Ipratropium bromide may also be given by inhalation as a nebulised solution. UK licensed product information recommends the following doses:

- under 6 years, for the treatment of acute asthma only: 125 to 250 micrograms, given no more often than every 6 hours up to a total daily dose of 1 mg
- 6 to 12 years, for the treatment of acute or chronic asthma: 250 micrograms, repeated if necessary up to a total daily dose of 1 mg
- 12 years and over: adult doses, see above.

Ipratropium bromide is used in the management of rhinorrhoea associated with **rhinitis**. A dose of 42 micrograms may be given into both nostrils two or three times daily. In the UK this dose may be given to children from 12 years of age, but in the USA this dose is licensed in children from 6 years of age.

US licensing also permits higher doses for up to 4 days when rhinorrhoea is associated with the common cold:

- 5 to 11 years: 84 micrograms into each nostril three times daily
- 12 years and over: adult doses, see above

Higher doses are also permitted in the USA for up to 3 weeks when rhinorrhoea is associated with seasonal allergic rhinitis. Children 5 years of age and over may be given the same dose as adults, see above.

Asthma. Ipratropium bromide is currently recommended as an adjunct to $beta_2$ agonists in the management of acute severe asthma, see p.1108. Antimuscarinic drugs, mainly ipratropium but also including oxitropium (p.1129), glycopyrronium and atropine, have been reviewed in the treatment of both acute and chronic asthma. A systematic review and meta-analysis[1] of the effectiveness of antimuscarinics in the treatment of acute asthma in children and adults, found they produced significant reductions in hospital admissions. Combined treatment with an inhaled $beta_2$ agonist also produced a significant increase in respiratory function.

Systematic reviews of antimuscarinic drugs have concluded that there is currently insufficient evidence to justify their routine use in adults[2] or children[3] with chronic asthma.

1. Rodrigo GJ, Castro-Rodriguez JA. Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis. *Thorax* 2005; **60:** 740–6.
2. Westby M, *et al.* Anticholinergic agents for chronic asthma in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 18/02/08).
3. McDonald NJ, *et al.* Anticholinergic therapy for chronic asthma in children over 2 years of age. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 18/02/08).

Chronic obstructive pulmonary disease. Inhaled antimuscarinics, such as ipratropium bromide, are currently recommended as bronchodilators in chronic obstructive pulmonary disease (COPD) guidelines, see p.1112. A systematic review compared regular treatment with ipratropium (given for at least 4 weeks) with treatment using regular short-acting $beta_2$ agonists in stable COPD;[1] it found small benefits on lung function outcomes and quality of life with ipratropium compared with a short-acting $beta_2$ agonist; a reduction in the requirements for oral corticosteroids was also seen. Combination therapy with ipratropium and a short-acting $beta_2$ agonist was associated with some clinically meaningful lung function outcomes compared with the $beta_2$ agonist alone, but these were not reflected in subjective improvements or symptom scores.

A systematic review comparing ipratropium with a long-acting $beta_2$ agonist in stable COPD,[2] found that salmeterol had more effect than ipratropium on lung function, but no major differences were seen between symptom responses to ipratropium and salmeterol. Combination treatment with these two drugs was better than salmeterol alone in terms of quality of life.

1. Appleton S, *et al.* Ipratropium bromide versus short acting beta-2 agonists for stable chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 18/02/08).
2. Appleton S, *et al.* Ipratropium bromide versus long-acting beta-2 agonists for stable chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 18/02/08).

Rhinitis. Ipratropium bromide is used intranasally for the treatment of rhinorrhoea in allergic and non-allergic rhinitis (p.565). It has also relieved rhinorrhoea and sneezing associated with the common cold.

References.

1. Georgitis JW, *et al.* Ipratropium bromide nasal spray in non-allergic rhinitis: efficacy, nasal cytological response and patient evaluation on quality of life. *Clin Exp Allergy* 1994; **24:** 1049–55.
2. Hayden FG, *et al.* Effectiveness and safety of intranasal ipratropium bromide in common colds: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1996; **125:** 89–97.
3. Dockhorn R, *et al.* Ipratropium bromide nasal spray 0.03% and beclomethasone nasal spray alone and in combination for the treatment of rhinorrhea in perennial rhinitis. *Ann Allergy Asthma Immunol* 1999; **82:** 349–59.
4. Bonadonna P, *et al.* Cold-induced rhinitis in skiers—clinical aspects and treatment with ipratropium bromide nasal spray: a randomized controlled trial. *Am J Rhinol* 2001; **15:** 297–301.
5. Kim KT, *et al.* Pediatric Atrovent Nasal Spray Study Group. Use of 0.06% ipratropium bromide nasal spray in children aged 2 to 5 years with rhinorrhea due to a common cold or allergies. *Ann Allergy Asthma Immunol* 2005; **94:** 73–9.

Preparations

BP 2008: Ipratropium Nebuliser Solution; Ipratropium Powder for Inhalation; Ipratropium Pressurised Inhalation.

Proprietary Preparations (details are given in Part 3)
Arg.: Aerotrop; Atrovent; Iprabron; ***Austral.:*** Aeron; Apoven; Atrovent; Ipratrin; Ipravent; ***Austria:*** Atrovent; Itrop; ***Belg.:*** Atronase; Atrovent; ***Braz.:*** Alvent†; Ares; Atrovent; Bromovent; Iprabon; Ipraneo; ***Canad.:*** Apo-Ipravent; Atrovent; Novo-Ipramide; ***Chile:*** Atrovent; Neorinol†; ***Cz.:*** Atrovent; Itrop†; ***Denm.:*** Atrovent; ***Fin.:*** Atrovent; ***Fr.:*** Atrovent; ***Ger.:*** Atrovent; Itrop; ***Gr.:*** Atrovent; ***Hong Kong:*** Atrovent; Cyclovent; Ipravent†; ***Hung.:*** Atrovent; ***India:*** Ipranase; Ipravent; ***Indon.:*** Atrovent; ***Irl.:*** Atrovent; Rinatec; ***Israel:*** Aerovent; Apovent; Atrovent; ***Ital.:*** Atem; Rinovagos; ***Jpn:*** Atrovent; ***Malaysia:*** Atrovent; ***Mex.:*** Atrovent; ***Neth.:*** Atrovent; Ipraxa; ***Norw.:*** Atrovent; Respontin†; ***NZ:*** Apo-Ipravent; Atrovent; Ipra†; ***Philipp.:*** Atrovent; ***Pol.:*** Atrovent; ***Port.:*** Atrovent; ***Rus.:*** Atrovent (Атровент); ***S.Afr.:*** Atrovent; Ipvent; ***Singapore:*** Atrovent; ***Spain:*** Atrovent; ***Swed.:*** Atrovent; ***Switz.:*** Atrovent; Rhinovent; ***Thai.:*** Atrovent; ***Turk.:*** Atrovent; ***UAE:*** Atropulm; ***UK:*** Atrovent; Respontin; Rinatec; ***USA:*** Atrovent; ***Venez.:*** Alovent.

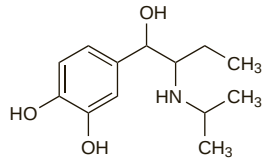
Multi-ingredient: ***Arg.:*** Berodual; Combivent; Ipradual; Iprasalb; Salbutral AC; Salbutrop†; ***Austral.:*** Combivent; ***Austria:*** Berodual; Berodualin; Combivent; Di-Promal; ***Belg.:*** Combivent; Duovent; ***Braz.:*** Combivent; Duovent; ***Canad.:*** Combivent; Duovent; ratio-Ipra Sal UDV; ***Chile:*** Berodual; Combivent; Salbutral AC; ***Cz.:*** Berodual; Combivent†; ***Denm.:*** Berodual; Combivent; ***Fin.:*** Atrodual; Atrovent Comp; ***Fr.:*** Bronchodual; Combivent; ***Ger.:*** Berodual; ***Gr.:*** Berodual; Berovent; ***Hong Kong:*** Berodual†; Combivent; ***Hung.:*** Berodual; ***India:*** Duolin; Fenovent; ***Indon.:*** Berodual; Combivent; ***Irl.:*** Combivent; Duovent; Ipramol; ***Ital.:*** Breva; Duovent; Ipraffen; ***Malaysia:*** Berodual; Combivent; Duovent; Ipramol; ***Mex.:*** Berodual; Combivent; ***Neth.:*** Berodual; Combivent; ***NZ:*** Combivent; Duolin; ***Philipp.:*** Berodual; Combipul; Combivent; Duavent; ***Pol.:*** Berodual; ***Port.:*** Berodual; Combivent; ***Rus.:*** Berodual (Бередуал); ***S.Afr.:*** Atrovent Beta; Berodual; Combivent; Duolin; Duovent; Sabax Combineb; Sabax Nebrafen; ***Singapore:*** Berodual; Combivent; Duovent; ***Spain:*** Berodual†; Combivent; Legis†; ***Swed.:*** Combivent; ***Switz.:*** Berodual; Dospir; ***Thai.:*** Berodual; Combivent; Inhalex; Punol; ***Turk.:*** Combivent; ***UK:*** Combivent; Duovent; Ipramol; ***USA:*** Combivent; DuoNeb; ***Venez.:*** Berodual; Combivent; Duolin; Duovent; Ipralin; Respidual.

Isoetarine *(BAN, rINN)* ⊗

Isoetariini; Isoetarin; Isoetarina; Isoétarine; Isoetarinum; Isoetharine *(USAN)*; Win-3406. 1-(3,4-Dihydroxyphenyl)-2-isopropylaminobutan-1-ol.

Изоэтарин

$C_{13}H_{21}NO_3$ = 239.3.
CAS — 530-08-5.
ATC — R03AC07; R03CC06.
ATC Vet — QR03AC07; QR03CC06.



Isoetarine Hydrochloride *(BANM, rINNM)* ⊗

Etyprenaline Hydrochloride; Hidrocloruro de isoetarina; Isoétarine, Chlorhydrate d'; Isoetarini Hydrochloridum; Isoetharine Hydrochloride; *N*-Isopropylethylnoradrenaline Hydrochloride.

Изоэтарина Гидрохлорид

$C_{13}H_{21}NO_3$,HCl = 275.8.
CAS — 50-96-4; 2576-92-3.
ATC — R03AC07; R03CC06.
ATC Vet — QR03AC07; QR03CC06.

Pharmacopoeias. In *US.*
USP 31 (Isoetharine Hydrochloride). A white to off-white, odourless, crystalline solid. Soluble in water; sparingly soluble in alcohol; practically insoluble in ether. A 1% solution in water has a pH of 4.0 to 5.6. Store in airtight containers.

Isoetarine Mesilate *(BANM, rINNM)* ⊗

Isoétarine, Mésilate d'; Isoetarini Mesilas; Isoetharine Mesylate; Isoetharine Methanesulphonate; *N*-Isopropylethylnoradrenaline Mesylate; Mesilato de isoetarina.

Изоэтарина Мезилат

$C_{13}H_{21}NO_3$,CH_4O_3S = 335.4.
CAS — 7279-75-6.
ATC — R03AC07; R03CC06.
ATC Vet — QR03AC07; QR03CC06.

Pharmacopoeias. In *US.*
USP 31 (Isoetharine Mesylate). White or practically white, odourless, crystals. Freely soluble in water; soluble in alcohol; practically insoluble in acetone and in ether. A 1% solution in water has a pH of 4.5 to 5.5. Store in airtight containers.

Profile
Isoetarine is a sympathomimetic with mainly beta-adrenergic activity. It has actions similar to those of salbutamol (p.1131) but is less selective for $beta_2$ adrenoceptors. Isoetarine has been used as a bronchodilator in the management of reversible airways obstruction.

Isoetarine is given by inhalation, as a nebulised solution of the hydrochloride in strengths up to 0.25%; a 1% solution can be given by a hand nebuliser.

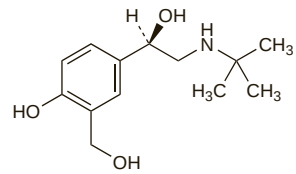
Preparations
USP 31: Isoetharine Inhalation Solution; Isoetharine Mesylate Inhalation Aerosol.

Levosalbutamol *(rINN)* ⊗

Levalbuterol; Lévosalbutamol; Levosalbutamolum. (*R*)-α^1-[(*tert*-Butylamino)methyl]-4-hydroxy-*m*-xylene-α,α′-diol.

Левосальбутамол

$C_{13}H_{21}NO_3$ = 239.3.
CAS — 34391-04-3.



Levosalbutamol Hydrochloride *(rINNM)* ⊗

Hidrocloruro de levosalbutamol; Levalbuterol Hydrochloride *(USAN)*; Lévosalbutamol, Chlorhydrate de; Levosalbutamoli Hydrochloridum. (*R*)-α^1-[(*tert*-Butylamino)methyl]-4-hydroxy-*m*-xylene-α,α′-diol hydrochloride.

Левосальбутамола Гидрохлорид

$C_{13}H_{21}NO_3$,HCl = 275.8.
CAS — 50293-90-8.

Pharmacopoeias. In *US.*
USP 31 (Levalbuterol Hydrochloride). A 1% solution has a pH of 4.5 to 5.5. Store in airtight containers at 20° to 25°, excursions permitted between 15° and 30°. Protect from light.

Levosalbutamol Sulfate *(rINNM)* ⊗

Levalbuterol Sulfate *(USAN)*; Lévosalbutamol, Sulfate de; Levosalbutamol Sulphate; Levosalbutamoli Sulfas; Sulfato de levosalbutamol. (*R*)-α^1-[(*tert*-Butylamino)methyl]-4-hydroxy-*m*-xylene-αα′-diol sulfate (2:1).

Левосальбутамола Сульфат

$(C_{13}H_{21}NO_3)_2$,H_2SO_4 = 576.7.
CAS — 148563-16-0.

Levosalbutamol Tartrate *(rINNM)* ⊗

Levalbuterol Tartrate *(USAN)*; Lévosalbutamol, Tartrate de; Levosalbutamoli Tartras; Tartrato de levosalbutamol. (α^1*R*)-α^1-{[(1,1-Dimethylethyl)amino]methyl}-4-hydroxy-1,3-benzenedimethanol (2*R*,3*R*)-2,3-dihydroxybutanedioate (2:1).

Левосальбутамола Тартрат

$2(C_{13}H_{21}NO_3)$,$C_4H_6O_6$ = 628.7.
CAS — 661464-94-4.

Adverse Effects and Precautions
As for Salbutamol, p.1131.

Incidence of adverse effects. Some studies have reported that beta-adrenergic adverse effects (e.g. nervousness and increased heart rate) are less frequent with inhaled levosalbutamol than with racemic salbutamol.[1-3] Despite preliminary evidence that the increased airway hyperresponsiveness occasionally seen with long-term racemic salbutamol (see Tolerance, p.1132) may be due to the *S*(+)-enantiomer, and therefore might not occur with levosalbutamol,[4] a small study was unable to find any favourable protective effect.[5]

1. Nelson HS, *et al.* Improved bronchodilation with levalbuterol compared with racemic albuterol in patients with asthma. *J Allergy Clin Immunol* 1998; **102:** 943–52.
2. Milgrom H, *et al.* Low-dose levalbuterol in children with asthma: safety and efficacy in comparison with placebo and racemic albuterol. *J Allergy Clin Immunol* 2001; **108:** 938–45.
3. Handley DA, *et al.* Dose-response evaluation of levalbuterol versus racemic albuterol in patients with asthma. *J Asthma* 2000; **37:** 319–27.
4. Perrin-Fayolle M. Salbutamol in the treatment of asthma. *Lancet* 1995; **346:** 1101.
5. Sjöswärd KN, *et al.* Single-isomer R-salbutamol is not superior to racemate regarding protection for bronchial hyperresponsiveness. *Respir Med* 2004; **98:** 990–9.

Interactions
As for Salbutamol, p.1132.

Pharmacokinetics

There is some systemic absorption of inhaled levosalbutamol. After a single dose levosalbutamol has a half-life of 3.3 hours. For details of the metabolism and excretion of salbutamol enantiomers, see Stereoselectivity, under Salbutamol p.1133.

Metabolism. There is evidence that levosalbutamol is metabolised faster than *S*(+)-salbutamol.

References.

1. Boulton DW, Fawcett JP. Enantioselective disposition of salbutamol in man following oral and intravenous administration. *Br J Clin Pharmacol* 1996; **41:** 35–40.
2. Lipworth BJ, *et al.* Pharmacokinetics and extrapulmonary β adrenoceptor activity of nebulised racemic salbutamol and its R and S isomers in healthy volunteers. *Thorax* 1997; **52:** 849–52.
3. Gumbhir-Shah K, *et al.* Pharmacokinetic and pharmacodynamic characteristics and safety of inhaled albuterol enantiomers in healthy volunteers. *J Clin Pharmacol* 1998; **38:** 1096–1106.
4. Boulton DW, Fawcett JP. The pharmacokinetics of levosalbutamol: what are the clinical implications? *Clin Pharmacokinet* 2001; **40:** 23–40.

Uses and Administration

Levosalbutamol, the *R*(−)-enantiomer of salbutamol (p.1131), may be used as an alternative to racemic salbutamol for the management of asthma (p.1108). It is given as the hydrochloride, sulfate, or tartrate but doses are usually expressed in terms of the base; 1.15 mg of levosalbutamol hydrochloride, 2.4 mg of levosalbutamol sulfate, and 2.63 mg of levosalbutamol tartrate are equivalent to about 1 mg of levosalbutamol. For the relief of acute bronchospasm, 1 or 2 inhalations of the equivalent of 45 micrograms of levosalbutamol can be given from a metered-dose aerosol, repeated every 4 to 6 hours as required.

Levosalbutamol may also be inhaled via a nebuliser; usual doses equivalent to levosalbutamol 630 micrograms are inhaled three times daily, increased if necessary to 1.25 mg three times daily. For children's doses, see Administration in Children below. In patients with asthma, as-required beta agonist therapy is preferable to regular use. An increased need for, or decreased duration of effect of, levosalbutamol indicates deterioration of asthma control and the need for review of therapy.

Levosalbutamol is also under investigation in a topical formulation for the treatment of cutaneous lupus erythematosus.

◊ General reviews.

1. Jenne JW. The debate on S-enantiomers of β-agonists: tempest in a teapot or gathering storm? *J Allergy Clin Immunol* 1998; **102:** 893–5.
2. Nowak R. Single-isomer levalbuterol: a review of the acute data. *Curr Allergy Asthma Rep* 2003; **3:** 172–8.
3. Berger WE. Levalbuterol: pharmacologic properties and use in the treatment of pediatric and adult asthma. *Ann Allergy Asthma Immunol* 2003; **90:** 583–91.
4. Datta D, *et al.* An evaluation of nebulized levalbuterol in stable COPD. *Chest* 2003; **124:** 844–9.
5. Kelly HW. Levalbuterol for asthma: a better treatment? *Curr Allergy Asthma Rep* 2007; **7:** 310–14.

Action. *In vitro*, levosalbutamol had slightly higher affinity than racemic salbutamol for $beta_1$ and $beta_2$ adrenoceptors.[1] The *S*(+)-enantiomer had low affinity for these receptors. All 3 were mildly selective for $beta_2$ adrenoceptors.

1. Penn RB, *et al.* Comparison of R-, S-, and RS-albuterol interaction with human β - and β -adrenergic receptors. *Clin Rev Allergy Immunol* 1996; **14:** 37–45.

Administration in children. Children aged 4 years and older may be given levosalbutamol via a metered-dose aerosol at the same dose as that used for adults, see Uses and Administration, above.

Children aged from 6 to 11 years of age may be given levosalbutamol via a nebuliser in doses from 310 to 630 micrograms three times daily.

Asthma. Controlled studies comparing levosalbutamol with racemic salbutamol for the treatment of asthma have produced variable results. Levosalbutamol provided greater bronchodilatation than the equivalent amount of the racemate in some studies.[1,2] A decrease in hospital admissions and an increase in patient-discharge rates have also been reported.[3-5] Two controlled studies comparing levosalbutamol with racemic salbutamol in children with acute asthma failed to show any clinical benefit over the racemate.[6,7] A review concluded that, although current studies did not provide evidence of a substantial advantage for levosalbutamol over racemic salbutamol, the data were insufficient to determine whether subsets of the patient population might benefit from single isomer therapy.[8]

1. Pleskow WW, *et al.* Pairwise comparison of levalbuterol versus racemic albuterol in the treatment of moderate-to-severe asthma. *Allergy Asthma Proc* 2004; **25:** 429–36.
2. Nowak R, *et al.* A comparison of levalbuterol with racemic albuterol in the treatment of acute severe asthma exacerbations in adults. *Am J Emerg Med* 2006; **24:** 259–67.
3. Carl JC, *et al.* Comparison of racemic albuterol and levalbuterol for the treatment of acute asthma. *J Pediatr* 2003; **143:** 731–6.
4. Schreck DM, Babin S. Comparison of racemic albuterol and levalbuterol in the treatment of acute asthma in the ED. *Am J Emerg Med* 2005; **23:** 842–7.
5. Truitt T, *et al.* Levalbuterol compared to racemic albuterol: efficacy and outcomes in patients hospitalized with COPD or asthma. *Chest* 2003; **123:** 128–35.
6. Qureshi F, *et al.* Clinical efficacy of racemic albuterol versus levalbuterol for the treatment of acute pediatric asthma. *Ann Emerg Med* 2005; **46:** 29–36.
7. Hardasmalani MD, *et al.* Levalbuterol versus racemic albuterol in the treatment of acute exacerbation of asthma in children. *Pediatr Emerg Care* 2005; **21:** 415–19.
8. Kelly HW. Levalbuterol for asthma: a better treatment? *Curr Allergy Asthma Rep* 2007; **7:** 310–14.

Preparations

USP 31: Levalbuterol Inhalation Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Albulair; Ventoplus; ***India:*** Levolin; ***USA:*** Xopenex.

Montelukast Sodium *(BANM, USAN, rINNM)*

L-706631; MK-476; Montelukast sódico; Montélukast Sodique; Natrii Montelukastum. Sodium 1-[({(*R*)-*m*-[(*E*)-2-(7-chloro-2-quinolyl)-vinyl]-α-[*o*-(1-hydroxy-1-methylethyl)phenethyl]-benzyl}thio)methyl] cyclopropaneacetate.

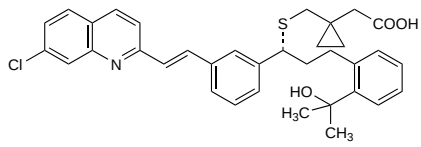
Натрий Монтелукаст

$C_{35}H_{35}ClNNaO_3S$ = 608.2.

CAS — 158966-92-8 (montelukast); 151767-02-1 (montelukast sodium).

ATC — R03DC03.

ATC Vet — QR03DC03.



(montelukast)

Adverse Effects and Precautions

As for Zafirlukast, p.1150.

◊ Suspected adverse effects reported to the UK CSM after the launch of montelukast included oedema, agitation and restlessness, allergy (including anaphylaxis, angioedema, and urticaria), chest pain, tremor, dry mouth, vertigo, and arthralgia.[1] Further suspected adverse effects included nightmares, sedation, palpitations, and increased sweating.[2] In March 2008 the FDA announced[3] that it was investigating a possible association between the use of montelukast and behaviour/mood changes, suicidality, and suicide. Other postmarketing adverse events that had been incorporated into the US licensed product information in the previous year had included: tremor, depression, suicidality, and anxiousness.

1. Committee on Safety of Medicines/Medicines Control Agency. Leukotriene antagonists: a new class of asthma treatment. *Current Problems* 1998; **24:** 14. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023231&RevisionSelectionMethod=LatestReleased (accessed 14/04/08)
2. Committee on Safety of Medicines/Medicines Control Agency. Leukotriene receptor antagonists: update on adverse reaction profiles. *Current Problems* 1999; **25:** 14. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023713&RevisionSelectionMethod=LatestReleased (accessed 14/04/08)
3. FDA. Early communication about an ongoing safety review of montelukast (Singulair) (issued 27th March 2008). Available at: http://www.fda.gov/cder/drug/early_comm/montelukast.htm (accessed 22/05/08)

Churg-Strauss syndrome. Churg-Strauss syndrome has been reported with the use of montelukast.[1-5] Relapse has occurred in a patient with Churg-Strauss syndrome who was in complete remission when montelukast therapy was started.[5] For discussion of the unresolved role of leukotriene antagonists in this disorder and precautions to be observed, see under Zafirlukast, p.1150.

1. Franco J, Artés MJ. Pulmonary eosinophilia associated with montelukast. *Thorax* 1999; **54:** 558–60.
2. Tuggey JM, Hosker HSR. Churg-Strauss syndrome associated with montelukast therapy. *Thorax* 2000; **55:** 805–6.
3. Meghjee SPL, White JS. Montelukast and Churg-Strauss syndrome. *Thorax* 2001; **56:** 244.
4. Gal AA, *et al.* Cutaneous lesions of Churg-Strauss syndrome associated with montelukast therapy. *Br J Dermatol* 2002; **147:** 618–19.
5. Solans R, *et al.* Montelukast and Churg-Strauss syndrome. *Thorax* 2002; **57:** 183–5.

Hepatic impairment. Although there is evidence of effects on the liver in patients receiving montelukast, and although it is largely eliminated by hepatic metabolism, montelukast (unlike zafirlukast) is not considered by UK licensed product information to be contra-indicated in hepatic impairment, and no dose adjustment is considered necessary in mild to moderate hepatic impairment.

Interactions

Licensed product information recommends caution when potent inducers of the cytochrome P450 isoenzyme CYP3A4 such as phenytoin, phenobarbital, or rifampicin are given with montelukast.

Corticosteroids. For a report of peripheral oedema in a patient given montelukast and *prednisone*, see Leukotriene Antagonists, p.1495.

Phenobarbital. Peak serum concentrations after a single dose of montelukast 10 mg were reduced by 20% in 14 healthy subjects who took phenobarbital 100 mg daily for 14 days, and area under the serum concentration-time curve was reduced by 38%. However, it was not thought that montelukast doses would need adjustment if given with phenobarbital.[1]

1. Holland S, *et al.* Metabolism of montelukast (M) is increased by multiple doses of phenobarbital (P). *Clin Pharmacol Ther* 1998; **63:** 231.

Pharmacokinetics

Peak plasma concentrations of montelukast are achieved in 3 to 4 hours after oral doses. The mean oral bioavailability is 64%. Montelukast is more than 99% bound to plasma proteins. It is extensively metabolised in the liver by cytochrome P450 isoenzymes CYP3A4, CYP2A6, and CYP2C9, and is excreted principally in the faeces via the bile.

◊ References.

1. Knorr B, *et al.* Montelukast dose selection in 6- to 14-year-olds: comparison of single-dose pharmacokinetics in children and adults. *J Clin Pharmacol* 1999; **39:** 786–93.
2. Knorr B, *et al.* Montelukast dose selection in children ages 2 to 5 years: comparison of population pharmacokinetics between children and adults. *J Clin Pharmacol* 1999; **41:** 612–19.
3. Migoya E, *et al.* Pharmacokinetics of montelukast in asthmatic patients 6 to 24 months old. *J Clin Pharmacol* 2004; **44:** 487–94.
4. Knorr B, *et al.* Pharmacokinetics and safety of montelukast in children aged 3 to 6 months. *J Clin Pharmacol* 2006; **46:** 620–7.
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Uses and Administration

Montelukast is a selective leukotriene receptor antagonist with actions and uses similar to those of zafirlukast (p.1150) although it is reported to have a longer duration of action. It is used as the sodium salt, but doses are expressed in terms of the base; montelukast sodium 10.38 mg is equivalent to about 10 mg of montelukast.

In the management of chronic asthma (see below), allergic rhinitis (see below), and as prophylaxis for exercise-induced asthma, montelukast sodium is given in doses equivalent to 10 mg of montelukast once daily in the evening. It should not be used to treat an acute asthma attack.

For details of doses in children, see below.

Administration in children. Montelukast sodium is available as oral granules and chewable tablets for use in children. Oral granules are suitable for infants as they may be given directly into the mouth or mixed with a small amount of soft food. UK licensed oral doses for the management of chronic asthma and as prophylaxis for exercise-induced asthma, expressed as montelukast, are as follows:

- 6 months to 5 years, 4 mg daily taken in the evening
- 6 to 14 years, 5 mg daily taken in the evening
- 15 years and over, use the adult dose, see above

In the USA these doses are licensed from 1 year of age in asthma and from 15 years in exercise-induced asthma. Montelukast is also licensed for use in allergic rhinitis (p.565) in the USA. The above doses can be given from 2 years of age in seasonal allergic rhinitis and from 6 months of age in perennial allergic rhinitis.

Asthma. Use of montelukast in asthma has been reviewed,[1-3] (further general references for leukotriene antagonists can be found under Zafirlukast, p.1151). Montelukast produced modest improvements compared with placebo in chronic asthma and exercise-induced asthma in both adults[4,5] and children.[6-8] In a systematic review[9] of studies in adults and children comparing leukotriene receptor antagonists with inhaled corticosteroids for mild to moderate asthma, in which more than half of the studies used montelukast, leukotriene antagonists were found to be less effective in maintaining asthma control. A more recent study in children came to a similar conclusion,[10] but another 12-month study in children with mild persistent asthma, reported that montelukast was not inferior to an inhaled corticosteroid (fluticasone);[11] similar numbers of days without rescue medication, the primary outcome in this study, were reported with both treatments. However, some of the conclusions drawn from the latter study have been questioned[12] since patients who received inhaled fluticasone achieved better secondary outcomes such as fewer asthma attacks and less requirement for systemic corticosteroids.

Addition of montelukast to an inhaled corticosteroid has significantly improved asthma control in adults[13] and children[14,15] with