Tulobuterol Hydrochloride *(BANM, rINNM)* ⊗

C-78; Hidrocloruro de tulobuterol; HN-078 (tulobuterol); Tulobutérol, Chlorhydrate de; Tulobuterolhydroklorid; Tulobuteroli Hydrochloridum; Tulobuterolihydrokloridi. 2-*tert*-Butylamino-1-*o*-chlorophenylethanol hydrochloride.

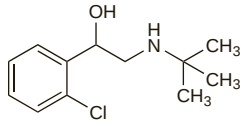
Тулобутерола Гидрохлорид

$C_{12}H_{18}ClNO,HCl$ = 264.2.

CAS — 41570-61-0 (tulobuterol); 56776-01-3 (tulobuterol hydrochloride).

ATC — R03AC11; R03CC11.

ATC Vet — QR03AC11; QR03CC11.



(tulobuterol)

Pharmacopoeias. In *Jpn.*

Profile

Tulobuterol is a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on $beta_2$ receptors ($a beta_2$ agonist). It has properties similar to those of salbutamol (p.1131).

Tulobuterol is used as a bronchodilator in the management of reversible airways obstruction, as in asthma (p.1108) and in some patients with chronic obstructive pulmonary disease (p.1112). It is given orally as the hydrochloride. The initial oral dose in adults is 1 or 2 mg of tulobuterol hydrochloride twice daily, which can be increased to 3 mg twice daily if necessary. An increased need for, or decreased duration of effect of, tulobuterol indicates deterioration of asthma control and the need for review of therapy. Tulobuterol has also been given as the base by inhalation from a metered-dose inhaler. A transdermal formulation of tulobuterol base is also available; a dose of 2 mg daily is used together with anti-inflammatory therapy.

For doses of tulobuterol used in children aged 14 years and under, see Administration in Children, below.

◊ References to the transdermal formulation of tulobuterol.

1. Uematsu T, *et al.* The pharmacokinetics of the β -adrenoceptor agonist, tulobuterol, given transdermally and by inhalation. *Eur J Clin Pharmacol*. 1993; **44:** 361–4.
2. Iikura Y, *et al.* Pharmacokinetics and pharmacodynamics of the tulobuterol patch, HN-078, in childhood asthma. *Ann Allergy* 1995; **74:** 147–51.
3. Fukuchi Y, *et al.* Clinical efficacy and safety of transdermal tulobuterol in the treatment of stable COPD: an open-label comparison with inhaled salmeterol. *Treat Respir Med* 2005; **4:** 447–55.
4. Yoshihara S, *et al.* The use of patch formulation of tulobuterol, a long-acting beta2-adrenoceptor agonist, in the treatment of severe pediatric asthma. *Ann Allergy Asthma Immunol* 2006; **96:** 879–80.
5. Fujimoto K, *et al.* Comparison of the clinical efficacy of salmeterol and sustained-release tulobuterol (patch) on inadequately controlled asthma patients on inhaled corticosteroids. *J Asthma* 2006; **43:** 501–7.
6. Nishiyama O, *et al.* Comparison of the effects of tulobuterol patch and salmeterol in moderate to severe asthma. *Clin Exp Pharmacol Physiol* 2006; **33:** 1016–21.
7. Kobayashi Y, *et al.* Addition of transdermal or inhaled long-acting β -agonists in adult asthmatic patients treated with inhaled corticosteroids: switchover study from tulobuterol patch to salmeterol dry powder inhaler. *J Asthma* 2007; **44:** 77–81.

Administration in children. Tulobuterol hydrochloride has been used to treat bronchospasm in children in the following *oral* doses:

- 1 to 6 years of age, 0.25 to 0.5 mg twice daily
- 6 to 10 years of age, 0.5 to 1 mg twice daily
- 10 to 14 years of age, 1 to 1.5 mg twice daily

In some countries, children 12 years of age and over may be given the adult dose of tulobuterol, see above.

Transdermal delivery of tulobuterol is also used in children, in the following doses:

- 6 months to 3 years of age, 0.5 mg once daily
- 3 to 9 years of age, 1 mg once daily
- 9 years of age and older, as for adults (see above)

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Bremax; ***Belg.:*** Respacal†; ***Ger.:*** Atenos; Brelomax; ***Jpn:*** Hokunalin; ***Mex.:*** Bremax; ***Philipp.:*** Bremax; ***Port.:*** Atenos†; ***Venez.:*** Bremax†; Bretol.

Zafirlukast *(BAN, USAN, rINN)*

ICI-204219; Tsafirlukasti; Zafirlukastum. Cyclopentyl 3-{2-methoxy-4-[(*o*-tolylsulfonyl)carbamoyl]benzyl}-1-methylindole-5-carbamate.

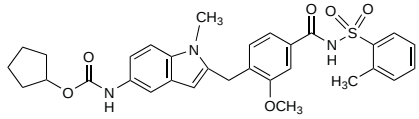
Зафирлукаст

$C_{31}H_{33}N_3O_6S$ = 575.7.

CAS — 107753-78-6.

ATC — R03DC01.

ATC Vet — QR03DC01.



Adverse Effects and Precautions

Headache, an increased incidence of respiratory-tract infection (in the elderly), and gastrointestinal disturbances have been reported with zafirlukast and other leukotriene antagonists. Other adverse effects have included generalised and abdominal pain, arthralgia, myalgia, fever, malaise, insomnia, and dizziness. Elevations in liver enzyme values have occurred, and rarely, symptomatic hepatitis or hyperbilirubinaemia (see also below); fatalities have occurred. Hypersensitivity reactions, including rashes, pruritus, urticaria, and angioedema, have been reported. There have also been rare reports of agranulocytosis, bleeding, bruising and oedema. There have been a few reports of systemic eosinophilia consistent with Churg-Strauss syndrome in patients receiving zafirlukast (see below); treatment should be withdrawn in these patients.

Zafirlukast and other leukotriene antagonists should not be used for the treatment of acute asthma attacks. Zafirlukast is contra-indicated in patients with hepatic impairment or cirrhosis.

Incidence of adverse effects. An observational study[1] of 7976 patients prescribed zafirlukast found it to be generally well tolerated. Similarly to UK licensed product information, the most frequently reported adverse effects (1 to 2% of patients) were headache, rash, abdominal pain, malaise, and gastrointestinal disturbances such as nausea, diarrhoea, and dyspepsia. Dizziness and palpitations were more common in the first month of treatment. An increased incidence of depression was also noted.

1. Twaites BR, *et al.* Safety of zafirlukast: results of a postmarketing surveillance study on 7976 patients in England. *Drug Safety* 2007; **30:** 419–29.

Churg-Strauss syndrome. Pulmonary infiltrates and eosinophilia, resembling the Churg-Strauss syndrome, with dilated cardiomyopathy, were reported after withdrawal of corticosteroid therapy in 8 patients taking zafirlukast.[1] Symptoms responded to withdrawal of zafirlukast and treatment with corticosteroids, with or without cyclophosphamide. It has been suggested that the patients' original asthmatic symptoms had been part of an unrecognised vasculitic syndrome that was unmasked by stopping corticosteroids.[2,3] However, others have reported Churg-Strauss syndrome associated with zafirlukast in those not receiving corticosteroids,[4,5] although these cases were not inconsistent with the view that treatment with leukotriene antagonists was coincidental.[6] It has also been noted that leukotriene receptor antagonists tend to be prescribed for patients with more severe asthma, which may be a precursor to the development of Churg-Strauss syndrome.[3] In addition, eosinophilic syndromes have been reported for other anti-asthma drugs including inhaled fluticasone and sodium cromoglicate, evidence supporting a non-drug-related aetiology.[6] However, the number of reports with zafirlukast and the other leukotriene antagonists, montelukast (see p.1126) and pranlukast,[7] means that a particular class-effect cannot be ruled out.[3,8] It has been suggested that patients should be monitored carefully (e.g. by measuring erythrocyte sedimentation rate, C reactive protein, and eosinophil counts) if the introduction of an anti-asthma drug such as a leukotriene antagonist permits the reduction of oral corticosteroid dosage.[9] In addition, in patients with asthma and features of multisystem disease, the possibility of underlying Churg-Strauss syndrome (p.1501) may be worth considering.

1. Wechsler ME, *et al.* Pulmonary infiltrates, eosinophilia, and cardiomyopathy following corticosteroid withdrawal in patients with asthma receiving zafirlukast. *JAMA* 1998; **279:** 455–7.
2. Churg A, Churg J. Steroids and Churg-Strauss syndrome. *Lancet* 1998; **352:** 32–3.
3. Keogh KA. Leukotriene receptor antagonists and Churg-Strauss syndrome: cause, trigger or merely an association? *Drug Safety* 2007; **30:** 837–43.
4. Katz RS, Papernik M. Zafirlukast and Churg-Strauss syndrome. *JAMA* 1998; **279:** 1949.
5. Green RL, Vayonis AG. Churg-Strauss syndrome after zafirlukast in two patients not receiving systemic steroid treatment. *Lancet* 1999; **353:** 725–6.
6. Wechsler M, Drazen JM. Churg-Strauss syndrome. *Lancet* 1999; **353:** 1970.
7. Kinoshita M, *et al.* Churg-Strauss syndrome after corticosteroid withdrawal in an asthmatic patient treated with pranlukast. *J Allergy Clin Immunol* 1999; **103:** 534–5.
8. Green RL, Vayonis AG. Churg-Strauss syndrome. *Lancet* 1999; **353:** 1971.
9. D'Cruz DP, *et al.* Difficult asthma or Churg-Strauss syndrome? *BMJ* 1999; **318:** 475–6.

Effects on the liver. Severe hepatotoxicity has been associated with zafirlukast.[1-4] The Canadian manufacturer reported[4] in April 2004 that from worldwide postmarketing surveillance of zafirlukast there had been 46 reports of hepatitis, 14 of hepatic failure, 3 of which progressed to fulminant hepatitis, and 59 reports of other clinically significant hepatic dysfunction; 7 fatalities had occurred. In most, but not all, cases symptoms had abated and liver enzymes had returned to normal after stopping zafirlukast. It was important that prescribers, patients and/or their carers were alert to the signs and symptoms of hepatotoxicity. Licensed product information for zafirlukast advises stopping treatment if hepatotoxicity is suspected, and performing liver function tests;

1. Grieco AJ, Burstein-Stein J. Oral montelukast versus inhaled salmeterol to prevent exercise-induced bronchoconstriction. *Ann Intern Med* 2000; **133:** 392.
2. Reinus JF, *et al.* Severe liver injury after treatment with the leukotriene receptor antagonist zafirlukast. *Ann Intern Med* 2000; **133:** 964–8.
3. Danese S, *et al.* Severe liver injury associated with zafirlukast. *Ann Intern Med* 2001; **135:** 930.
4. AstraZeneca Canada. Important safety information regarding reports of serious hepatic events in patients receiving Accolate (zafirlukast) (issued 14th April 2004). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/accolate_2_hpc-cps-eng.pdf (accessed 09/07/08)

Lupus. Zafirlukast was thought to be responsible for the development of lupus in a 9-year-old girl.[1]

1. Finkel TH, *et al.* Drug-induced lupus in a child after treatment with zafirlukast (Accolate). *J Allergy Clin Immunol* 1999; **103:** 533–4.

Renal impairment. The UK licensed product information states that zafirlukast should be used with caution in patients with moderate or severe renal impairment because of limited experience in this group. However, the US product information mentions no such caution, and states that the pharmacokinetics of zafirlukast in patients with renal impairment do not appear to differ from those in patients with normal renal function. Only about 10% of a dose is reported to be excreted in the urine.

Interactions

Zafirlukast is metabolised by hepatic cytochrome P450, specifically the CYP2C9 isoenzyme, and has been shown to inhibit the activity of isoenzymes CYP2C9 and CYP3A4. Therefore, use with other drugs that are metabolised by these hepatic enzymes may result in increases in plasma concentrations, and possibly, adverse effects. Patients receiving warfarin may develop prolongation of the prothrombin time and anticoagulant dosage should be adjusted accordingly. Erythromycin, terfenadine, and theophylline may reduce plasma concentrations of zafirlukast; zafirlukast has rarely been reported to increase plasma-theophylline concentrations. Increased plasma concentrations of zafirlukast have been seen when given with high doses of aspirin.

Pharmacokinetics

Peak plasma concentrations of zafirlukast occur about 3 hours after oral doses. The absolute bioavailability is uncertain, but taking it with food reduces both the rate and extent of absorption, decreasing bioavailability by about 40%. Zafirlukast is about 99% bound to plasma proteins. It is extensively metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP2C9, and excreted principally in faeces, as unchanged drug and metabolites. About 10% of a dose is excreted in urine as metabolites. The terminal elimination half-life of zafirlukast is about 10 hours. Studies in *animals* suggest that small amounts cross the placenta; it is also distributed into breast milk.

◊ Reviews.

1. Dekhuijzen PNR, Koopmans PP. Pharmacokinetic profile of zafirlukast. *Clin Pharmacokinet* 2002; **41:** 105–14.

Uses and Administration

Zafirlukast is a selective and competitive antagonist of the leukotriene C_4, D_4, and E_4 receptors (p.1108), stimulation of which by circulating leukotrienes is thought

to play a role in the pathogenesis of asthma. The drug suppresses both early and late bronchoconstrictor responses to inhaled antigens or irritants, but is not suitable for the management of acute attacks of asthma.

Zafirlukast is used in the management of chronic asthma (see below). It is given orally in doses of 20 mg twice daily, taken at least 1 hour before or 2 hours after meals. For details of doses in children, see below.

◊ General references.

1. García-Marcos L, *et al.* Benefit-risk assessment of antileukotrienes in the management of asthma. *Drug Safety* 2003; **26:** 483–518.
2. Anonymous. Leukotriene receptor antagonists—an update. *Drug Ther Bull* 2005; **43:** 85–8.
3. Currie GP, McLaughlin K. The expanding role of leukotriene receptor antagonists in chronic asthma. *Ann Allergy Asthma Immunol* 2006; **97:** 731–41.
4. Riccioni G, *et al.* Antileukotriene drugs: clinical application, effectiveness and safety. *Curr Med Chem* 2007; **14:** 1966–77.

Administration in children. In the management of chronic asthma, US licensed product information recommends a zafirlukast dose of 10 mg twice daily orally in children aged from 5 to 11 years. Children 12 years of age and over may be given the adult dose, see above. In the UK, zafirlukast is unlicensed in children under 12 years of age.

Asthma. Zafirlukast produces modest improvement in mild-to-moderate asthma,[1,2] which was of a similar order to that seen with inhaled sodium cromoglicate in one study,[3] but less than that of inhaled salmeterol in another.[4] It has also been found to be less effective than inhaled fluticasone in persistent asthma.[5-7] Guidelines for the management of asthma (p.1108) permit the use of zafirlukast as an alternative to inhaled corticosteroids in patients with mild persistent asthma, who cannot be managed with inhaled $beta_2$ agonists on an as-needed basis alone. It can also be considered for use in moderate or severe persistent asthma, usually added to standard therapy of inhaled corticosteroids and long-acting inhaled $beta_2$ agonists. Combination of anti-leukotriene drugs with inhaled corticosteroids alone seems, however, to be less effective than a combination of the latter with long-acting inhaled $beta_2$ agonists. In a study in patients presenting to the emergency room with acute severe asthma, adding zafirlukast to standard therapy in hospital and for 28 days after discharge was associated with a reduced rate of relapse, and a reduction in the need for extended care.[8]

1. Suissa S, *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; **126:** 177–83.
2. Fish JE, *et al.* Zafirlukast for symptomatic mild-to-moderate asthma: a 13-week multicenter study. *Clin Ther* 1997; **19:** 675–90.
3. Nathan RA, *et al.* Two first-line therapies in the treatment of mild asthma: use of peak flow variability as a predictor of effectiveness. *Ann Allergy Asthma Immunol* 1999; **82:** 497–503.
4. Busse W, *et al.* Comparison of inhaled salmeterol and oral zafirlukast in patients with asthma. *J Allergy Clin Immunol* 1999; **103:** 1075–80.
5. Busse W, *et al.* Fluticasone propionate compared with zafirlukast in controlling persistent asthma: a randomized double-blind, placebo-controlled trial. *J Fam Pract* 2001; **50:** 595–602.
6. Nathan RA, *et al.* A comparison of short-term treatment with inhaled fluticasone propionate and zafirlukast for patients with persistent asthma. *Am J Med* 2001; **111:** 195–202.
7. Brabson JH, *et al.* Efficacy and safety of low-dose fluticasone propionate compared with zafirlukast in patients with persistent asthma. *Am J Med* 2002; **113:** 15–21.
8. Silverman RA, *et al.* Zafirlukast treatment for acute asthma: evaluation in a randomized, double-blind, multicenter trial. *Chest* 2004; **126:** 1480–9.

Rhinitis. Although it was reported to improve symptoms of seasonal allergic rhinitis (p.565) in one study,[1] zafirlukast 20 mg twice daily was not effective when compared with placebo and intranasal beclometasone in another.[2] Some benefits have been reported in perennial allergic rhinitis, in particular an improvement in nasal obstruction.[3,4] A review of the role of leukotrienes in allergic rhinitis concluded that leukotriene receptor antagonists have modest efficacy given alone but can be usefully added to other treatments.[5]

1. Donnelly AL, *et al.* The leukotriene D -receptor antagonist, ICI 204,219, relieves symptoms of acute seasonal allergic rhinitis. *Am J Respir Crit Care Med* 1995; **151:** 1734–9.
2. Pullerits T, *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; **159:** 1814–18.
3. Jiang R-S. Efficacy of a leukotriene receptor antagonist in the treatment of perennial allergic rhinitis. *J Otolaryngol* 2006; **35:** 117–21.
4. Ho C-Y, Tan C-T. Comparison of antileukotrienes and antihistamines in the treatment of allergic rhinitis. *Am J Rhinol* 2007; **21:** 439–43.
5. Peters-Golden M, Henderson WR. The role of leukotrienes in allergic rhinitis. *Ann Allergy Asthma Immunol* 2005; **94:** 609–18.

Urticaria. Leukotriene antagonists, such as zafirlukast, are reported to have some benefit in the management of chronic urticaria (p.1584).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Accolate; Vanticon†; Zafirasmal†; ***Austral.:*** Accolate; ***Belg.:*** Accolate; Resma; ***Braz.:*** Accolate; ***Canad.:*** Accolate; ***Chile:*** Accolate; ***Cz.:*** Accolate; ***Fin.:*** Accolate; ***Hong Kong:*** Accolate; ***Hung.:*** Accolate; ***India:*** Zuvair; ***Indon.:*** Accolate; ***Irl.:*** Accolate; ***Ital.:*** Accoleit; Zafirst; ***Mex.:*** Accolate; ***Philipp.:*** Accolate; ***Pol.:*** Accolate; ***Port.:*** Accolate; ***Rus.:*** Accolate (Аколат); ***S.Afr.:*** Accolate; ***Singapore:*** Accolate; ***Spain:*** Accolate; Aeronix; Olmoran; ***Switz.:*** Accolate; ***Thai.:*** Accolate†; ***Turk.:*** Accolate; ***UK:*** Accolate; ***USA:*** Accolate; ***Venez.:*** Accolate.

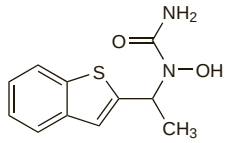
Zileuton *(BAN, USAN, rINN)*

A-64077; Abbott-64077; Zileutón; Zileutonum. (±)-1-(1-Benzo[*b*]thien-2-ylethyl)-*N*-hydroxyurea.

Зилейтон

$C_{11}H_{12}N_2O_2S$ = 236.3.

CAS — 111406-87-2.



Pharmacopoeias. In *US.*

USP 31 (Zileuton). A white to off-white powder. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

The most commonly reported adverse effects associated with zileuton treatment are headache, pain including pharyngolaryngeal pain, gastrointestinal disturbances, myalgia, and sinusitis. Hypersensitivity, urticaria, rash, and leucopenia have been reported in a few patients. Zileuton has also been associated with raised liver enzyme values and severe hepatic injury.

Zileuton is not suitable for the treatment of acute asthma attacks.

Effects on the liver. Cases of severe hepatotoxicity including fatalities, jaundice, hyperbilirubinaemia, and raised liver enzymes have been reported in patients taking zileuton. US licensed product information therefore contraindicates the use of zileuton in patients with active liver disease or liver transaminase elevations greater than or equal to three times the upper limit of normal. Caution is required in patients with a history of liver disease or who consume substantial quantities of alcohol. Alanine aminotransferase (ALT) is considered the most sensitive indicator of liver injury due to zileuton. Most rises in ALT concentrations occurred in the first 3 months of zileuton therapy,[1] and monitoring is therefore recommended before starting zileuton therapy, once a month for the first 3 months of therapy, every 2 to 3 months for the remainder of the first year of therapy, and periodically thereafter.

1. Watkins PB, *et al.* Clinical pattern of zileuton-associated liver injury: results of a 12-month study in patients with chronic asthma. *Drug Safety* 2007; **30:** 805–15.

Interactions

Zileuton has been reported to impair the metabolism of some drugs metabolised via hepatic cytochrome P450 enzymes, including propranolol, terfenadine, theophylline, and warfarin.

Pharmacokinetics

Zileuton is reported to be well absorbed from the gastrointestinal tract after oral dosage, with peak plasma concentrations of immediate-release preparations occurring within about 2 hours of a dose. It is about 93% bound to plasma proteins. It is extensively metabolised in the liver by the cytochrome P450 isoenzymes CYP1A2, CYP2C9, and CYP3A4, and excreted in the urine, largely as glucuronide metabolites. The elimination half-life is reported to be about 2.5 hours for the immediate-release preparation and about 3 hours for the controlled-release preparation.

◊ References.

1. Wong SL, *et al.* The pharmacokinetics of single oral doses of zileuton 200 to 800 mg, its enantiomers, and its metabolites, in normal healthy volunteers. *Clin Pharmacokinet* 1995; **29** (suppl 2): 9–21.
2. Awni WM, *et al.* Pharmacokinetics and pharmacodynamics of zileuton after oral administration of single and multiple dose regimens of zileuton 600 mg in healthy volunteers. *Clin Pharmacokinet* 1995; **29** (suppl 2): 22–33.
3. Braeckman RA, *et al.* The pharmacokinetics of zileuton in healthy young and elderly volunteers. *Clin Pharmacokinet* 1995; **29** (suppl 2): 42–8.
4. Awni WM, *et al.* Population pharmacokinetics of zileuton, a selective 5-lipoxygenase inhibitor, in patients with rheumatoid arthritis. *Eur J Clin Pharmacol* 1995; **48:** 155–60.
5. Awni WM, *et al.* The effect of mild or moderate hepatic impairment (cirrhosis) on the pharmacokinetics of zileuton. *Clin Pharmacokinet* 1995; **29** (suppl 2): 49–61.
6. Awni WM, *et al.* Pharmacokinetics of zileuton and its metabolites in patients with renal impairment. *J Clin Pharmacol* 1997; **37:** 395–404.
7. Dubé LM, *et al.* Zileuton, a leukotriene synthesis inhibitor in the management of chronic asthma: clinical pharmacokinetics and safety. *Clin Rev Allergy Immunol* 1999; **17:** 213–21.

Uses and Administration

Zileuton is an orally active 5-lipoxygenase inhibitor and therefore inhibits leukotriene formation (p.1108). It is used in the management of chronic asthma (see below) but has no bronchodilator properties and is not suitable for the management of acute attacks. Zileuton is given in oral doses of 600 mg 4 times daily as an immediate-release preparation. A controlled-release formulation of zileuton is also available; the usual oral dose is 1.2 g twice daily.

It has also been tried in other disorders including arthritis, allergic rhinitis, and inflammatory bowel disease.

Asthma. Zileuton has been found to be of some benefit in asthma, including that provoked by cold air, exercise, and NSAIDs. US guidelines for the management of asthma (p.1108) permit its use in addition to inhaled corticosteroid therapy in moderate persistent asthma. Combination of anti-leukotriene drugs with inhaled corticosteroids alone seems however to be less effective than a combination of the latter with long-acting inhaled $beta_2$ agonists. Due to a lack of data on efficacy and the need for liver function monitoring, zileuton is also considered a less desirable treatment option for addition to inhaled corticosteroids than the leukotriene receptor antagonists.

An intravenous form of zileuton is under investigation for use in asthma.

References.

1. Israel E, *et al.* The effects of a 5-lipoxygenase inhibitor on asthma induced by cold, dry air. *N Engl J Med* 1990; **323:** 1740–4.
2. Israel E, *et al.* The effect of inhibition of 5-lipoxygenase by zileuton in mild-to-moderate asthma. *Ann Intern Med* 1993; **119:** 1059–66.
3. McGill KA, Busse WW. Zileuton. *Lancet* 1996; **348:** 519–24.
4. Israel E, *et al.* Effect of treatment with zileuton, a 5-lipoxygenase inhibitor, in patients with asthma: a randomized controlled trial. *JAMA* 1996; **275:** 931–6.
5. O'Connor BJ, *et al.* Zileuton added to low-dose inhaled beclomethasone for the treatment of moderate to severe persistent asthma. *Respir Med* 2007; **101:** 1088–96.

Inflammatory bowel disease. Despite initial hopes that inhibition of lipoxygenase might prove of benefit in patients with ulcerative colitis,[1] a study in those with mild or moderately active relapsing disease found that the symptomatic benefits of zileuton were confined to those not already receiving sulfasalazine.[2] A subsequent study showed zileuton was not significantly better than placebo in maintaining remission.[3] For a discussion of inflammatory bowel disease and its management, see p.1697.

1. Laursen LS, *et al.* Selective 5-lipoxygenase inhibition in ulcerative colitis. *Lancet* 1990; **335:** 683–5.
2. Laursen LS, *et al.* Selective 5-lipoxygenase inhibition by zileuton in the treatment of relapsing ulcerative colitis: a randomized double-blind placebo-controlled multicentre trial. *Eur J Gastroenterol Hepatol* 1994; **6:** 209–15.
3. Hawkey CJ, *et al.* A trial of zileuton versus mesalazine or placebo in the maintenance of remission of ulcerative colitis. *Gastroenterology* 1997; **112:** 718–24.

Rhinitis. A study in 8 patients with allergic rhinitis (p.565) found that a single dose of zileuton 800 mg reduced the response to a nasal antigen challenge 3 hours later,[1] including reduced sneezing and nasal congestion.

1. Knapp HR. Reduced allergen-induced nasal congestion and leukotriene synthesis with an orally active 5-lipoxygenase inhibitor. *N Engl J Med* 1990; **323:** 1745–8.

Preparations

Proprietary Preparations (details are given in Part 3)

USA: Zyflo.