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.

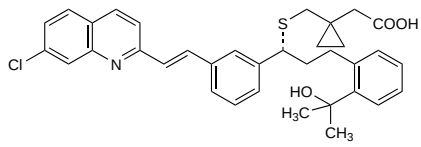
Натрий Монтелукаст

$C_{35}H_{35}ClNNaO_3S$ = 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.
5. Kearns GL, *et al.* Pharmacokinetics and safety of montelukast oral granules in children 1 to 3 months of age with bronchiolitis. *J Clin Pharmacol* 2008; **48:** 502–11.

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

mild to moderate asthma. Significant improvements in quality of life have also been reported,[16] in association with a fall in the levels of exhaled inflammatory mediators leading the authors of this study to conclude that leukotriene receptor antagonists may provide a complementary effect to inhaled corticosteroids when suppression of inflammation is incomplete. Another study[17] has reported that the use of montelukast did permit reduction in the dose of inhaled corticosteroid; adding montelukast to an inhaled corticosteroid (budesonide) may be as effective as doubling the dose of the corticosteroid.[18]

There is some evidence that montelukast may be more effective than inhaled salmeterol for the chronic treatment of exercise-induced asthma,[19,20] and although a later study[21] found similar effects on lung function with the two drugs, a more favourable effect was seen on gas exchange during moderate exercise with the use of montelukast.

An intravenous form of montelukast is under investigation for the treatment of severe acute asthma.[22,23]

1. Anonymous. Montelukast for persistent asthma. *Med Lett Drugs Ther* 1998; **40:** 71–3.
2. Anonymous. Montelukast and zafirlukast in asthma. *Drug Ther Bull* 1998; **36:** 65–8.
3. Jarvis B, Markham A. Montelukast: a review of its therapeutic potential in persistent asthma. *Drugs* 2000; **59:** 891–928.
4. Leff JA, *et al.* Montelukast, a leukotriene-receptor antagonist, for the treatment of mild asthma and exercise-induced bronchoconstriction. *N Engl J Med* 1998; **339:** 147–52.
5. Reiss TF, *et al.* Montelukast, a once-daily leukotriene receptor antagonist, in the treatment of chronic asthma: a multicenter, randomized, double-blind trial. *Arch Intern Med* 1998; **158:** 1213–20.
6. Knorr B, *et al.* Montelukast for chronic asthma in 6- to 14-year-old children: a randomized, double-blind trial. *JAMA* 1998; **279:** 1181–6.
7. Kemp JP, *et al.* Montelukast once daily inhibits exercise-induced bronchoconstriction in 6- to 14-year-old children with asthma. *J Pediatr* 1998; **133:** 424–8.
8. Knorr B, *et al.* Montelukast, a leukotriene receptor antagonist, for the treatment of persistent asthma in children aged 2 to 5 years. Abstract: *Pediatrics* 2001; **108:** 754–5. Full version: http://pediatrics.aappublications.org/cgi/content/full/108/3/e48 (accessed 14/04/08)
9. Ducharme FM, Di Salvio F. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 14/04/08).
10. Ostrom NK, *et al.* Comparative efficacy and safety of low-dose fluticasone propionate and montelukast in children with persistent asthma. *J Pediatr* 2005; **147:** 213–20.
11. Garcia Garcia ML, *et al.* Montelukast, compared with fluticasone, for control of asthma among 6- to 14-year-old patients with mild asthma: the MOSAIC study. *Pediatrics* 2005; **116:** 360–9.
12. Turkalj M, Plavec D. "Inferiority complex" for a reason. *Pediatrics* 2006; **117:** 588–90.
13. Vaquerizo MJ, *et al.* CASIOPEA (Capacidad de Singulair Oral en la Prevencion de Exacerbaciones Asmaticas) Study Group. Effect of montelukast added to inhaled budesonide on control of mild to moderate asthma. *Thorax* 2003; **58:** 204–10.
14. Phipatanakul W, *et al.* Montelukast improves asthma control in asthmatic children maintained on inhaled corticosteroids. *Ann Allergy Asthma Immunol* 2003; **91:** 49–54.
15. Johnston NW, *et al.* Attenuation of the September epidemic of asthma exacerbations in children: a randomized, controlled trial of montelukast added to usual therapy. *Pediatrics* 2007; **120:** e702–e712.
16. Biernacki WA, *et al.* Effect of montelukast on exhaled leukotrienes and quality of life in asthmatic patients. *Chest* 2005; **128:** 1958–63.
17. Löfdahl C-G, *et al.* Randomised, placebo controlled trial of effect of a leukotriene receptor antagonist, montelukast, on tapering inhaled corticosteroids in asthma. *BMJ* 1999; **319:** 87–90.
18. Price DB, *et al.* Clinical Outcomes with Montelukast as a Partner Agent to Corticosteroid Therapy (COMPACT) International Study Group. Randomised controlled trial of montelukast plus inhaled budesonide versus double dose inhaled budesonide in adult patients with asthma. *Thorax* 2003; **58:** 211–16.
19. Villaran C, *et al.* Montelukast versus salmeterol in patients with asthma and exercise-induced bronchoconstriction. *J Allergy Clin Immunol* 1999; **104:** 547–53.
20. Edelman JM, *et al.* Oral montelukast compared with inhaled salmeterol to prevent exercise-induced bronchoconstriction: a randomized, double-blind trial. *Ann Intern Med* 2000; **132:** 97–104.
21. Steinshamn S, *et al.* Effects of montelukast and salmeterol on physical performance and exercise economy in adult asthmatics with exercise-induced bronchoconstriction. *Chest* 2004; **126:** 1154–60.
22. Dockhorn RJ, *et al.* Comparison of the effects of intravenous and oral montelukast on airway function: a double blind, placebo controlled, three period, crossover study in asthmatic patients. *Thorax* 2000; **55:** 260–5.
23. Camargo CA, *et al.* A randomized controlled trial of intravenous montelukast in acute asthma. *Am J Respir Crit Care Med* 2003; **167:** 528–33.

Bronchiolitis. Bronchiolitis due to RSV infection is often followed by post-bronchiolitic reactive airways disease, characterised by asthma-like wheeze and other symptoms. In a pilot study,[1] montelukast 5 mg orally daily was given for 4 weeks to infants who had been admitted for moderate to severe bronchiolitis. Symptom-free days and nights were increased, daytime cough was reduced, and exacerbations were delayed compared with placebo. The benefit of montelukast over placebo was only apparent after the first 2 weeks of treatment. Although the safety and efficacy of such treatment remains to be properly established,[2] there is some interest in whether montelukast can prevent or modify more persistent asthma that has been associated with RSV.

1. Bisgaard H. Study Group on Montelukast and Respiratory Syncytial Virus. A randomized trial of montelukast in respiratory syncytial virus postbronchiolitis. *Am J Respir Crit Care Med* 2003; **167:** 379–83.
2. Szefler SJ, Simoes EAF. Montelukast for respiratory syncytial virus bronchiolitis: significant effect or provocative findings? *Am J Respir Crit Care Med* 2003; **167:** 290–1.

Cystic fibrosis. A small study in children with cystic fibrosis (p.166) found that montelukast reduced eosinophilic inflammation.[1] A later study,[2] reported improved lung function and a reduction in coughing and wheezing, and concluded that montelukast may have measurable anti-inflammatory activity in patients with cystic fibrosis. In a small group of adult patients with cystic fibrosis[3] montelukast improved symptoms, in particular exercise tolerance and peak expiratory flow rates. The patients who benefited the most had positive *Aspergillus* serology, and the authors suggested that colonisation of the airways in cystic fibrosis by *Aspergillus* stimulates T helper cell inflammation and leukotriene synthesis. A review of leukotriene receptor antagonists in cystic fibrosis[4] concluded that clinical benefit seemed likely in a subset of patients with cystic fibrosis who experience bronchial hyperresponsiveness similar to that seen in asthma.

A study into the pharmacokinetics of montelukast in cystic fibrosis[5] found that the dose of montelukast and the dosing interval do not need to be modified if the goal of therapy is to achieve similar serum concentrations as for asthma treatment; however the effectiveness of these concentrations for the inflammatory lung disease of patients with cystic fibrosis was unknown.

1. Schmitt-Grohé S, *et al.* Anti-inflammatory effects of montelukast in mild cystic fibrosis. *Ann Allergy Asthma Immunol* 2002; **89:** 599–605.
2. Stelmach I, *et al.* Effects of montelukast treatment on clinical and inflammatory variables in patients with cystic fibrosis. *Ann Allergy Asthma Immunol* 2005; **95:** 372–80.
3. Morice AH, *et al.* Montelukast sodium in cystic fibrosis. *Thorax* 2001; **56:** 244–5.
4. Schmitt-Grohé S, Zielen S. Leukotriene receptor antagonists in children with cystic fibrosis lung disease: anti-inflammatory and clinical effects. *Pediatr Drugs* 2005; **7:** 353–63.
5. Graff GR, *et al.* Montelukast pharmacokinetics in cystic fibrosis. *J Pediatr* 2003; **142:** 53–6.

Eczema. Despite early indications from some small clinical studies and case reports[1-3] that montelukast might be of benefit in eczema (p.1579) larger, more recent studies have failed to show any improvement compared with placebo.[4,5]

1. Capella GL, *et al.* A randomized trial of leukotriene receptor antagonist montelukast in moderate-to-severe atopic dermatitis of adults. *Eur J Dermatol* 2001; **11:** 209–13.
2. Hon KLE, *et al.* Brief case series: montelukast, at doses recommended for asthma treatment, reduces disease severity and increases soluble CD14 in children with atopic dermatitis. *J Dermatolog Treat* 2005; **16:** 15–18.
3. Angelova-Fischer I, Tsankov N. Successful treatment of severe atopic dermatitis with cysteinyl leukotriene receptor antagonist montelukast. *Acta Dermatovenerol Alp Panonica Adriat* 2005; **14:** 115–19.
4. Veien NK, *et al.* Montelukast treatment of moderate to severe atopic dermatitis in adults: a randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol* 2005; **53:** 147–9.
5. Friedmann PS, *et al.* A double-blind, placebo-controlled trial of montelukast in adult atopic eczema. *Clin Exp Allergy* 2007; **37:** 1536–40.

Gastrointestinal disorders. Benefit has been reported[1] with the use of montelukast in patients with eosinophilic oesophagitis, a rare condition involving eosinophilic infiltration of the oesophagus with intermittent painful dysphagia. A systematic review with recommendations for the diagnosis and treatment of eosinophilic oesophagitis[2] concluded that although leukotriene receptor antagonists had been shown to induce symptomatic relief at high doses, no significant improvements in histology were noted and their use for the treatment of eosinophilic oesophagitis is not supported by the current literature.

1. Attwood SEA, *et al.* Eosinophilic oesophagitis: a novel treatment using montelukast. *Gut* 2003; **52:** 181–5.
2. Furuta GT, *et al.* American Gastroenterological Association; North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology* 2007; **133:** 1342–63. Also available at: http://download.journals.elsevierhealth.com/pdfs/journals/0016-5085/PIIS0016508507014746.pdf (accessed 14/04/08)

Graft-versus-host disease. A pilot study in refractory, chronic graft-versus-host disease (GVHD) after allogeneic haematopoietic stem cell transplantation (p.1811),[1] saw an improvement in 15 of 19 patients after montelukast was added to their standard immunosuppressive regimens; in 4 patients signs of chronic GVHD were resolved, 2 showed significant improvement, and 9 showed moderate improvement.

1. Or R, *et al.* Sparing effect by montelukast treatment for chronic graft versus host disease: a pilot study. *Transplantation* 2007; **83:** 577–81.

Mastocytosis. Montelukast has been tried, with some success, in the treatment of systemic mastocytosis (p.1138) in an infant.[1]

1. Tolar J, *et al.* Leukotriene-receptor inhibition for the treatment of systemic mastocytosis. *N Engl J Med* 2004; **350:** 735–6.

Rhinitis. Montelukast is used in allergic rhinitis (p.565), where large placebo-controlled studies have shown it to relieve symptoms in both seasonal allergic rhinitis,[1,2] and perennial allergic rhinitis.[3] However, a meta-analysis[4] of leukotriene antagonists (mainly montelukast) for management of allergic rhinitis concluded that while leukotriene antagonists were modestly more effective than placebo and of similar efficacy to antihistamines, in reducing nasal symptoms and improving rhinoconjunctivitis, they were less effective than corticosteroids even when used with antihistamines. A later systematic review[5] commented that some studies in allergic rhinitis using a combination of montelukast and an antihistamine had produced results comparable with intranasal corticosteroids. Also, in patients with both allergic rhinitis and asthma, montelukast had resulted in significant improvements in both when compared with placebo.

1. Philip G, *et al.* Montelukast for treating seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled trial performed in the spring. *Clin Exp Allergy* 2002; **32:** 1020–8.
2. van Adelsberg J, *et al.* Randomized controlled trial evaluating the clinical benefit of montelukast for treating spring seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 2003; **90:** 214–22.
3. Patel P, *et al.* Randomized, double-blind, placebo-controlled study of montelukast for treating perennial allergic rhinitis. *Ann Allergy Asthma Immunol* 2005; **95:** 551–7.
4. Wilson AM, *et al.* Leukotriene receptor antagonists for allergic rhinitis: a systematic review and meta-analysis. *Am J Med* 2004; **116:** 338–44.
5. Nayak A, Langdon RB. Montelukast in the treatment of allergic rhinitis: an evidence-based review. *Drugs* 2007; **67:** 887–901.

Sleep-disordered breathing. Montelukast with an intranasal corticosteroid has been reported to be beneficial in a small study in children with residual sleep-disordered breathing after tonsillectomy and adenoidectomy.[1]

1. Kheirandish L, *et al.* Intranasal steroids and oral leukotriene modifier therapy in residual sleep-disordered breathing after tonsillectomy and adenoidectomy in children. *Pediatrics* 2006; **117:** e61–e66.

Urticaria. Montelukast has been investigated in the treatment of urticaria (p.1584) with variable results.[1] However, urticaria has also been described as a suspected adverse effect of montelukast therapy (see above).

Montelukast has been reported to be more effective than placebo when used with the antihistamine desloratadine in the treatment of delayed pressure urticaria.[2]

1. McBayne TO, Siddall OM. Montelukast treatment of urticaria. *Ann Pharmacother* 2006; **40:** 939–42.
2. Nettis E, *et al.* Desloratadine in combination with montelukast suppresses the dermagraphometer challenge test papule, and is effective in the treatment of delayed pressure urticaria: a randomized, double-blind, placebo-controlled study. *Br J Dermatol* 2006; **155:** 1279–82.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Lukair†; Singulair; ***Austral.:*** Singulair; ***Austria:*** Singulair; ***Belg.:*** Singulair; ***Braz.:*** Singulair; ***Canad.:*** Singulair; ***Chile:*** Brondilat; Leukast†; Singulair; ***Cz.:*** Singulair; ***Denm.:*** Singulair; ***Fin.:*** Singulair; ***Fr.:*** Singulair; ***Ger.:*** Singulair; ***Gr.:*** Singulair; ***Hong Kong:*** Singulair; ***Hung.:*** Singulair; ***India:*** Montair; Montelast; ***Irl.:*** Singulair; ***Israel:*** Singulair; ***Ital.:*** Lukasm; Montegen; Singulair; ***Jpn:*** Kipres; ***Malaysia:*** Singulair; ***Mex.:*** Singulair; ***Neth.:*** Singulair; ***Norw.:*** Singulair; ***NZ:*** Singulair; ***Philipp.:*** Singulair; ***Pol.:*** Singulair; ***Port.:*** Lukair; Singulair; Singulergy; Synglarin; ***Rus.:*** Singulair (Сингуляр); ***S.Afr.:*** Singulair; ***Singapore:*** Singulair; ***Spain:*** Singulair; ***Swed.:*** Singulair; ***Switz.:*** Singulair; ***Thai.:*** Singulair; ***Turk.:*** Singulair; ***UK:*** Singulair; ***USA:*** Singulair; ***Venez.:*** Airon; Inuvic; Monukast; Singulair.

Multi-ingredient: ***India:*** Montair Plus.

Nedocromil Sodium *(BANM, USAN, rINNM)*

FPL-59002 (nedocromil); FPL-59002KC (nedocromil calcium); FPL-59002KP (nedocromil sodium); Natrii Nedocromilum; Nédocromil Sodique; Nedocromilo sódico; Nedocromilum Natricum; Nedokromiilinatrium; Nedokromil Sodyum; Nedokromilnatrium. Disodium 9-ethyl-6,9-dihydro-4,6-dioxo-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate.

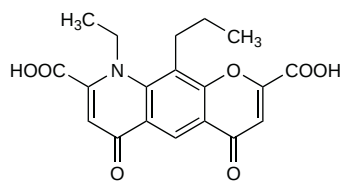
Натрий Недокромил

$C_{19}H_{15}NNa_2O_7$ = 415.3.

CAS — 69049-73-6 (nedocromil); 69049-74-7 (nedocromil sodium); 101626-68-0 (nedocromil calcium).

ATC — R01AC07; R03BC03; S01GX04.

ATC Vet — QR01AC07; QR03BC03; QS01GX04.



(nedocromil)

NOTE. Nedocromil Calcium is also *USAN*.