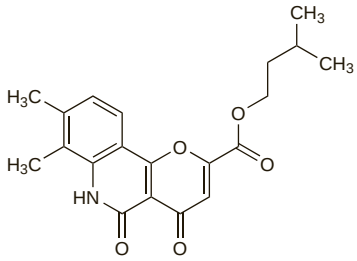
Repirinast *(USAN, rINN)*

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.

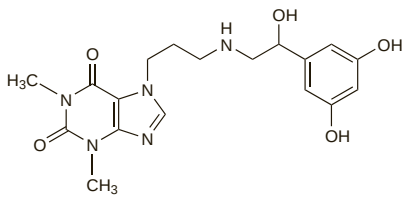
Репротерола Гидрохлорид

$C_{18}H_{23}N_5O_5$,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.

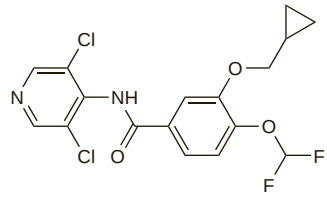
Рофлумиласт

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

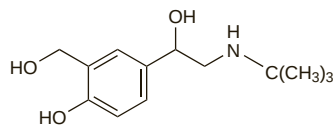
Сальбутамол

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