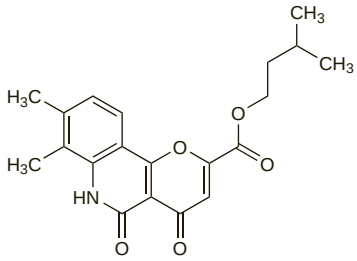
Repirinast *(USAN, rINN)*

MY-5116; Répirinast; Repirinastum. Isopentyl 5,6-dihydro-7,8-dimethyl-4,5-dioxo-4*H*-pyrano[3,2-*c*]quinoline-2-carboxylate.

Репиринаст

$C_{20}H_{21}NO_5$ = 355.4.

CAS — 73080-51-0.



Profile
Repirinast is an orally active anti-allergic with a stabilising action on mast cells resembling that of sodium cromoglicate (p.1136). It has been given orally in the management of asthma (p.1108).

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

Reproterol Hydrochloride *(BANM, USAN, rINNM)* ⊗

D-1959 (reproterol); Hidrocloruro de reproterol; Réprotérol, Chlorhydrate de; Reproteroli Hydrochloridum; W-2946M. 7-{3-[(3,5,β-Trihydroxyphenethyl)amino]propyl}theophylline hydrochloride.

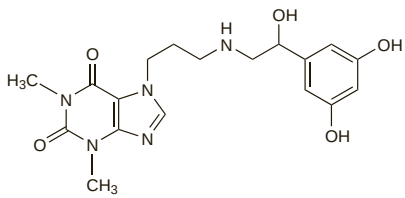
Репротерола Гидрохлорид

$C_{18}H_{23}N_5O_5$,HCl = 425.9.

CAS — 54063-54-6 (reproterol); 13055-82-8 (reproterol hydrochloride).

ATC — R03AC15; R03CC14.

ATC Vet — QR03AC15; QR03CC14.



(reproterol)

Profile
Reproterol 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).

Reproterol hydrochloride 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).

For the relief of acute attacks of bronchospasm the usual dose of reproterol hydrochloride is 1 or 2 inhalations of 500 micrograms from a metered-dose aerosol repeated every 3 to 6 hours as required. Reproterol is often used with sodium cromoglicate in combined preparations. In patients with asthma, 'as-required' beta agonist therapy is preferable to regular use. An increased need for, or decreased duration of effect of, reproterol indicates deterioration of asthma control and the need for review of therapy. It has also been given orally: adult doses are 10 to 20 mg three times daily. A slow intravenous injection of 90 micrograms, repeated after 10 minutes if necessary, has been used in the treatment of status asthmaticus.

For doses of reproterol used in children, see Administration in Children, below.

Administration in children. Reproterol hydrochloride has been given via a metered-dose aerosol to relieve bronchospasm in children from 6 years of age at the same dose used in adults (see Uses and Administration, above). Reproterol is often used with sodium cromoglicate in combined preparations.

Reproterol hydrochloride has also been given orally to children from 6 years of age at a dose of 10 mg three times daily.

Preparations
Proprietary Preparations (details are given in Part 3)
Ger.: Bronchospasmin; ***Ital.:*** Broncospasmine†.

Multi-ingredient: ***Ger.:*** Aarane N; Allergospasmin; ***Switz.:*** Aarane†; Allergospasmine†.

Roflumilast *(USAN, rINN)*

APTA-2217; B-9302-107; BY-217; BYK-20869; Roflumilastum. 3-(Cyclopropylmethoxy)-*N*-(3,5-dichloro-4-pyridyl)-4-(difluoromethoxy)benzamide.

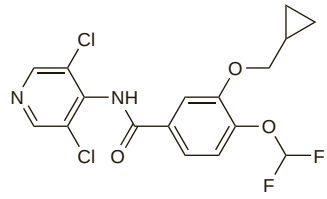
Рофлумиласт

$C_{17}H_{14}Cl_2F_2N_2O_3$ = 403.2.

CAS — 162401-32-3.

ATC — R03DX07.

ATC Vet — QR03DX07.



Profile
Roflumilast is a phosphodiesterase type-4 inhibitor. It is under investigation in the treatment of asthma and chronic obstructive pulmonary disease.

◊ References.

1. Spina D. Phosphodiesterase-4 inhibitors in the treatment of inflammatory lung disease. *Drugs* 2003; **63:** 2575–94.
2. Lipworth BJ. Phosphodiesterase-4 inhibitors for asthma and chronic obstructive pulmonary disease. *Lancet* 2005; **365:** 167–75.
3. Rabe KF, *et al.* Roflumilast—an oral anti-inflammatory treatment for chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2005; **366:** 563–71.
4. Karish SB, Gagnon JM. The potential role of roflumilast: the new phosphodiesterase-4 inhibitor. *Ann Pharmacother* 2006; **40:** 1096–1104.
5. Bateman ED, *et al.* Efficacy and safety of roflumilast in the treatment of asthma. *Ann Allergy Asthma Immunol* 2006; **96:** 679–86.
6. Calverley PM, *et al.* Effect of 1-year treatment with roflumilast in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007; **176:** 154–61.
7. Hermann R, *et al.* Steady-state pharmacokinetics of roflumilast and roflumilast N-oxide in patients with mild and moderate liver cirrhosis. *Clin Pharmacokinet* 2007; **46:** 403–16.
8. Bethke TD, *et al.* Dose-proportional intraindividual single- and repeated-dose pharmacokinetics of roflumilast, an oral, once-daily phosphodiesterase 4 inhibitor. *J Clin Pharmacol* 2007; **47:** 26–36.
9. Field SK. Roflumilast: an oral, once-daily selective PDE-4 inhibitor for the management of COPD and asthma. *Expert Opin Invest Drugs* 2008; **17:** 811–8.

Salbutamol *(BAN, rINN)* ⊗

AH-3365; Albuterol *(USAN)*; Salbutamoli; Salbutamolis; Salbutamolum; Sch-13949W; Szalbutamol. 2-*tert*-Butylamino-1-(4-hydroxy-3-hydroxymethylphenyl)ethanol.

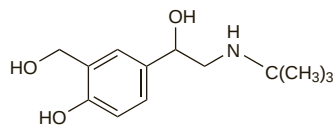
Сальбутамол

$C_{13}H_{21}NO_3$ = 239.3.

CAS — 18559-94-9.

ATC — R03AC02; R03CC02.

ATC Vet — QR03AC02; QR03CC02.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *US*, and *Viet.*
Ph. Eur. 6.2 (Salbutamol). A white or almost white, crystalline powder. Sparingly soluble in water; soluble in alcohol. Protect from light.
USP 31 (Albuterol). A white crystalline powder. Sparingly soluble in water; soluble in alcohol. Protect from light.

Salbutamol Sulfate *(rINNM)* ⊗

Albuterol Sulfate *(USAN)*; Salbutamol Hemisulphate; Salbutamol, sulfate de; Salbutamol Sulphate *(BANM)*; Salbutamoli sulfas; Salbutamolio sulfatas; Salbutamolisulfaatti; Salbutamolsulfat; Salbutamol-sulfát; Salbutamolu siarczan; Sulfato de salbutamol; Szalbutamol-szulfát.

Сальбутамола Сульфат

$(C_{13}H_{21}NO_3)_2,H_2SO_4$ = 576.7.

CAS — 51022-70-9.

ATC — R03AC02; R03CC02.

ATC Vet — QR03AC02; QR03CC02.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*
Ph. Eur. 6.2 (Salbutamol Sulphate). A white or almost white crystalline powder. Freely soluble in water; practically insoluble or very slightly soluble in alcohol and in dichloromethane. Protect from light.
USP 31 (Albuterol Sulfate). A white or practically white powder. Freely soluble in water; slightly soluble in alcohol, in chloroform, and in ether. Protect from light.

Stability. For mention of the stability of a 1:1 mixture of salbutamol and ipratropium nebuliser solutions, see under Ipratropium, p.1124.

Adverse Effects
As for Sympathomimetics, p.1407. Salbutamol has mainly beta-agonist effects and, like other beta agonists, may cause fine tremor of skeletal muscle (particularly the hands), palpitations, tachycardia, nervous tension, headaches, peripheral vasodilatation, and rarely muscle cramps. Inhalation causes fewer adverse effects than systemic dosage, and the more selective $beta_2$ agonists cause fewer adverse effects than less selective beta agonists. Potentially serious hypokalaemia has been reported after large doses. Myocardial ischaemia has also been reported. Hypersensitivity reactions have occurred, including paradoxical bronchospasm, angioedema, urticaria, hypotension, and collapse.

The high doses of salbutamol used intravenously to delay premature labour have additionally been associated with nausea and vomiting, and with severe adverse cardiac and metabolic effects and pulmonary oedema.

Effects on the CNS. Visual hallucinations lasting for an hour have been reported[1] after use of nebulised salbutamol in an elderly patient. At the time of the report the manufacturers were aware of 3 cases of hallucinations in children given oral salbutamol but no such reaction had been previously reported in adults given recommended doses.

Hyperactivity and restlessness have been reported with the use of salbutamol; however, a small placebo-controlled study of 19 children,[2] failed to show a statistically significant difference in activity levels after a nebulised dose of salbutamol.

1. Khanna PB, Davies R. Hallucinations associated with the administration of salbutamol via a nebuliser. *BMJ* 1986; **292:** 1430.
2. Hadjikoumi I, *et al.* Bronchodilator therapy and hyperactivity in preschool children. *Arch Dis Child* 2002; **86:** 202–4. Also available at: http://adc.bmj.com/cgi/reprint/86/3/202 (accessed 15/01/08)

Effects on electrolytes and metabolism. Salbutamol, in common with other $beta_2$-agonists, may cause *hypokalaemia* and *hyperglycaemia*. These effects are related to the dose and route of salbutamol used; hypokalaemia is more common after parenteral and nebulised use. Hypokalaemia may be potentiated by therapy with corticosteroids, diuretics, or xanthines, and by hypoxia; potassium concentrations should therefore be monitored in severe asthma.

Effects on the eyes. It has been suggested that salbutamol and to a greater extent ritodrine may contribute to retinopathy in the premature infant when used for premature labour.[1]

A case of acute angle-closure glaucoma was attributed to dilatation of the pupil by stimulation of the sympathetic nervous system secondary to local absorption of nebulised salbutamol in the eye; the patient also had other risk factors for developing glaucoma.[2] For reports of glaucoma precipitated by the combined use of ipratropium bromide and salbutamol via a nebuliser, see Ipratropium Bromide, p.1124.

1. Michie CA, *et al.* Do maternal β-sympathomimetics influence the development of retinopathy in the premature infant? *Arch Dis Child* 1994; **71:** F149.
2. Rho DS. Acute angle-closure glaucoma after albuterol nebulizer treatment. *Am J Ophthalmol* 2000; **130:** 123–4.

Effects on the heart. The main adverse cardiac effect of salbutamol is tachycardia due to increased sympathetic effects on the cardiovascular system. Such tachycardia is dose dependent and is more common after systemic than inhaled therapy. A meta-analysis[1] of randomised, placebo-controlled studies in patients with asthma or chronic obstructive pulmonary disease (COPD) confirmed that single doses of $beta_2$ agonists can cause an increase in heart rate and a reduction in potassium concentrations (see also Effects on Electrolytes and Metabolism, above). The

longer-term effects of $beta_2$ agonists on the cardiovascular system were also assessed and an increased risk of adverse cardiovascular events due to sinus tachycardia was found. There was also a trend towards an increase in major adverse events including ventricular tachycardia, atrial fibrillation, syncope, heart failure, myocardial infarction, cardiac arrest, and sudden death. Myocardial ischaemia has been reported in association with salbutamol when used to delay premature labour.[2] Eleven of 17 reports were considered serious, including one fatality. Most of these reports involved the use of parenteral formulations; none involved the use of inhaled salbutamol formulations for the relief of bronchospasm. However, there is some evidence that high doses of inhaled salbutamol can decrease coronary flow reserve, and might exacerbate ischaemia in patients with coronary artery disease.[3] Case-control studies[4,5] have also suggested that the use of inhaled $beta_2$ agonists is associated with an increased risk of myocardial infarction, and another case-control study[6] found an increased risk of cardiac arrest in patients with asthma being treated with inhaled short-acting $beta_2$ agonists, but not in those with COPD. In contrast, however, a cohort study[7] of patients with COPD found no increase in the risk of myocardial infarction associated with the use of $beta_2$ agonists given by inhalation, nebulisation, or mouth. Case-control and cohort studies have also suggested that patients with pre-existing heart failure may be at increased risk of hospitalisation from arrhythmias[8] or exacerbation of heart failure[9,10] with the use of $beta_2$ agonists.

A causal relationship cannot necessarily be established from these case-control and cohort studies, however, because of confounding factors such as co-morbidity, and because the extent of $beta_2$ agonist use could only be estimated from prescription record systems.

See also Pregnancy, below.

1. Salpeter SR, *et al.* Cardiovascular effects of β-agonists in patients with asthma and COPD: a meta-analysis. *Chest* 2004; **125:** 2309–21.
2. GlaxoSmithKline, Canada. Health Canada endorsed important safety information on Ventolin I.M. injection and Ventolin I.V. infusion solution: for pregnant women & labour and delivery (issued 12th June 2007). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/ventolin_hpc-cps-eng.pdf (accessed 09/07/08)
3. Kochiadakis GE, *et al.* Effect of inhaled salbutamol on coronary circulation in humans. *Int J Cardiol* 2007; **117:** 408–10.
4. Au DH, *et al.* The risk of myocardial infarction associated with inhaled β-adrenoceptor agonists. *Am J Respir Crit Care Med* 2000; **161:** 827–30.
5. Au DH, *et al.* Association between inhaled β-agonists and the risk of unstable angina and myocardial infarction. *Chest* 2002; **121:** 846–51.
6. Lemaitre RN, *et al.* Inhaled beta-2 adrenergic receptor agonists and primary cardiac arrest. *Am J Med* 2002; **113:** 711–16.
7. Suissa S, *et al.* Inhaled short acting β agonist use in COPD and the risk of acute myocardial infarction. *Thorax* 2003; **58:** 43–6.
8. Bouvy ML, *et al.* Use of sympathomimetic drugs leads to increased risk of hospitalization for arrhythmias in patients with congestive heart failure. *Arch Intern Med* 2000; **160:** 2477–80.
9. Au DH, *et al.* Risk of mortality and heart failure exacerbations associated with inhaled β-adrenoceptor agonists among patients with known left ventricular systolic dysfunction. *Chest* 2003; **123:** 1964–9.
10. Au DH, *et al.* Association between chronic heart failure and inhaled β-2-adrenoceptor agonists. *Am Heart J* 2004; **148:** 915–20.

Effects on the respiratory system. Paradoxical bronchoconstriction has occasionally been reported after bronchodilating therapy. With nebuliser solutions, it has been suggested that the preservatives present could be responsible (see also under Ipratropium, p.1124), or that the pH may contribute if non-neutral. In addition, regular use of $beta_2$ agonists such as salbutamol (as opposed to use on an as-needed basis) has been shown to increase airway hyperresponsiveness to various stimuli and to lead to the possible development of tolerance to the bronchoprotective effect (see below).

The increased risk of pulmonary oedema associated with salbutamol is mentioned under Pulmonary Oedema, below.

Increased mortality. The increased incidence of morbidity and mortality that occurred in asthmatic patients mainly involved fenoterol, but salbutamol has been implicated. The debate on the relevance of beta agonist therapy to this increased morbidity and mortality is discussed under Fenoterol on p.1121.

Overdosage. Reports of overdosage with salbutamol[1-6] have generally only described the features that may be expected with $beta_2$ agonists such as tachycardia, CNS stimulation, tremor, hypokalaemia, and hyperglycaemia. Symptomatic treatment of the adverse effects has proved successful although it is unlikely to be required after repeated inhalation. Activated charcoal may be considered after oral overdose in patients who have taken a potentially toxic amount and present within 1 hour. The plasma-potassium concentration and pulse rate have been found to correlate with the plasma concentration of salbutamol.[7]

1. Morrison GW, Farebrother MJB. Overdose of salbutamol. *Lancet* 1973; **ii:** 681.
2. O'Brien IAD, *et al.* Hypokalaemia due to salbutamol overdosage. *BMJ* 1981; **282:** 1515–16.
3. Prior JG, *et al.* Self-poisoning with oral salbutamol. *BMJ* 1981; **282:** 1932.
4. Connell JMC, *et al.* Metabolic consequences of salbutamol poisoning reversed by propranolol. *BMJ* 1982; **285:** 779.
5. Spiller HA, *et al.* A two-year retrospective study of accidental pediatric albuterol ingestions. *Pediatr Emerg Care* 1993; **9:** 338–40.
6. Leikin JB, *et al.* Hypokalemia after pediatric albuterol overdose: a case series. *Am J Emerg Med* 1994; **12:** 64–6.
7. Lewis LD, *et al.* A study of self poisoning with oral salbutamol—laboratory and clinical features. *Hum Exp Toxicol* 1993; **12:** 397–401. Correction. *ibid.* 1994; **13:** 371.

Pregnancy. Most adverse effects associated with salbutamol in pregnancy relate to the cardiovascular and metabolic effects of the very high doses given by intravenous infusion in attempts to delay premature labour (see also under Pulmonary Oedema, below). Maternal effects include myocardial ischaemia,[1,2] unifocal ventricular ectopics associated with the hypokalaemic response to intravenous salbutamol,[3] and heart failure in a hypertensive woman.[4] Similarly, serious fetal and neonatal cardiovascular complications have also been associated with tocolytic salbutamol.[5]

Metabolic acidosis after salbutamol infusions in diabetic women has also been reported.[6,7]

For reports of retinopathy in the infant see Effects on the Eyes above.

1. Whitehead MI, *et al.* Myocardial ischaemia after withdrawal of salbutamol for pre-term labour. *Lancet* 1979; **ii:** 904.
2. GlaxoSmithKline, Canada. Health Canada endorsed important safety information on Ventolin I.M. injection and Ventolin I.V. infusion solution: for pregnant women & labour and delivery (issued 12th June 2007). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/ventolin_hpc-cps-eng.pdf (accessed 09/07/08)
3. Chew WC, Lew LC. Ventricular ectopics after salbutamol infusion for preterm labour. *Lancet* 1979; **ii:** 1383–4.
4. Whitehead MI, *et al.* Acute congestive cardiac failure in a hypertensive woman receiving salbutamol for premature labour. *BMJ* 1980; **280:** 1221–2.
5. Katz VL, Seeds JW. Fetal and neonatal cardiovascular complications from β-sympathomimetic therapy for tocolysis. *Am J Obstet Gynecol* 1989; **161:** 1–4.
6. Chapman MG. Salbutamol-induced acidosis in pregnant diabetics. *BMJ* 1977; **1:** 639–40.
7. Thomas DJB, *et al.* Salbutamol-induced diabetic ketoacidosis. *BMJ* 1977; **2:** 438.

Pulmonary oedema. Pulmonary oedema has occurred in women given $beta_2$ agonists, including salbutamol,[1-4] for premature labour. The risk factors, the most important of which is fluid overload, are discussed under Precautions, below.

1. Hawker F. Pulmonary oedema associated with β -sympathomimetic treatment of premature labour. *Anaesth Intensive Care* 1984; **12:** 143–51.
2. Pisani RJ, Rosenow EC. Pulmonary edema associated with tocolytic therapy. *Ann Intern Med* 1989; **110:** 714–18.
3. Chapuis C, *et al.* Œdème aigu du poumon au décours d'une tocolyse par nicardipine et salbutamol lors d'une menace d'accouchement prématuré sur grossesse gémellaire. *J Gynecol Obstet Biol Reprod (Paris)* 2005; **34:** 493–6.
4. Hamel H, *et al.* Œdème pulmonaire et tocolyse par bêta-mimétiques. *Rev Mal Respir* 2002; **19:** 241–4.

Tolerance. Some studies suggest that regular inhalation of a short-acting $beta_2$ agonist, although it continues to produce bronchodilatation, increases airway hyperresponsiveness and may reduce the protective effect against bronchoconstriction provoked by stimuli such as bradykinin, methacholine, or allergen.[1-6] Such tolerance is considered another argument against regular use of short-acting drugs.[1] Reduced bronchoprotective effects have also been demonstrated with long-acting $beta_2$ agonists (see Salmeterol, p.1135).

It has been suggested that reduced benefit with salbutamol may be due to the *S*(+)-enantiomer,[7,8] which unlike the *R*(–)-enantiomer (levosalbutamol, p.1125) does not possess bronchodilating activity. Stereoselective metabolism (see under Pharmacokinetics, below) means that regular use of the racemate could lead to accumulation of the *S*-enantiomer, which provides a possible mechanism for the effect. Genetic polymorphism of the $beta_2$-adrenoceptor has also been proposed as another possible mechanism.[9,10]

1. Cockcroft DW, *et al.* Regular inhaled salbutamol and airway responsiveness to allergen. *Lancet* 1993; **342:** 833–7.
2. O'Connor BJ, *et al.* Tolerance to the nonbronchodilator effects of inhaled β -agonists in asthma. *N Engl J Med* 1992; **327:** 1204–8.
3. Cockcroft DW, *et al.* Regular use of inhaled albuterol and the allergen-induced late asthmatic response. *J Allergy Clin Immunol* 1995; **96:** 44–9.
4. Inman MD, O'Byrne PM. The effect of regular inhaled albuterol on exercise-induced bronchoconstriction. *Am J Respir Crit Care Med* 1996; **153:** 65–9.
5. Crowther SD, *et al.* Varied effects of regular salbutamol on airway responsiveness to inhaled spasmogens. *Lancet* 1997; **350:** 1450.
6. Hancox RJ, *et al.* Tolerance to beta-agonists during acute bronchoconstriction. *Eur Respir J* 1999; **14:** 283–7.
7. Perrin-Fayolle M. Salbutamol in the treatment of asthma. *Lancet* 1995; **346:** 1101.
8. Handley D. The asthma-like pharmacology and toxicology of (S)-isomers of β agonists. *J Allergy Clin Immunol* 1999; **104** (suppl): S69–S76.
9. Israel E, *et al.* Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomised, placebo-controlled cross-over trial. *Lancet* 2004; **364:** 1505–12.
10. Broadley KJ. β-Adrenoceptor responses of the airways: for better or worse? *Eur J Pharmacol* 2006; **533:** 15–27.

Precautions

Salbutamol and other beta agonists should be given with caution in hyperthyroidism, myocardial insufficiency, arrhythmias, susceptibility to QT-interval prolongation, hypertension, and diabetes mellitus (especially on intravenous use—blood glucose should be monitored since ketoacidosis has been reported).

In *severe asthma* particular caution is also required to avoid inducing hypokalaemia as this effect may be potentiated by hypoxia or by the effect of other anti-asthma drugs on potassium (see Interactions, below); plasma-potassium concentrations should be monitored.

$Beta_2$ agonists such as salbutamol are not appropriate for use alone in the treatment of more than mild asthma (see Asthma, p.1108). Increasing need for, or decreased duration of effect of, inhaled salbutamol and other short-acting $beta_2$ agonists indicates deterioration of asthma control and the likely requirement for increased anti-inflammatory therapy.

In *women being treated for premature labour* the risk of pulmonary oedema means that the patient's state of hydration and cardiac and respiratory function should be monitored very carefully; the volume of infusion fluid should be kept to the minimum (normally using glucose 5% as the diluent), and $beta_2$-agonist therapy should be stopped immediately and diuretic therapy started if signs of pulmonary oedema develop. Other risk factors for pulmonary oedema include multiple pregnancy and heart disease. Ischaemic heart disease or significant risk factors for ischaemic heart disease are specific contra-indications; where heart disease is suspected assessment by a physician experienced in cardiology is needed. Eclampsia and severe pre-eclampsia are also contra-indications, with special care needed in mild to moderate pre-eclampsia. Other contra-indications include intra-uterine infection, intra-uterine fetal death, antepartum haemorrhage (which requires immediate delivery), placenta praevia, and cord compression; $beta_2$ agonists should not be used for threatened miscarriage. See also Uses and Administration, below.

For details of the precautions to be observed with sympathomimetics in general, see p.1407.

Abuse. Salbutamol inhalers have been subject to abuse, particularly by children and young adults.[1-5] This has occurred in both asthmatic and non-asthmatic individuals and has been thought to be for the effect of sympathetic stimulation and for the effect of the fluorocarbon propellants. The introduction of fluorocarbon-free inhalers should reduce the latter motivation, although not the former.

1. Brennan PO. Inhaled salbutamol: a new form of drug abuse? *Lancet* 1983; **ii:** 1030–1.
2. Thompson PJ, *et al.* Addiction to aerosol treatment: the asthmatic alternative to glue sniffing. *BMJ* 1983; **287:** 1515–16.
3. Brennan PO. Addiction to aerosol treatment. *BMJ* 1983; **287:** 1877.
4. Wickramasinghe H, Liebeschuetz HJ. Addiction to aerosol treatment. *BMJ* 1983; **287:** 1877.
5. O'Callaghan C, Milner AD. Aerosol treatment abuse. *Arch Dis Child* 1988; **63:** 70.

Interactions

Use of salbutamol and other $beta_2$ agonists with corticosteroids, diuretics, or xanthines increases the risk of hypokalaemia, and monitoring of potassium concentrations is recommended in severe asthma, where such combination therapy is common (see also Effects on Electrolytes and Metabolism, above). For an outline of interactions associated with sympathomimetics in general, see p.1407.

$Beta_2$ agonists. Patients receiving *salmeterol* may require salbutamol to control an acute attack of bronchospasm. One study indicated that the effects might be additive,[1] but another showed that patients receiving salmeterol had reduced sensitivity to salbutamol and might need higher doses of the latter for acute relief.[2] However, a study in asthmatics admitted to a hospital emergency department with acute exacerbations of their illness, found that previous salmeterol therapy did not reduce the effectiveness of standard doses of salbutamol.[3] Others have also noted attenuation of the bronchoprotective effects of a $beta_2$ agonist (in this case, *fenoterol*) by salmeterol.[4]

1. Smyth ET, *et al.* Interaction and dose equivalence of salbutamol and salmeterol in patients with asthma. *BMJ* 1993; **306:** 543–5.

2. Grove A, Lipworth BJ. Bronchodilator subsensitivity to salbutamol after twice daily salmeterol in asthmatic patients. *Lancet* 1995; **346:** 201–6.
3. Korosec M, *et al.* Salmeterol does not compromise the bronchodilator response to albuterol during acute episodes of asthma. *Am J Med* 1999; **107:** 209–13.
4. van Veen A, *et al.* Regular use of long-acting β -adrenoceptor agonists attenuates the bronchoprotective efficacy of short-acting β -adrenoceptor agonists in asthma. *Br J Clin Pharmacol* 2000; **50:** 499P.

Beta blockers. Non-cardioselective beta blockers oppose the bronchodilator effects of beta-agonist bronchodilators and are contra-indicated in asthmatic patients as they may cause serious bronchoconstriction, even if given as eye drops. No adverse interaction normally occurs between beta-agonist bronchodilators and cardioselective beta blockers; however, bronchospasm can sometimes occur in asthmatic patients, particularly if high doses are used. In a case-control study in postoperative coronary artery bypass graft patients, use of sotalol with salbutamol led to an increased risk for postoperative atrial fibrillation.[1]

1. Vader C, *et al.* Interaction between sotalol and albuterol after CABG: influence on postoperative arrhythmias and length of stay at an intensive care unit. *Br J Clin Pharmacol* 2002; **53:** 555P–556P.

Cardiac glycosides. Hypokalaemia produced by $beta_2$ agonists may result in an increased susceptibility to digitalis-induced arrhythmias although salbutamol intravenously and by mouth can also decrease serum concentrations of *digoxin* (see $Beta_2$ Agonists, p.1262).

Corticosteroids. Corticosteroids and $beta_2$ agonists may both produce falls in plasma potassium concentrations; there is evidence that such falls can be exacerbated by use together.[1] The possibility of enhanced hyperglycaemic effects from such a combination should also be borne in mind.

It has been suggested that in acute severe asthma, corticosteroids may modify beta receptors, reversing the beta receptor desensitisation and downregulation caused by $beta_2$ agonists and enhancing the bronchodilator response.[2] In chronic asthma there is little evidence to support this theory; however, combination therapy with corticosteroids and $beta_2$ agonists has been found to have beneficial effects on asthma control; the exact mechanism for this remains unclear.

1. Taylor DR, *et al.* Interaction between corticosteroid and beta-agonist drugs: biochemical and cardiovascular effects in normal subjects. *Chest* 1992; **102:** 519–24.
2. Taylor DR, Hancox RJ. Interactions between corticosteroids and β agonists. *Thorax* 2000; **55:** 595–602.

Diuretics. Hypokalaemia is known to be a possible adverse effect during treatment with $beta_2$ agonists such as salbutamol or terbutaline, and this may be enhanced if diuretics are also given;[1,2] in addition the arrhythmogenic potential of this interaction may be clinically important in patients with ischaemic heart disease.[1]

1. Lipworth BJ, *et al.* Prior treatment with diuretic augments the hypokalemic and electrocardiographic effects of inhaled albuterol. *Am J Med* 1989; **86:** 653–7.
2. Newnham DM, *et al.* The effects of frusemide and triamterene on the hypokalaemic and electrocardiographic responses to inhaled terbutaline. *Br J Clin Pharmacol* 1991; **32:** 630–2.

Neuromuscular blockers. Salbutamol given intravenously has been reported to enhance the neuromuscular blockade produced by *pancuronium* and by *vecuronium* (see Sympathomimetics, p.1905).

Xanthines. An enhanced hypokalaemic effect may occur when salbutamol is given with *theophylline*.[1,2] See also under Terbutaline, p.1139 and Sympathomimetics, under Theophylline, p.1145 for the potentiation of other effects.

1. Whyte KF, *et al.* Salbutamol induced hypokalaemia: the effect of theophylline alone and in combination with adrenaline. *Br J Clin Pharmacol* 1988; **25:** 571–8.
2. Kolski GB, *et al.* Hypokalemia and respiratory arrest in an infant with status asthmaticus. *J Pediatr* 1988; **112:** 304–7.

Pharmacokinetics

Salbutamol is readily absorbed from the gastrointestinal tract. When given by inhalation, 10 to 20% of the dose reaches the lower airways. The remainder is retained in the delivery system or is swallowed and absorbed from the gut.

Salbutamol is subject to first-pass metabolism in the liver and possibly in the gut wall but does not appear to be metabolised in the lung; the main metabolite is the inactive sulfate conjugate.

Salbutamol is rapidly excreted, mainly in the urine, as metabolites and unchanged drug; a smaller proportion is excreted in the faeces.

The plasma half-life of salbutamol has been estimated to range from 4 to 6 hours.

◊ General references.

1. Walker SR, *et al.* The clinical pharmacology of oral and inhaled salbutamol. *Clin Pharmacol Ther* 1972; **13:** 861–7.
2. Hetzel MR, Clark TJH. Comparison of intravenous and aerosol salbutamol. *BMJ* 1976; **2:** 919.
3. Lin C, *et al.* Isolation and identification of the major metabolite of albuterol in human urine. *Drug Metab Dispos* 1977; **5:** 234–8.
4. Morgan DJ, *et al.* Pharmacokinetics of intravenous and oral salbutamol and its sulphate conjugate. *Br J Clin Pharmacol* 1986; **22:** 587–93.
5. Lipworth BJ, *et al.* Single dose and steady-state pharmacokinetics of 4 mg and 8 mg oral salbutamol controlled-release in patients with bronchial asthma. *Eur J Clin Pharmacol* 1989; **37:** 49–52.
6. Rey E, *et al.* Pharmacokinetics of intravenous salbutamol in renal insufficiency and its biological effects. *Eur J Clin Pharmacol* 1989; **37:** 387–9.
7. Hindle M, Chrystyn H. Determination of the relative bioavailability of salbutamol to the lung following inhalation. *Br J Clin Pharmacol* 1992; **34:** 311–15.
8. Milliez JM, *et al.* Pharmacokinetics of salbutamol in the pregnant woman after subcutaneous administration with a portable pump. *Obstet Gynecol* 1992; **80:** 182–5.

Stereoselectivity. The *R*(−)-enantiomer of salbutamol (levosalbutamol—p.1125) is preferentially metabolised and is therefore cleared from the body more rapidly than the *S*(+)-enantiomer, which lacks bronchodilator activity but may be implicated in some of the adverse effects of salbutamol (see Tolerance, under Adverse Effects, above).

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. Boulton DW, *et al.* Transplacental distribution of salbutamol enantiomers at Caesarian section. *Br J Clin Pharmacol* 1997; **44:** 587–90.
3. 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.
4. Ward JK, *et al.* Enantiomeric disposition of inhaled, intravenous and oral racemic-salbutamol in man — no evidence of enantioselective lung metabolism. *Br J Clin Pharmacol* 2000; **49:** 15–22.

Uses and Administration

Salbutamol is a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on $beta_2$ receptors (a $beta_2$ agonist—p.1108). This results in its bronchodilating action being more prominent than its effect on the heart.

Salbutamol and salbutamol sulfate are used as bronchodilators in the management of reversible airways obstruction, as in asthma and in some patients with chronic obstructive pulmonary disease. Salbutamol also decreases uterine contractility and may be given as the sulfate to arrest premature labour (p.2003).

Inhalation results in the rapid onset (within 5 minutes) of bronchodilatation, which lasts for about 3 to 6 hours. After oral doses, the onset of action is within 30 minutes, with a peak effect between 2 to 3 hours after the dose, and a duration of action of up to 6 hours; modified-release preparations that have a longer duration of action are available.

Salbutamol is used as the base or sulfate in aerosol inhalers and as the sulfate in other preparations. The dosage is expressed in terms of salbutamol base; salbutamol sulfate 1.2 mg is equivalent to about 1 mg of salbutamol.

For the relief of **acute bronchospasm**, 1 or 2 inhalations of salbutamol 100 micrograms may be given from a conventional *metered-dose aerosol* as required, up to 4 times daily. Two inhalations may also be given just before exertion for the prophylaxis of exercise-induced bronchospasm. (In the USA these inhalations may be expressed as supplying 100 micrograms, the amount delivered *into* the mouthpiece, or 90 micrograms, the amount delivered *from* the mouthpiece.) Current asthma guidelines (see p.1108) recommend that inhaled short-acting $beta_2$ agonists such as salbutamol be used on an as-required, not regular, basis. In those patients requiring more than occasional use of salbutamol, anti-inflammatory therapy is also needed. An increased requirement for, or decreased duration of effect of, salbutamol indicates deterioration of asthma control and the need for increased anti-inflammatory therapy. Salbutamol sulfate is now available in chlorofluorocarbon (CFC)-free aerosols. Doses for these aerosols (expressed in terms of salbutamol) are the same as for conventional aerosols.

Salbutamol may also be inhaled as the sulfate from dry powder *inhalation capsules* or *discs*, particularly by patients who experience difficulty in using aerosol formulations. Owing to differences in the relative bioavailability to the lungs between these dry powder systems and the inhalation aerosol a 200-microgram dose (expressed in terms of salbutamol) from an inhalation capsule or disc is about equivalent in activity to a 100-microgram dose from a conventional aerosol; usual recommended doses are 200 or 400 micrograms up to four times daily.

When inhalation is ineffective, *oral* salbutamol may be given in a dose of 2 to 4 mg three or four times daily as the sulfate; some patients may require doses of up to 8 mg three or four times daily, but such increased doses are unlikely to be tolerated or to provide much extra benefit. Elderly patients should be given the lower doses initially. Modified-release preparations are also available; a usual adult dose is 8 mg twice daily.

In more severe or unresponsive bronchospasm salbutamol sulfate may be given intermittently via a *nebuliser* in adults and children. Licensed doses are 2.5 to 5 mg of salbutamol repeated up to 4 times daily; continuous use is also possible, usually at a rate of 1 to 2 mg/hour. However, guidelines allow for more frequent use or continuous use at a higher rate in acute severe asthma (see under Asthma, p.1108). Single-dose units of 0.1% or 0.2%, or a concentrated solution of salbutamol 0.5%, are available for nebulisation. Continuous use is usually as a 0.005 to 0.01% solution in sodium chloride 0.9%. Patients with acute severe asthma may require supplemental oxygen.

In acute severe asthma where delivery via nebuliser is not available, 4 to 6 inhalations of salbutamol 100 micrograms from a metered-dose inhaler may be given at intervals of 10 to 20 minutes via a large volume spacer.

In the management of a severe attack of bronchospasm a slow *intravenous injection* of salbutamol 250 micrograms as a solution containing 50 micrograms/mL as the sulfate may be required; alternatively salbutamol may be given by intravenous infusion of a solution containing 5 mg in 500 mL (10 micrograms/mL) at a usual rate of 3 to 20 micrograms/minute according to the patient's need; higher dosages have been used in patients with respiratory failure.

Salbutamol sulfate can also be given for bronchospasm by *subcutaneous* or *intramuscular* injection in doses of salbutamol 500 micrograms every 4 hours as required.

For the arrest of uncomplicated **premature labour** between 24 and 33 weeks of gestation salbutamol sulfate is given by *intravenous infusion*, preferably with the aid of a syringe pump at a concentration of 200 micrograms/mL of salbutamol in glucose 5%. If no syringe pump is available then the infusion should be with a more dilute solution of 20 micrograms/mL in glucose 5%. The same dose is used as with the syringe pump. The recommended initial rate of infusion is 10 micrograms/minute increased at intervals of 10 minutes until there is a response; the rate is then increased slowly until contractions cease. The usual effective dose is 10 to 45 micrograms/minute. The infusion should be maintained at the rate at which contractions cease for 1 hour, then reduced by decrements of 50% at intervals of 6 hours. Prolonged therapy should be avoided as the risks to the mother (see Precautions, above) increase after 48 hours, and there is a lack of evidence of benefit from further treatment.

The maternal pulse should be monitored throughout the infusion and the infusion rate adjusted to avoid a maternal heart rate of more than 140 beats/minute. A close watch should also be kept on the patient's state of hydration since fluid overload is considered to be a key risk factor for pulmonary oedema.

Salbutamol may subsequently be given *orally* in a dose of 4 mg three or four times daily but such usage is not recommended by the *BNF*, given the problems with prolonged therapy already mentioned.

For doses of salbutamol used in children, see Administration in Children below.

Administration. $Beta_2$ agonists are used extensively in the management of reversible airways obstruction. A common, effective, and convenient method of dosage is by a pressurised aerosol inhaler. With this route relief is provided rapidly and fewer systemic adverse effects are likely to occur than with oral use. It is important that patients using conventional inhalers employ the correct technique, which involves coordinating actuation of the aerosol with inhalation; if patients have difficulty with this, alternatives are available. Spacer devices may be used with inhalers. These are added on to the inhaler and reduce the velocity of the aerosol; also more propellant may evaporate before inhalation allowing a greater proportion of the drug to reach the lungs, and coordination of actuation of the aerosol and inhalation is less important. Breath-actuated aerosol inhalers and dry powder inhalers are also available and are actuated by the patient's inspiration and thus avoid entirely the need for coordination of actuation and inhalation; however, inhalation of the dry powder has occasionally caused irritation of the throat or coughing.

The oral route can be used although generally a form of inhaled therapy as described above is preferable. Formulations intended for oral use are commercially available, including modified-release formulations. Nebulisation is an alternative method of delivery and this may be used in the management of severe acute attacks as may parenteral therapy.

Chlorofluorocarbon (CFC) propellants in pressurised aerosol inhalers are being replaced by hydrofluoroalkane (HFA) propellants. Conventional and breath-actuated HFA preparations are available. HFA aerosols may feel and taste different to CFC aerosols.

Administration in children. For the treatment of reversible airways obstruction, including nocturnal asthma, and prevention of exercise-induced **bronchospasm** in children, the *BNFC* suggests the following doses:

by aerosol inhalation

- 1 month to 18 years of age, 100 or 200 micrograms (1 or 2 inhalations) up to four times daily, for occasional use only

by inhalation of dry powder from inhalation capsules or discs

- 5 to 12 years of age, 200 micrograms up to four times daily, for occasional use only
- over 12 years of age, doses as for adults, see Uses and Administration, above

Inhaled therapy is generally considered first-line treatment, but oral therapy may be necessary if an inhaler device cannot be used. In the UK salbutamol syrup is licensed for children from 2 years of age and modified-release oral preparations from 3 years of age.

by mouth using an immediate-release preparation

- 1 month to 2 years of age, 100 micrograms/kg (up to a maximum dose of 2 mg) three or four times daily
- 2 to 6 years of age, 1 to 2 mg three or four times daily
- 6 to 12 years of age, 2 mg three or four times daily
- over 12 years of age, doses as for adults, see Uses and Administration, above

by mouth using a modified-release preparation

- 3 to 12 years of age, 4 mg twice daily
- over 12 years of age, as for adults, see above

In the management of acute mild to moderate **exacerbations** of asthma, salbutamol may be given using a metered-dose aerosol inhaler via a spacer device. For children of all ages, 1 inhalation (100 micrograms) may be given every 15 to 30 seconds up to a maximum of 10 inhalations. The dose may be repeated after 20 to 30 minutes if required. In more severe exacerbations, salbutamol can be given intermittently via a nebuliser. A dose of 2.5 mg, which can be increased to 5 mg in children over 5 years of age, can be repeated every 20 to 30 minutes if necessary. Immediate transfer to hospital and inhalation of oxygen is also required. Children under 18 months of age often respond poorly to bronchodilators; nebulised $beta_2$ agonists have been associated with mild paradoxical bronchospasm and transient worsening of oxygen saturation.

Although parenteral salbutamol is not licensed in the UK for use in children, the *BNFC* recommends the following doses in the management of **acute severe** or life-threatening acute asthma:

by intravenous injection over 5 minutes

- 1 month to 2 years of age, 5 micrograms/kg as a single dose
- 2 to 18 years of age, 15 micrograms/kg (to a maximum of 250 micrograms) as a single dose

by continuous intravenous infusion

- 1 month to 18 years of age, 60 to 300 micrograms/kg per hour, adjusted according to response and heart rate. Doses above 120 micrograms/kg per hour require close monitoring

Salbutamol can be used to treat severe **hyperkalaemia** in children (see Hyperkalaemia below). The *BNFC* recommends:

by intravenous injection over 5 minutes

- children of all ages, 4 micrograms/kg as a single dose; repeated if necessary

by inhalation of nebulised solution (although intravenous injection is preferred)

- children of all ages, 2.5 or 5 mg as a single dose; repeated if necessary

Asthma. Short-acting $beta_2$ agonists such as salbutamol are used for short-term relief in all patients with symptomatic asthma (p.1108). High doses are used in acute asthma, but current recommendations for chronic asthma are for low doses to be inhaled as required rather than regularly. When patients with mild asthma find that symptomatic relief is needed more than 2 or 3 times a week, then that should be a sign for additional treatment with anti-inflammatory drugs. Increasing need for, or decreased effect of, short-acting $beta_2$ agonists indicates deteriorating asthma and the requirement for stepping up therapy. In one placebo-controlled study,[1] patients with stable asthma receiving regular high doses of a short-acting inhaled $beta_2$ agonist were able to reduce the dose considerably with no change in asthma control, lending further support to the recommendation for 'as-required' rather than regular use of these drugs. The discussion under Fenoterol on p.1121 on the increased mortality that has been observed in asthma patients and the connection with asthma therapy includes a view that regular use might have contributed to the increased mortality. However, a systematic review[2] of studies of short-acting $beta_2$ agonists, most of which used salbutamol, found no clear clinical advantage or detriment from regular use compared with taking them as required.

1. Harrison TW, *et al.* Randomised placebo controlled trial of β agonist dose reduction in asthma. *Thorax* 1999; **54:** 98–102.
2. Walters EH, *et al.* Inhaled short acting beta2-agonist use in chronic asthma: regular versus as needed treatment. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 15/01/08).

Bronchiolitis. Acute bronchiolitis (inflammation of the bronchioles associated with viral respiratory-tract infection, usually due to RSV—see p.860) is a poorly defined respiratory condition seen in infants and young children. The diagnostic criteria, and the usual management, vary considerably from country to country. $Beta_2$ agonists such as salbutamol are widely prescribed in the USA, but not in the UK, and attempts to establish their benefits have produced conflicting results.[1] Modest benefit (but no difference in hospital admission rate) has been reported from a meta-analysis of bronchodilator therapy in general,[2] but a meta-analysis of $beta_2$-agonist therapy in bronchiolitis did not show it to be effective.[3] Some comparative studies have suggested that nebulised adrenaline is more effective than salbutamol.[4,5] However, one study in hospitalised children found no benefit from nebulised salbutamol in terms of improved oxygenation or length of hospital stay,[6] and another[7] found no difference in efficacy between nebulised adrenaline, salbutamol, and sodium chloride 0.9%.

The use of oral salbutamol in infants with acute viral bronchiolitis has been found to be no more effective than placebo and so is not recommended.[8]

1. Everard ML. Acute bronchiolitis—a perennial problem. *Lancet* 1996; **348:** 279–80.
2. Gadomski AM, Bhasale AL. Bronchodilators for bronchiolitis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 25/01/08).
3. Flores G, Horwitz RI. Efficacy of β -agonists in bronchiolitis: a reappraisal and meta-analysis. *Pediatrics* 1997; **100:** 233–9.
4. Reijonen T, *et al.* The clinical efficacy of nebulized racemic epinephrine and albuterol in acute bronchiolitis. *Arch Pediatr Adolesc Med* 1995; **149:** 686–92.
5. Menon K, *et al.* A randomized trial comparing the efficacy of epinephrine with salbutamol in the treatment of acute bronchiolitis. *J Pediatr* 1995; **126:** 1004–7.
6. Dobson JV, *et al.* The use of albuterol in hospitalized infants with bronchiolitis. *Pediatrics* 1998; **101:** 361–8.
7. Patel H, *et al.* A randomized, controlled trial of the effectiveness of nebulized therapy with epinephrine compared with albuterol and saline in infants hospitalized for acute viral bronchiolitis. *J Pediatr* 2002; **141:** 818–24.
8. Patel H, *et al.* Randomized, double-blind, placebo-controlled trial of oral albuterol in infants with mild-to-moderate acute viral bronchiolitis. *J Pediatr* 2003; **142:** 509–14.

Chronic obstructive pulmonary disease. Salbutamol and other $beta_2$ agonist bronchodilators form part of the first-line treatment of chronic obstructive pulmonary disease (p.1112).

Cough. For studies of inhaled salbutamol in the treatment of cough, see under Beclometasone, p.1518.

Hyperkalaemia. Salbutamol can lower plasma-potassium concentrations by promoting intracellular uptake,[1,2] and this effect has been used in treating mild hyperkalaemia (p.1669) associated with chronic disorders such as renal failure[3,4] and hyperkalaemic periodic paralysis.[5] However, such use is controversial: the effects of salbutamol may be inconsistent[6] and some clinicians prefer to avoid the use of $beta_2$ agonists because of fears that large doses may induce cardiac arrhythmias.[7]

Salbutamol has been used to lower plasma-potassium concentrations in children[8] and premature neonates[9] with some success. For doses of salbutamol used to treat severe hyperkalaemia in children, see Administration in Children above.

1. Bushe C. Salbutamol for hyperkalaemia. *Lancet* 1983; **ii:** 797.
2. Anonymous. Hyperkalaemia—silent and deadly. *Lancet* 1989; **i:** 1240.
3. Allon M, *et al.* Nebulized albuterol for acute hyperkalemia in patients on hemodialysis. *Ann Intern Med* 1989; **110:** 426–9.
4. McClure RJ, *et al.* Treatment of hyperkalaemia using intravenous and nebulised salbutamol. *Arch Dis Child* 1994; **70:** 126–8.
5. Wang P, Clausen T. Treatment of attacks in hyperkalaemic familial periodic paralysis by inhalation of salbutamol. *Lancet* 1976; **i:** 221–3.
6. Wong S-L, Maltz HC. Albuterol for the treatment of hyperkalemia. *Ann Pharmacother* 1999; **33:** 103–6.
7. Halperin ML, Kamel KS. Potassium. *Lancet* 1998; **352:** 135–40.
8. Helfrich E, *et al.* Salbutamol for hyperkalaemia in children. *Acta Paediatr* 2001; **90:** 1213–16.
9. Singh BS, *et al.* Efficacy of albuterol inhalation in treatment of hyperkalemia in premature neonates. *J Pediatr* 2002; **141:** 16–20.

Lymphangioleiomyomatosis. Inhaled $beta_2$ agonists are often helpful in treating the reversible component of airway obstruction in women with pulmonary lymphangioleiomyomatosis, and a trial of treatment is warranted.[1,2] For mention of the use of medroxyprogesterone in this rare disease, see Respiratory Disorders, p.2114.

1. Johnson S. Lymphangioleiomyomatosis: clinical features, management and basic mechanisms. *Thorax* 1999; **54:** 254–64.
2. Johnson SR, Tattersfield AE. Clinical experience of lymphangioleiomyomatosis in the UK. *Thorax* 2000; **55:** 1052–7.

Muscular dystrophies. There is some evidence that $beta_2$ agonists affect muscle strength and have an anabolic effect. Salbutamol has therefore been investigated in a small number of patients in the management of muscular dystrophies (p.1507). Oral doses of modified-release salbutamol up to 12 mg daily have been used in boys aged between 5 and 11 years with Duchenne or Becker muscular dystrophies,[1,2] and doses of 8 or 16 mg twice daily have been given to adults with facioscapulohumeral dystrophy.[3,4] Although some improvements in muscle strength and muscle mass have been reported, not all muscle groups respond and the long-term effects of treatment are not known.

1. Fowler EG, *et al.* Pilot trial of albuterol in Duchenne and Becker muscular dystrophy. *Neurology* 2004; **62:** 1006–8.
2. Skura CL, *et al.* Albuterol increases lean body mass in ambulatory boys with Duchenne or Becker muscular dystrophy. *Neurology* 2008; **70:** 137–43.
3. Kissel JT, *et al.* Randomized, double-blind, placebo-controlled trial of albuterol in facioscapulohumeral dystrophy. *Neurology* 2001; **57:** 1434–40.
4. van der Kooi EL, *et al.* Strength training and albuterol in facioscapulohumeral muscular dystrophy. *Neurology* 2004; **63:** 702–8.

Premature labour. $Beta_2$ agonists such as salbutamol have been used as tocolytics in the management of premature labour (p.2003), and can postpone labour for a few days, but the risk of adverse cardiovascular and metabolic events including pulmonary oedema (see above) means that great care and appropriate monitoring of the patient's heart rate and state of hydration are needed.

Proctalgia fugax. Inhalation of salbutamol from a metered-dose inhaler at the beginning of an attack has been shown to reduce the duration of pain in patients with proctalgia fugax.[1]

1. Eckardt VF, *et al.* Treatment of proctalgia fugax with salbutamol inhalation. *Am J Gastroenterol* 1996; **91:** 686–9.

Preparations

BP 2008: Salbutamol Injection; Salbutamol Nebuliser Solution; Salbutamol Oral Solution; Salbutamol Powder for Inhalation; Salbutamol Pressurised Inhalation; Salbutamol Tablets;
USP 31: Albuterol Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Airomir†; Airsalbu; Amocasin; Asmatol; Butamol; Duopack; Medihaler†; Microterol; Nebutrax; Respiret; Salbulin; Salbutol; Salbutral; Salbutral + Aeromed; Ventolin; Yontal; Zoom; ***Austral.:*** Airomir; Asmol; Butamol; Epaq; Respax; Ventolin; ***Austria:*** Buventol; Sultanol; ***Belg.:*** Airomir; Docsalbuta; Ventolin; ***Braz.:*** Acobelin†; Aero-Ped†; Aerodini; Aerogreen†; Aerojet; Aerolin; Aerotamol†; Aerotrat; Asmakil; Asmaliv; Bronconal; Bronquil†; Butovent; Dilamol; Oxiterol†; Prodotamol; Pulmoflux; Salburin†; Salbutalin†; Salbutam; Salbutamax; Salbutib†; Salrolin†; Teoden†; Tussiliv; ***Canad.:*** Airomir; Apo-Salvent; Novo-Salmol†; Ventodisk; Ventolin; ***Chile:*** Aero-Sal†; Aerolin; Airomir; Asmavent; Broncoterol†; Bropil; Butotal; Fesema; Respolin; Salbutral; Sinasmal; ***Cz.:*** Apo-Salvent†; Asthalin†; Broncovaleas†; Butovent†; Buventol; Ecosal; Etinoline†; Salamol†; Steri-Neb Salamol†; Ventodisks†; Ventolin; Volmax†; ***Denm.:*** Airomir; Buventol; Salbudan†; Salbuvent; Ventoline; Volmax; ***Fin.:*** Airomir; Buventol; Salbuvent†; Ventoline; ***Fr.:*** Airomir; Asmasal; Buventol; Salbumol; Spreor†; Ventexxair†; Ventilastin; Ventodisks†; Ventoline; ***Ger.:*** Apsomol; Asthmalitan; Broncho Fertiginhalat; Broncho Inhalat; Bronchospray; Epaq; Loftan; Padiamol; Pentamol; Salbu; Salbubreathe; Salbuhexal; Salbulair; Salbulind; Salbupp†; Salmundin†; Salvent†; Sultanol; Ventilastin; Volmac; ***Gr.:*** Aerolin; Asthmotrat; Buventol†; Normobron; Salbunova; ***Hong Kong:*** Airomir; Apo-Salvent†; Azmacon; Buto Asma†; Cybutol; Respolin; Respreve†; Salamol; Salmol; Ventodisks; Ventolin; Ventomol; Volmax; Zenmolin; ***Hung.:*** Ac-Butamol†; Buventol; Ecosal; Huma-Salmol†; Salvuron†; Ventolin; ***India:*** Asthalin; Derihaler; Salbetol; Salmaplon; Salsol; ***Indon.:*** Asmacare; Azmacon; Buventol; Fartolin; Glisend; Hivent; Lasal; Librentin; Pritasma; Salbron; Salbuven; Suprasma; Ventolin; Volmax; ***Irl.:*** Aerolin; Airomir; Asmasal; Gerivent; Salamol; Steri-Neb Salamol; Ventamol; Ventodisks†; Ventolin; ***Israel:*** Ventolin; Volmax†; ***Ital.:*** Aerotec†; Broncovaleas; Salbufax†; Salbutard†; Ventmax; Ventolin; Volmax; ***Malaysia:*** Airomir; Asmovent†; Beatolin; Butahale†; Buventol; Colin†; Respolin†; Salbuterol†; Salmax; Salmol†; Ventamol†; Ventolin; Volmax; ***Mex.:*** Anebron†; Apo-Salvent; Assal; Avedox-FC; Azyrol; Biorenyn; Bolbasalt†; Bonair; Butotal†; Capacit; Cobamol; Dicoterol; Exafil; Oladin; Salamol; Salbulin†; Salbutalan; Salcomed; Unibron; Ventolin; Volmax; Zibil; ***Neth.:*** Airomir; Butovent; Ventolin; ***Norw.:*** Airomir; Buventol; Ventoline; ***NZ:*** Airomir; Apo-Salvent; Asmigen; Asmol†; Buventol; Respigen; Respolin; Salamol; Salapin; Ventolin; Volmax; ***Philipp.:*** Activent; Airomir; Amoltex; Asbunyl; Asfrenon; Asmacaire; Asmalin; Astagen; Asvimol; Axmaxolv; Cletal; Emplusal; Hivent; Librentin; Provexel NS; Prox-S; Resdil; Rhinol; Salbumed; Salvex; Sedalin; Venalax; Ventar; Vento-Broncho; Ventolin; Ventosal; ***Pol.:*** Steri-Neb Salamol; Velaspir; Ventodisk; Ventolin; ***Port.:*** Ventilan; ***Rus.:*** Salamol (Саламол); Salben (Сальбен); Salgim (Сальгим); Saltos (Сальтос); Ventolin (Вентолин); ***S.Afr.:*** Airomir; Asthavent; Breatheze†; Cybutol†;

Salbulin†; Venteze; Ventodisk†; Ventolin; Volmax; ***Singapore:*** Airomir†; Azmasol; Butahale; Buto Asma†; Buventol; Medolin; Respolin†; Sabutol†; Salamol†; Salbuair; Salmol; Venderol; Ventolin; Volmax; ***Spain:*** Aldobronquial; Asmasal†; Buto Air; Buto Asma; Emican†; Respiroma; Ventadur; Ventilastin; Ventolin; ***Swed.:*** Airomir; Buventol; Ventoline; ***Switz.:*** Airomir†; Buventol†; Ecovent; Ventodisk; Ventolin; Volmax; ***Thai.:*** Airomir†; Asmasal; Asthmolin†; Butamol; Buto Asma; Butovent; Buventol; Respolin†; Salbusian; Salbutac; Salda; Salmol; Solia; Venterol; Ventolin; Violin; Volmax†; Zebu; ***Turk.:*** Asthavent; Salbulin; Salbutam; Salbutol; Ven-o-sal; Ventodisks; Ventolin; Volmax; ***UAE:*** Butalin; ***UK:*** Airomir; Asmasal; Kentamol†; Pulvinal Salbutamol; Salamol; Salapin; Salbulin; Ventmax; Ventodisks†; Ventolin; Volmax; ***USA:*** Accuneb; ProAir; Proventil; Ventolin; Volmax†; VoSpire; ***Venez.:*** Asthalin; Butahale†; Butoas; Respolin†; Salbulis; Salbumed; Salburol; Salbutan; Ventolin†.

Multi-ingredient: ***Arg.:*** Beclasma; Butocort; Butosol; Combivent; Fatigan Bronquial†; Iprasalb; Salbutol Beclo; Salbutral AC; Salbutrop†; Ventide; Ventolin Compuesto†; ***Austral.:*** Combivent; ***Austria:*** Combivent; Di-Promal; Ventide; ***Belg.:*** Combivent; ***Braz.:*** Aeroflux; Aerotide; Clenil Compositum; Combivent; ***Canad.:*** Combivent; ratio-Ipra Sal UDV; ***Chile:*** Aero-Plus; Aerosoma; Asmavent-B; Beclasma†; Belomet; Broncoterol-B†; Butotal B; Combivent; Herolan Aerosol; Salbutral AC; Ventide; ***Cz.:*** Combivent†; Intal Plus†; ***Denm.:*** Combivent; ***Fin.:*** Atrodual; Redol Comp; ***Fr.:*** Combivent; ***Gr.:*** Berovent; ***Hong Kong:*** Combivent; Ventide; Ventolin Expectorant; ***India:*** Aerocort; Albutamol; Ambrodil-S; Amcof; Asthacrom; Asthalin AX; Asthalin Expectorant; Axalin-AX; Axalin†; Bronchilet†; Budesal†; Deletus A†; Duolin; Kofarest; Mucolinc; Okaril; Pulmo-Rest; Pulmo-Rest Expectorant; Suprivent; Suprivent-A; Theo-Asthalin; Ventorlin; ***Indon.:*** Combivent; Fartolin Expectorant; Lasal Expectorant; Proventol Expectorant; Salbron Expectorant; Salbuven Expectorant; Teosal; Ventide; Ventolin Expectorant; ***Irl.:*** Combivent; Ipramol; ***Ital.:*** Breva; Clenil Compositum; Plenaer; Ventolin Espettorante†; Ventolin Flogo†; Zarent†; ***Malaysia:*** Beatolin Expectorant†; Combivent; Ipramol; Salbutamol Expectorant; Ventamol Expectorant†; Ventolin Expectorant; ***Mex.:*** Aeroflux; Broxol Air; Combivent; Flamebin; Fluvicil; Fluxol; Fultac; Mucoflux; Musaldox; Neumyn-AS; Removil; Salamflux; Sibilex; Ulax-C; Ventide; ***Neth.:*** Combivent; ***NZ:*** Combivent; Duolin; ***Philipp.:*** Asbunyl Plus; Asfrenon GF; Asmalin Broncho; Broncaire Expectorant; Clarituss Plus; Combipul; Combivent; Duavent; Hicaryl; Histaril; Neovent; Pecof; Pulmovent; Salvex XP; SGX; Solmux-Broncho (Reformulated); Ventar EXP; Vento-Broncho G; Ventolin Expectorant; Venzadril; ***Port.:*** Combivent; Propavente; ***Rus.:*** Ascoril Expectorant (Аскорил Экспекторант); Biasten (Биастен); ***S.Afr.:*** Combivent; Duolin; Sabax Combineb; ***Singapore:*** Clenil Compositum†; Combivent; Ventide†; ***Spain:*** Butosol; Combivent; Legis†; ***Swed.:*** Combivent; ***Switz.:*** Dospir; ***Thai.:*** Almasal; Asmasal Expectorant†; Biovent; Clenil Compositum; Combivent; Royalin; Salmol Expectorant; Ventide†; Ventolin Expectorant; ***Turk.:*** Combivent; Ventide; ***UK:*** Combivent; Ipramol; ***USA:*** Combivent; DuoNeb; ***Venez.:*** Aerocort; Aeroflux; Beclomet Compositum†; Beclosal; Broxodin; Butosol; Combivent; Duolin; Ipralin; Salbomex†; Salbutide†; Venticort; Ventide.

Salmeterol Xinafoate *(BANM, USAN, rINNM)* ⊗

GR-33343G; Salmaterol Xinafoate; Salmeterol 1-Hydroxy-2-naphthoate; Salmeterol Ksinafoat; Salmétérol, xinafoate de; Salmeteroli xinafoas; Salmeteroliksinafoaatti; Salmeterolio ksinafoatas; Salmeterol-xinafoát; Sameterolxinafoat; Xinafoato de Salmeterol. (*RS*)-5-{1-Hydroxy-2-[6-(4-phenylbutoxy)hexylamino]ethyl}-salicyl alcohol 1-hydroxy-2-naphthoate.

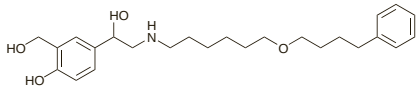
Салметерола Ксинафоат

$C_{25}H_{37}NO_4,C_{11}H_8O_3$ = 603.7.

CAS — 89365-50-4 (salmeterol); 94749-08-3 (salmeterol xinafoate).

ATC — R03AC12.

ATC Vet — QR03AC12.



(salmeterol)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Salmeterol Xinafoate). A white or almost white powder. Practically insoluble in water; slightly soluble in dehydrated alcohol; soluble in methyl alcohol. Protect from light.

Adverse Effects and Precautions

As for Salbutamol, p.1131. Inhalation of salmeterol may be associated with paradoxical bronchospasm, and it should not be used in patients who are not also receiving an inhaled corticosteroid.

Salmeterol is not appropriate for the treatment of acute bronchospasm or for patients whose asthma is deteriorating.

Effects on the cardiovascular system. A pooled analysis[1] of safety data from 7 studies of salmeterol in chronic obstructive pulmonary disease found no evidence of an increased risk of cardiovascular adverse effects. The duration of these studies had ranged from 12 weeks to 1 year.

1. Ferguson GT, *et al.* Cardiovascular safety of salmeterol in COPD. *Chest* 2003; **123:** 1817–24.

Effects on the respiratory system. Transient paradoxical bronchoconstriction with breathlessness, wheeze, or cough has been reported in 6 asthmatic patients after inhalation of salmeterol from a metered-dose aerosol but not after inhalation of the dry powder formulation by diskhaler.[1] The fluorocarbon propellants in the metered-dose aerosol were suspected as the irritants causing bronchoconstriction.

1. Wilkinson JRW, *et al.* Paradoxical bronchoconstriction in asthmatic patients after salmeterol by metered dose inhaler. *BMJ* 1992; **305:** 931–2.

Effects on the skin. Urticarial rash associated with inhaled salmeterol, of which the propellant was not the cause, has been reported. Although many urticarial reactions and a variety of rashes had been attributed to beta-agonist therapy their reproducibility had not always been documented.[1]

1. Hatton MQF, *et al.* Salmeterol rash. *Lancet* 1991; **337:** 1169–70.

Increased mortality. Interim results from a large controlled study (SMART)[1] designed to evaluate the safety of salmeterol compared with placebo, found a small but statistically significant increase in respiratory-related and asthma-related deaths or life-threatening episodes in the total population receiving salmeterol compared with placebo. This imbalance occurred mainly in the African-American subpopulation, and combined with difficulties in enrolment, led to early termination of the study. Various factors may have influenced the differences in outcomes seen with salmeterol; greater disease severity was noted at baseline in the African-American subgroup compared to Caucasian subjects, and nearly half of all participants were not receiving inhaled corticosteroids.

A subsequent meta-analysis[2] of 19 placebo-controlled studies of patients with asthma who were taking the long-acting beta$_2$ agonists salmeterol or formoterol (see p.1122), reported an increased risk of hospitalisation for an asthma exacerbation, life-threatening asthma attacks, and asthma-related deaths compared with placebo. A sub-group analysis that examined studies in which more than 75% of patients were also receiving inhaled corticosteroids also found an increased risk of hospital admission. The applicability of this review to therapy as recommended by current guidelines has been questioned,[3] as many of the studies included in the primary analysis did not require inhaled corticosteroids to be used, and studies which compared different asthma maintenance regimens were excluded because they were not placebo-controlled. Concomitant asthma treatments and adherence to treatment,[4,5] differences in baseline disease severity,[1,4] racial or genetic factors,[1] polymorphism,[6] tolerance,[6,7] and masking of underlying airway inflammation by long-acting beta$_2$ agonists[6] have all been proposed as possible explanations for the increased risk of adverse outcomes reported with long-acting beta$_2$ agonists.

In contrast to the above studies, a case-control study[8] that included 532 patients under age 65 who had died from asthma, matched with 532 controls with a hospital admission for asthma, found no evidence of adverse effects on mortality with medium to long-term use of inhaled long-acting beta$_2$ agonists. An earlier observational cohort study also found no evidence that salmeterol contributed to deaths reported from asthma.[9]

Current guidelines advocate use of a long-acting beta$_2$ agonist in addition to inhaled corticosteroids, and not as monotherapy, see Management of Asthma, p.1108

A recent review[10] by the UK MHRA concluded that:

- epidemiological data indicated that since the introduction of long-acting beta-agonists there had been a reduction in asthma-related hospitalisations in adolescents and a decrease in asthma related-mortality in all ages.
- data from controlled clinical study did not reflect the safety concern from postmarketing studies, possibly due to more consistent use of corticosteroids in controlled settings
- the data supported the use of long-acting beta-agonists with inhaled corticosteroids consistent with the UK guidelines on the management of asthma and that to aid compliance in the concomitant use of a corticosteroid, a combination inhaler should be used when appropriate

1. Nelson HS, *et al.* The salmeterol multicenter asthma research trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest* 2006; **129:** 15–26.
2. Salpeter SR, *et al.* Meta-analysis: effect of long-acting β-agonists on severe asthma exacerbations and asthma-related deaths. *Ann Intern Med* 2006; **144:** 904–12.
3. Ernst P, *et al.* Safety and effectiveness of long-acting inhaled β-agonist bronchodilators when taken with inhaled corticosteroids. *Ann Intern Med* 2006; **145:** 692–4.
4. Glassroth J. The role of long-acting β-agonists in the management of asthma: analysis, meta-analysis, and more analysis. *Ann Intern Med* 2006; **144:** 936–7.
5. Nelson HS, Dorinsky PM. Safety of long-acting β-agonists. *Ann Intern Med* 2006; **145:** 706.
6. Currie GP, *et al.* Long-acting β -agonists in asthma: not so SMART? *Drug Safety* 2006; **29:** 647–56.
7. Weinberger M, Abu-Hasan M. Life-threatening asthma during treatment with salmeterol. *N Engl J Med* 2006; **355:** 852–3.
8. Anderson HR, *et al.* Bronchodilator treatment and deaths from asthma: case-control study. Abridged version: *BMJ* 2005; **330:** 117. Full version: http://www.bmj.com/cgi/content/full/330/7483/117 (accessed 15/01/08)
9. Mann RD, *et al.* Salmeterol: a study by prescription-event monitoring in a UK cohort of 15,407 patients. *J Clin Epidemiol* 1996; **49:** 247–50.
10. MHRA/CHM. Long-acting β agonists for asthma: review. *Drug Safety Update* 2008: **1** (6): 9. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2033510&RevisionSelectionMethod=LatestReleased (accessed 22/05/08)

Tolerance. As with short-acting beta$_2$ agonists (see Salbutamol, p.1132), there is evidence that regular use of long-acting beta$_2$ agonists such as salmeterol produces tachyphylaxis to their protective effect against bronchoconstriction, as provoked by stimuli such as allergen, methacholine, or exercise.[1-4] The authors of a study of the long-term effect of salmeterol on exercise-induced asthma concluded that the decreased bronchoprotective effect over time was due to a decrease in duration of action (to less than 9 hours) rather than tachyphylaxis,[5] but this interpretation was criticised.[6,7]

There is also some evidence to suggest that symptomatic relief by short-acting beta$_2$ agonists is significantly reduced by regular use of long-acting beta$_2$ agonists.[8,9] Receptor downregulation, induced by regular use of a long-acting beta$_2$ agonist, has been suggested as the mechanism for this reduction in response and may lead to patients requiring higher doses of beta$_2$ agonists to attain relief from an acute asthma attack.[9,10] One study suggested that the greater tachyphylaxis to short-acting beta$_2$ agonists seen with salmeterol compared with formoterol might represent the expression of partial antagonism by salmeterol at beta$_2$ receptors.[8] Whatever the mechanism, the reduced bronchoprotective effect is perhaps more of a concern with long-acting beta$_2$ agonists, since, unlike the short-acting beta$_2$ agonists, their use on a regular basis is recommended.[11] See also Beta$_2$ Agonists, under Interactions of Salbutamol, p.1132.

1. Cheung D, *et al.* Long-term effects of a long-acting β -adrenoceptor agonist, salmeterol, on airway hyperresponsiveness in patients with mild asthma. *N Engl J Med* 1992; **327:** 1198–1203.
2. Bhagat R, *et al.* Rapid onset of tolerance to the bronchoprotective effect of salmeterol. *Chest* 1995; **108:** 1235–9.
3. Booth H, *et al.* Salmeterol tachyphylaxis in steroid treated asthmatic subjects. *Thorax* 1996; **51:** 1100–4.
4. Simons FER, *et al.* Tolerance to the bronchoprotective effect of salmeterol in adolescents with exercise-induced asthma using concurrent inhaled glucocorticoid treatment. *Pediatrics* 1997; **99:** 655–9.
5. Nelson JA, *et al.* Effect of long-term salmeterol treatment on exercise-induced asthma. *N Engl J Med* 1998; **339:** 141–6.
6. Aziz I, Lipworth BJ. Exercise-induced asthma. *N Engl J Med* 1998; **339:** 1783.
7. Dickey BF, Adachi R. Exercise-induced asthma. *N Engl J Med* 1998; **339:** 1783–4.
8. van Veen A, *et al.* A comparison of salmeterol and formoterol in attenuating airway responses to short-acting β -agonists. *Pulm Pharmacol Ther* 2003; **16:** 153–61.
9. Haney S, Hancox RJ. Tolerance to bronchodilation during treatment with long-acting beta-agonists, a randomised controlled trial. Abridged version: *Respir Res* 2005; **6:** 107. Full version: http://respiratory-research.com/content/6/1/107 (accessed 15/01/08)
10. Lipworth BJ. Airway subsensitivity with long-acting β -agonists: is there cause for concern? *Drug Safety* 1997; **16:** 295–308.
11. Abisheganaden J, Bonshey HA. Long-acting inhaled β -agonists and the loss of "bronchoprotective" efficacy. *Am J Med* 1998; **104:** 494–7.

Interactions

As for Salbutamol, p.1132.

◊ For a study suggesting a decreased effect of salbutamol in patients receiving salmeterol, as well as a report of additive effects, see Beta$_2$ Agonists under Interactions of Salbutamol, p.1132.

Pharmacokinetics

Plasma concentrations of salmeterol are negligible after inhalation of therapeutic doses.

◊ Reviews.

1. Cazzola M, *et al.* Clinical pharmacokinetics of salmeterol. *Clin Pharmacokinet* 2002; **41:** 19–30.

Uses and Administration

Salmeterol is a direct-acting sympathomimetic with beta-adrenoceptor stimulant activity and a selective action on beta$_2$ receptors (a beta$_2$ agonist). When given by inhalation, salmeterol acts as a bronchodilator. The onset of action is about 10 to 20 minutes but the full effect may not be apparent until after several doses. Unlike short-acting beta$_2$ agonists (see Salbutamol, p.1133), salmeterol is therefore not suitable for the symptomatic relief of an acute attack of bronchospasm. However, it is long-acting with a duration of action of about 12 hours and is indicated where the regular use of a long-acting beta$_2$ agonist is required for persistent reversible airways obstruction, as in chronic asthma or in some patients with chronic obstructive pulmonary disease. It may be useful in protecting against nocturnal and exercise-induced asthma attacks. Short-acting