Contraindications
Accolate should not be given to patients who have previously experienced hypersensitivity to the product or any of its ingredients.
Accolate is contraindicated in patients with hepatic impairment or cirrhosis; it has not been studied in patients with hepatitis or in long term studies of patients with cirrhosis.
Accolate is contraindicated in children under 12 years of age until safety information is available.

Special warning and precautions for use
Accolate should be taken regularly to achieve benefit, even during symptom free periods. Accolate therapy should normally be continued during acute exacerbations of asthma.
Accolate does not allow a reduction in existing steroid treatment.
As with inhaled steroids and cromones (disodium cromoglycate, nedocromil sodium), Accolate is not indicated for use in the reversal of bronchospasm in acute asthma attacks.
Accolate has not been evaluated in the treatment of labile (brittle) or unstable asthma.
Cases of eosinophilic conditions, including Churg-Strauss Syndrome and eosinophilic pneumonia have been reported in association with Accolate usage. Presentations may involve various body systems including vasculitic rash, worsening pulmonary symptoms, cardiac complications or neuropathy. A causal relationship has neither been confirmed nor refuted. If a patient develops an eosinophilic condition or a Churg-Strauss Syndrome type illness Accolate should be stopped, a re-challenge test should not be performed and treatment should not be restarted.
Elevations in serum transaminases can occur during treatment with Accolate. These are usually asymptomatic and transient but could represent early evidence of hepatotoxicity, and have very rarely been associated with more severe hepato-cellular injury.
theophylline levels. However, during post-marketing surveillance, there have been rare cases of patients experiencing increased theophylline levels when co-administered Accolate.

Co-administration with terfenadine resulted in a 54% decrease in AUC for zafirlukast, but with no effect on plasma terfenadine levels.

Co-administration with acetylsalicylic acid (“aspirin”, 650 mg four times a day) may result in increased plasma levels of zafirlukast, by approximately 45%.

Co-administration with erythromycin will result in decreased plasma levels of zafirlukast, by approximately 40%.

The clearance of zafirlukast in smokers may be increased by approximately 20%.

At concentrations of 10 microgram/ml and above, zafirlukast causes increases in the assay value for bilirubin in animal plasma. However, zafirlukast has not been shown to interfere with the 2,5-dichlorophenyl diazonium salt method of bilirubin analysis of human plasma.

Pregnancy and lactation

Pregnancy

The safety of Accolate in human pregnancy has not been established. In animal studies, zafirlukast did not have any apparent effect on fertility and did not appear to have any teratogenic or selective toxic effect on the foetus. The potential risks should be weighed against the benefits of continuing therapy during pregnancy and Accolate should be used during pregnancy only if clearly needed.

Lactation

Zafirlukast is excreted in human breast milk. Accolate should not be administered to mothers who are breast-feeding.

Effects on ability to drive and use machines

There is no evidence that Accolate affects the ability to drive and use machinery.

Undesirable effects

The following have been reported in association with the administration of Accolate.

Gastrointestinal: nausea, vomiting, abdominal pain (common)
Hepatobiliary: Symptomatic hepatitis with and without hyperbilirubinaemia (rare), hyperbilirubinaemia, without elevated liver function tests (rare), hepatic failure (very rare), fulminant hepatitis (very rare)
General: malaise (common)
Musculoskeletal: arthralgia (rare), myalgia (rare)
Skin: rash (including blistering), Pruritus, hypersensitivity reactions including urticaria and angioedema (rare) and oedema (uncommon)
Neurological: Insomnia, headache (common)
Haematologic: bruising (rare), bleeding disorders, including menorrhagia (rare), thrombocytopenia (rare), and agranulocytosis (very rare)
The above events have usually resolved following cessation of therapy. Headache and gastrointestinal disturbance are usually mild and do not necessitate withdrawal from therapy.

In placebo-controlled clinical trials, an increased incidence of infection has been observed in elderly patients given Accolate (7.8% vs 1.4%). Infections were usually mild, predominantly affecting the respiratory tract.

**Overdose**
Limited information exists with regard to the effects of overdosage of Accolate in humans.
Management should be supportive. Removal of excess medication by gastric lavage may be helpful.

**Pharmacodynamic properties**

ATC Code: R03D C01.
Pharmacotherapeutic Group: Leukotriene receptor antagonists.
The cysteinyl leukotrienes (LTC4, LTD4 and LTE4) are potent inflammatory eicosanoids released from various cells including mast cells and eosinophils. These important pro-asthmatic mediators bind to cysteinyl leukotriene receptors found in the human airway. Leukotriene production and receptor occupation has been implicated in the pathophysiology of asthma. Effects include smooth muscle contraction, airway oedema and altered cell activity associated with the inflammatory process, including eosinophil influx to the lung.
Accolate is a competitive highly selective and potent oral peptide leukotriene antagonist of LTC4, LTD4 and LTE4 components of slow reacting substance of anaphylaxis. In vitro studies have shown that Accolate antagonises the contractile activity of all three peptide leukotrienes (leukotriene C4, D4, and E4) in human conducting airway smooth muscle to the same extent. Animal studies have shown Accolate to be effective in preventing peptide leukotriene-induced increases in vascular permeability, which give rise to oedema in the airways, and to inhibit peptide leukotriene-induced influx of eosinophils into airways.
The specificity of Accolate has been shown by its action on leukotriene receptors and not prostaglandin, thromboxane, cholinergic and histamine receptors.

In a placebo-controlled study where segmental bronchoprovocation with allergen was followed by bronchoalveolar lavage 48 hours later, zafirlukast decreased the rise in basophils, lymphocytes and histamine, and reduced the stimulated production of superoxide by alveolar macrophages. Accolate attenuated the increase in bronchial hyperresponsiveness that follows inhaled allergen challenge. Further, methacholine sensitivity was diminished by long-term dosing with Accolate 20 mg twice daily.

Further, in clinical trials evaluating chronic therapy with Accolate, the lung function measured when plasma levels were at trough showed sustained improvements over baseline.

Accolate shows a dose dependent inhibition of bronchoconstriction induced by inhaled LTD4. Asthmatic patients are approximately 10-fold more sensitive to the bronchoconstricting activity of inhaled LTD4. A single oral dose of Accolate can enable an asthmatic patient to inhale 100 times more LTD4 and shows significant protection at 12 and 24 hours.

Accolate inhibits the bronchoconstriction caused by several kinds of challenge, such as the response to sulphur dioxide, exercise and cold air. Accolate attenuates the early and late phase inflammatory reaction caused by various antigens such as grass, cat dander, ragweed and mixed antigens.

In asthmatic patients not adequately controlled by beta-agonist therapy (given as required) Accolate improves symptoms (reducing daytime and nocturnal
asthmatic symptoms), improves lung function, reduces the need for concomitant beta-agonist medication and reduces incidence of exacerbations. Similar benefits have been seen in patients with more severe asthma receiving high dose inhaled steroids.

In clinical studies, there was a significant first-dose effect on baseline bronchomotor tone observed within 2 hours of dosing, when peak plasma concentrations had not yet been achieved. Initial improvements in asthma symptoms occurred within the first week, and often the first few days, of treatment with Accolate.

**Pharmacokinetic properties**

Peak plasma concentrations of zafirlukast are achieved approximately 3 hours after oral administration of Accolate. Administration of Accolate with food increased the variability in the bioavailability of zafirlukast and reduced bioavailability in most (75%) subjects. The net reduction was approximately 40%.

Following twice-daily administration of Accolate (30 to 80 mg bd), accumulation of zafirlukast in plasma was low (not detectable - 2.9 times first dose values; mean 1.45; median 1.27). The terminal half-life of zafirlukast is approximately 10 hours. Steady-state plasma concentrations of zafirlukast were proportional to the dose and predictable from single-dose pharmacokinetic data.

Zafirlukast is extensively metabolised. Following a radiolabelled dose the urinary excretion accounts for approximately 10% dose and faecal excretion for 89%. Zafirlukast is not detected in urine. The metabolites identified in human plasma were found to be at least 90-fold less potent than zafirlukast in a standard in-vitro test of activity.

Zafirlukast is approximately 99% protein bound to human plasma proteins, predominantly albumin, over the concentration range 0.25 to 4.0 microgram/ml.

Pharmacokinetic studies in special populations have been performed in a relatively small number of subjects, and the clinical significance of the following kinetic data is not established.

Pharmacokinetics of zafirlukast in adolescents and adults with asthma were similar to those of healthy adult males. When adjusted for body weight, the pharmacokinetics of zafirlukast are not significantly different between men and women.

Elderly subjects and subjects with stable alcoholic cirrhosis demonstrated an approximately two-fold increase in Cmax and AUC compared to normal subjects given the same doses of Accolate.

There are no significant differences in the pharmacokinetics of zafirlukast in patients with mild renal impairment and in normal subjects. However, there are no conclusive data available in patients with moderate or severe renal impairment, hence the recommendation for caution is used in this patient population.

**Pre-clinical safety data**

After multiple doses of greater than 40 mg/kg/day for up to 12 months, liver enlargement associated with degenerative/fatty change or glycogen deposition was seen in rats, mice and dogs. Histiocytic aggregates were seen in a number of tissues of dogs. Male mice given 300 mg/kg zafirlukast daily had an increased incidence of hepatocellular adenomas compared to control animals. Rats given 2000 mg/kg zafirlukast daily had an increased incidence of urinary bladder papilloma compared to control animals. Zafirlukast was not mutagenic in a range of tests. The clinical significance of these findings during the long term use of Accolate in man is uncertain. There were no other notable findings from the preclinical testing.

**Special precautions for storage**

Do not store above 30oC.

**Shelf-life**

Please refer to expiry date on the blister strip or outer carton.

**Pack size**

Please refer to the outer carton for pack size.

**Date of revision of the text**

March 2005