reply [letter]. JAMA 1998 Jun 24; 279: 1950
128. Wechsler ME, Pauwels R, Drazen JM. Leukotriene modifiers and Churg-Strauss syndrome: adverse effect or response to corticosteroid withdrawal? Drug Saf 1999 Oct; 21: 241-51
129. Do antileukotrienes uncover Churg-Strauss syndrome? Drug Ther Perspect 1999; 13 (10): 14-6
130. Churg A, Churg J. Steroids and Churg-Strauss syndrome [letter]. Lancet 1998 Jul 4; 352: 32-3
131. D'Cruz DP, Barnes NC, Lockwood CM. Difficult asthma or Churg-Strauss syndrome? Steroids may be masking undiagnosed cases of Churg-Strauss syndrome. BMJ 1999 Feb 20; 318: 475-6
132. Frosi A, Foresi A, Bozzoni M, et al. Churg-Strauss syndrome and antiasthma therapy [letter]. Lancet 1999 Mar 27; 353: 1102
133. Green RL, Vayonis AG. Churg-Strauss syndrome. Reply [letter]. Lancet 1999 Jun 5; 353: 1971
134. Wechsler ME, Drazen JM. Zafirlukast and Churg-Strauss syndrome [letter]. Chest 1999 Jul; 116: 266-7
135. Wechsler M, Drazen JM. Churg-Strauss syndrome [letter]. Lancet 1999 Jun 5; 353: 1970
136. Wechsler ME, Drazen JM. Leukotriene modifiers and Churg-Strauss syndrome: an update [abstract]. Am J Respir Crit Care Med 2000 Mar; 161 (Pt 2 Suppl.): A195
137. Wan Y. AstraZeneca revises zafirlukast (Accolate) labeling in the US. DI Zone News. London, S. East and Eastern Drug Information Service, Guy's Medicines Information Centre. London, 2000 Sep 21
138. Kemp JP. Guidelines update: where do the new therapies fit in the management of asthma? Drugs 2000; 59 Suppl. 1: 23-8
139. Renwick DS, Connolly MJ. Improving outcomes in elderly patients with asthma. Drugs Aging 1999; 14 (1): 1-9
140. Kelloway JS, Wyatt RA, Adlis SA. Comparison of patient's compliance with prescribed oral and inhaled asthma medications. Arch Intern Med 1994; 154: 1349-53
141. Adinoff AD, Schwartz HJ, Rickard KA, et al. Salmeterol compared with current therapies in chronic asthma. J Fam Pract 1998; 47 (4): 278-84
142. Taylor DR, Town GI, Herbison GP, et al. Asthma control during long-term treatment with regular inhaled salbutamol and salmeterol. Thorax 1998; 53 (9): 744-52
143. Wilding P, Clark M, Coon JT, et al. Effect of long-term treatment with salmeterol on asthma control: a double blind, randomised crossover study. BMJ 1997 May 17; 314: 1441-6
144. Nathan RA, Pinnas JL, Schwartz HJ, et al. A six-month, placebo-controlled comparison of the safety and efficacy of salmeterol or beclomethasone for persistent asthma. Ann Allergy Asthma Immunol 1999; 82 (6): 521-9
145. Ramage L, Lipworth BJ, Ingram CG, et al. Reduced protection against exercise induced bronchoconstriction after chronic dosing with salmeterol. Respir Med 1994; 88 (5): 363-8
146. Booth H, Bish R, Walters J, et al. Salmeterol tachyphylaxis in steroid treated asthmatic patients. Thorax 1996; 51 (11): 1100-4
147. Dottorini ML, Tantucci C, Peccini F, et al. Diurnal change of bronchial caliber and airway responsiveness in asthmatics during long-term treatment with long-acting beta 2-agonist salmeterol. Int J Clin Pharmacol Ther 1996; 34 (10): 438-43
148. Kalra S, Swystun VA, Bhagat R, et al. Inhaled corticosteroids do not prevent the development of tolerance to the bronchoprotective effect of salmeterol. Chest 1996; 109 (4): 953-6
149. Grove A, Lipworth BJ. Bronchodilator subsensitivity to salbutamol after twice daily salmeterol in asthmatic patients. Lancet 1995 Jul 22; 346: 201-6
150. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: a systematic review and meta-analysis. Arch Intern Med 1999; 159 (9): 941-55

Correspondence: *Christopher J. Dunn*, Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 10, New Zealand.
E-mail: demail@adis.co.nz