one year with tiotropium compared with 6 per 1000 patients given placebo for one year. The FDA had not yet confirmed the analyses and urged caution in interpreting these preliminary results.

1. FDA. Early communication about ongoing safety review of tiotropium (marketed as Spiriva HandiHaler) (issued 18th March 2008). Available at: http://www.fda.gov/cder/drug/early_comm/tiotropium.htm (accessed 22/05/08)

Effects on the skin. Subacute cutaneous lupus erythematosus has been reported in a patient inhaling tiotropium.[1] Skin lesions developed one week after introduction of the drug, resolved when the drug was stopped, and recurred on rechallenge.

Inhaled tiotropium has also been associated with a photosensitive lichenoid eruption in another patient,[2] 22 months after starting treatment. The lesions resolved when the drug was stopped; patch testing however, gave a negative result. Rechallenge was not attempted.

1. Pham H-C, Saurat J-H. Inhalation route inducing subacute cutaneous lupus erythematosus with tiotropium. *Arch Dermatol* 2005; **141:** 911–12.
2. Pérez-Pérez L, *et al.* Photosensitive lichenoid eruption and inhaled tiotropium bromide. *Dermatology* 2007; **214:** 97–8.

Interactions

For interactions associated with antimuscarinics in general, see Atropine, p.1220. However, these interactions are not usually seen with antimuscarinics, such as tiotropium, given by inhalation.

Pharmacokinetics

After inhalation, some tiotropium bromide is absorbed from the lung, with the majority deposited in the gastrointestinal tract. In healthy subjects a systemic bioavailability of about 20% is reported after dry powder inhalation, and about 33% after inhalation of the solution. Tiotropium is about 72% bound to plasma proteins. It is excreted largely unchanged in the urine, although it may undergo some metabolism by non-enzymatic cleavage and by the cytochrome P450 isoenzymes CYP2D6 and CYP3A4. The terminal elimination half-life is between 5 and 6 days.

Uses and Administration

Tiotropium bromide is a quaternary ammonium antimuscarinic that is structurally related to ipratropium but has a prolonged bronchodilator action. It is used similarly to ipratropium (p.1124) in the maintenance treatment of reversible airways obstruction, as in chronic obstructive pulmonary disease (below); tiotropium is not suitable for the initial treatment of acute bronchospasm. Tiotropium bromide can be given as inhalation powder in capsules containing 22.5 micrograms of tiotropium bromide monohydrate, equivalent to 18 micrograms of tiotropium, and supplying 10 micrograms of tiotropium from the mouthpiece of the inhaler device. The contents of one capsule are inhaled daily, at the same time each day.

Tiotropium bromide can also be given as inhalation solution via a metered-dose inhaler. Each metered dose contains 3.124 micrograms of tiotropium bromide monohydrate equivalent to 2.5 micrograms of tiotropium. Two doses of 2.5 micrograms are inhaled daily, at the same time each day.

◊ References.

1. Hvizdos KM, Goa KL. Tiotropium bromide. *Drugs* 2002; **62:** 1195–1203.

Chronic obstructive pulmonary disease. In chronic obstructive pulmonary disease (COPD; p.1112) tiotropium bromide has been shown to be effective at improving dyspnoea,[1-3] health-related quality of life,[1,3] symptom-limited exercise tolerance,[2] lung function measurements,[3] and reducing exacerbations[1,3,4] compared with placebo.

Tiotropium has also been found to be more effective than ipratropium at improving dyspnoea, health-related quality of life,[5] and lung function,[5,6] and reducing exacerbations;[5] consideration of tiotropium as first-line maintenance treatment in COPD has been suggested.

Similarly, tiotropium has produced better bronchodilatation, reduced dyspnoea, and improved health-related quality of life scores compared with salmeterol.[7]

Combining tiotropium therapy with an inhaled corticosteroid and a long-acting beta$_2$ agonist did not statistically influence rates of COPD exacerbations but did improve lung function, quality of life, and hospitalisation rates in patients with moderate to severe COPD.[8]

A systematic review[9] and a meta-analysis[10] confirmed that tiotropium reduces exacerbations and related hospitalisations, improves quality of life and symptoms in stable COPD. Tiotropium may also have slowed the decline in forced expiratory volume (FEV) seen in COPD; however, the authors concluded that further studies are required to evaluate the effect of tiotropium on FEV and to clarify its role in relation to long-acting beta$_2$ agonists.

The role of tiotropium in the management of COPD has been extensively reviewed.[11-14]

1. Casaburi R, *et al.* A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur Respir J* 2002; **19:** 217–24.
2. Maltais F, *et al.* Improvements in symptom-limited exercise performance over 8 h with once-daily tiotropium in patients with COPD. *Chest* 2005; **128:** 1168–78.
3. Brusasco V, *et al.* Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. *Thorax* 2003; **58:** 399–404.
4. Niewoehner DE, *et al.* Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. *Ann Intern Med* 2005; **143:** 317–26.
5. Vincken W, *et al.* Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium. *Eur Respir J* 2002; **19:** 209–16.
6. van Noord JA, *et al.* A randomised controlled comparison of tiotropium and ipratropium in the treatment of chronic obstructive pulmonary disease. *Thorax* 2000; **55:** 289–94.
7. Donohue JF, *et al.* A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. *Chest* 2002; **122:** 47–55.
8. Aaron SD, *et al.* Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 2007; **146:** 545–55.
9. Barr RG, *et al.* Tiotropium for stable chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 18/02/08).
10. Barr RG, *et al.* Tiotropium for stable chronic obstructive pulmonary disease: a meta-analysis. *Thorax* 2006; **61:** 854–62. Correction. *ibid.*; **62:** 191.
11. Gross NJ. Tiotropium bromide. *Chest* 2004; **126:** 1946–53.
12. Olin JL. Tiotropium: an inhaled anticholinergic for chronic obstructive pulmonary disease. *Am J Health-Syst Pharm* 2005; **62:** 1263–9.
13. Somand H, Remington TL. Tiotropium: a bronchodilator for chronic obstructive pulmonary disease. *Ann Pharmacother* 2005; **39:** 1467–75.
14. Burns G, Bianchi S. Chronic obstructive pulmonary disease: the evidence for use of tiotropium. *Br J Hosp Med* 2006; **67:** 85–91.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Spiriva; ***Austral.:*** Spiriva; ***Austria:*** Spiriva; ***Belg.:*** Spiriva; ***Braz.:*** Spiriva; ***Canad.:*** Spiriva; ***Chile:*** Spiriva; ***Cz.:*** Spiriva; ***Denm.:*** Spiriva; ***Fin.:*** Spiriva; ***Fr.:*** Spiriva; ***Ger.:*** Spiriva; ***Gr.:*** Spiriva; ***Hong Kong:*** Spiriva; ***Hung.:*** Spiriva; ***India:*** Tiova; ***Indon.:*** Spiriva; ***Irl.:*** Spiriva; ***Israel:*** Spiriva; ***Ital.:*** Spiriva; ***Jpn:*** Spiriva; ***Malaysia:*** Spiriva; ***Mex.:*** Spiriva; ***Neth.:*** Spiriva; ***Norw.:*** Spiriva; ***NZ:*** Spiriva; ***Philipp.:*** Spiriva; ***Pol.:*** Spiriva; ***Port.:*** Spiriva; ***Rus.:*** Spiriva (Спирива); ***S.Afr.:*** Spiriva; ***Singapore:*** Spiriva; ***Spain:*** Spiriva; ***Swed.:*** Spiriva; ***Switz.:*** Spiriva; ***Thai.:*** Spiriva; ***Turk.:*** Spiriva; ***UK:*** Spiriva; ***USA:*** Spiriva; ***Venez.:*** Spiriva.

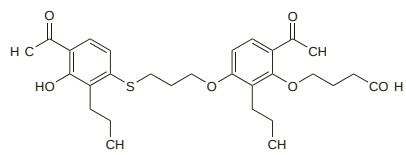
Multi-ingredient: ***India:*** Duova.

Tipelukast *(USAN, rINN)*

KCA-757; MN-001; Tipélukast; Tipelukastum. 4-(6-Acetyl-3-{3-[(4-acetyl-3-hydroxy-2-propylphenyl)sulfanyl]propoxy}-2-propylphenoxy)butanoic acid.

Типелукаст

$C_{29}H_{38}O_7S$ = 530.7.
CAS — 125961-82-2.



Profile

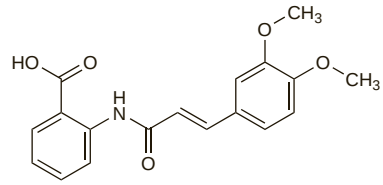
Tipelukast is a leukotriene receptor antagonist (p.1108), a phosphodiesterase inhibitor, and 5-lipoxygenase inhibitor that is under investigation for the treatment of asthma.

Tranilast *(USAN, rINN)*

MK-341; N-5′; Tranilastum. *N*-(3,4-Dimethoxycinnamoyl)anthranilic acid.

Траниласт

$C_{18}H_{17}NO_5$ = 327.3.
CAS — 53902-12-8.



Adverse Effects and Precautions

Adverse effects reported with tranilast have included gastrointestinal disturbances, headache, drowsiness or insomnia, dizziness, malaise, and skin rashes and generalised pruritus. Rarely, liver function disturbance or jaundice, renal dysfunction, cystitis-like symptoms, anaemia, leucopenia, thrombocytopenia, palpitations, oedema, facial flushing, and stomatitis may occur. Tranilast should be used with caution in patients with impaired hepatic or renal function. Haematological monitoring is recommended.

Irritation and blepharitis have been reported after topical application to the eye.

Licensed product information advises against the use of tranilast in pregnancy because of teratogenicity in *animal* studies.

Tranilast should not be used for the treatment of acute asthma attacks. The general cautions described under sodium cromoglicate (p.1136) also apply.

Uses and Administration

Tranilast has a stabilising action on mast cells resembling that of sodium cromoglicate (p.1137). It is also stated to inhibit collagen synthesis in fibroblasts. It is used in the prophylactic management of asthma (p.1108) and in allergic rhinitis (p.565), conjunctivitis (p.564), and eczema (p.1579). It is also used in the management of keloids and hypertrophic scarring. The usual oral adult dose is 100 mg three times daily. For details of doses in children, see below. Eye drops containing tranilast 0.5% are used four times daily for allergic conjunctivitis.

Tranilast has been investigated for the prevention of restenosis after coronary artery revascularisation procedures but was found to be ineffective.

Administration in children. Tranilast is given to children for the prophylactic management of asthma, in allergic rhinitis and eczema, and in the management of keloids and hypertrophic scars. An oral daily dose of 5 mg/kg, given in 3 divided doses, may be used.

Sarcoidosis. For a mention of possible benefit from tranilast in cutaneous sarcoidosis, see p.1512.

Preparations

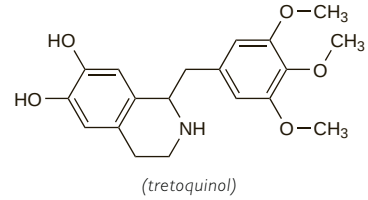
Proprietary Preparations (details are given in Part 3)
Jpn: Rizaben.

Tretoquinol Hydrochloride *(plNNM)* ⊗

AQ-110 (tretoquinol); Hidrocloruro de tretoquinol; Ro-07-5965; Trétoquinol, Chlorhydrate de; Tretoquinoli Hydrochloridum; Trimethoquinol Hydrochloride; Trimetoquinol Hydrochloride. (–)-1,2,3,4-Tetrahydro-1-(3,4,5-trimethoxybenzyl)isoquinoline-6,7-diol hydrochloride monohydrate.

Третохинола Гидрохлорид

$C_{19}H_{23}NO_5$,HCl,H_2O = 399.9.
CAS — 30418-38-3 (tretoquinol); 18559-59-6 (anhydrous tretoquinol hydrochloride).
ATC — R03AC09; R03CC09.
ATC Vet — QR03AC09; QR03CC09.



(tretoquinol)

Pharmacopoeias. In *Jpn.*

Profile

Tretoquinol is a direct-acting sympathomimetic reported to have a selective action on beta$_2$ receptors (a beta$_2$ agonist). It has properties similar to those of salbutamol (p.1131). It is given as the hydrochloride for its bronchodilating properties in the management of reversible airways obstruction, as in asthma (p.1108) or in some patients with chronic obstructive pulmonary disease (p.1112).

Preparations

Proprietary Preparations (details are given in Part 3)
Indon.: Inolin; ***Jpn:*** Inolin†.

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.

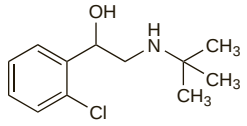
Тулобутерола Гидрохлорид

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

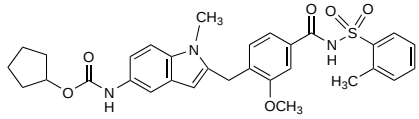
Зафирлукаст

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