age, at the same doses used in adults (see Uses and Administration, above).

Fenoterol hydrobromide is also given orally to children for the relief of bronchospasm in the following doses:

- children aged 1 to 3 years, 1.25 mg three times daily
- children aged 4 to 10 years, 2.5 mg three times daily
- children aged over 10 years, as for adults (see Uses and Administration, above)

Preparations

BP 2008: Fenoterol Pressurised Inhalation.

Proprietary Preparations (details are given in Part 3)
Arg.: Alveofen; Asmopul; Berotec; ***Austral.:*** Berotec†; ***Austria:*** Berotec; ***Belg.:*** Berotec; ***Braz.:*** Berotec; Bromifen; Bromotec; Febiotec†; Fenozan; ***Canad.:*** Berotec; ***Chile:*** Berotec†; Parsistene†; ***Cz.:*** Berotec; Partusisten†; ***Denm.:*** Berotec; ***Fin.:*** Berotec†; ***Ger.:*** Berotec; Partusisten; ***Hong Kong:*** Berotec†; ***Hung.:*** Berotec; ***Indon.:*** Berotec; ***Ital.:*** Dosberotec; ***Jpn:*** Berotec; ***Malaysia:*** Berotec; Feno; ***Mex.:*** Berotec†; Partusisten; ***Neth.:*** Berotec; Partusisten; ***Norw.:*** Berotec; ***Philipp.:*** Berotec; ***Pol.:*** Berotec; ***Port.:*** Berotec; ***Rus.:*** Berotec (Беротек); Partusisten (Партусистен); ***S.Afr.:*** Berotec; ***Singapore:*** Berotec; ***Spain:*** Berotec†; ***Swed.:*** Berotec†; ***Switz.:*** Berotec; ***Thai.:*** Berotec; ***Venez.:*** Berotec†; Segamol.

Multi-ingredient: ***Arg.:*** Berodual; Duotec†; Ipradual; ***Austria:*** Berodual; Berodualin; Ditec; ***Belg.:*** Duovent; ***Braz.:*** Duovent; Fymnal†; ***Canad.:*** Duovent; ***Chile:*** Berodual; ***Cz.:*** Berodual; Ditec†; ***Denm.:*** Berodual; ***Fin.:*** Atrovent Comp; ***Fr.:*** Bronchodual; ***Ger.:*** Berodual; Ditec†; ***Gr.:*** Berodual; ***Hong Kong:*** Berodual†; ***Hung.:*** Berodual; Duotec†; ***India:*** Fenovent; ***Indon.:*** Berodual; ***Irl.:*** Duovent; ***Ital.:*** Duovent; Iprafen; ***Malaysia:*** Berodual; Duovent; ***Mex.:*** Berodual; Berosolvon; ***Neth.:*** Berodual; ***Philipp.:*** Berodual; ***Pol.:*** Berodual; ***Port.:*** Berodual; ***Rus.:*** Berodual (Бородуал); Ditec (Дитек); ***S.Afr.:*** Atrovent Beta; Berodual; Duovent; Sabax Nebrafen; ***Singapore:*** Berodual; Duovent; ***Spain:*** Berodual†; ***Switz.:*** Berodual; ***Thai.:*** Berodual; Inhalex; Punol; ***UK:*** Duovent; ***Venez.:*** Berodual; Berosolvon†; Duovent; Respidual.

Fenspiride Hydrochloride *(USAN, rINNM)*

Decaspiride; Fenspiride, Chlorhydrate de; Fenspiridi Hydrochloridum; Hidrocloruro de fenspirida; JP-428; NAT-333; NDR-5998A. 8-Phenethyl-1-oxa-3,8-diazaspiro[4.5]decan-2-one hydrochloride.

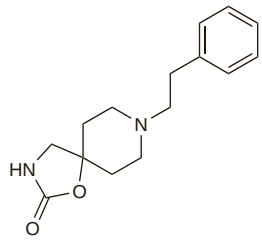
Фенспирида Гидрохлорид

$C_{15}H_{20}N_2O_2.HCl$ = 296.8.

CAS — 5053-06-5 (fenspiride); 5053-08-7 (fenspiride hydrochloride).

ATC — R03BX01; R03DX03.

ATC Vet — QR03BX01; QR03DX03.



(fenspiride)

Profile

Fenspiride is reported to have bronchodilator and anti-inflammatory properties. It is given as the hydrochloride in asthma (p.1108) and other respiratory disorders in usual oral doses of 160 to 240 mg daily in divided doses before meals. It has also been given rectally and by intramuscular or intravenous injection.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Pneumorel; ***Hong Kong:*** Pneumorel; ***Ital.:*** Pneumorel; ***Pol.:*** Eurespal; ***Port.:*** Fenspin†; Pneumorel; ***Rus.:*** Eurespal (Эреспал).

Formoterol Fumarate *(BANM, USAN, rINNM)* ⊗

BD-40A; CGP-25827A; Eformoterol Fumarat; Eformoterol Fumarate; Formoterol Fumarat; Formotérol, fumarate de; Formoterolfumarat; Formoterol-fumarát; Formoteroli fumaras; Formoterolifumaraatti; Formoterolio fumaratas; Formoterolu fumaran; Fumarato de formoterol; YM-08316. (±)-2′-Hydroxy-5′-[(*RS*)-1-hydroxy-2-{[(*RS*)-*p*-methoxy-α-methylphenethyl]amino}ethyl]formanilide fumarate.

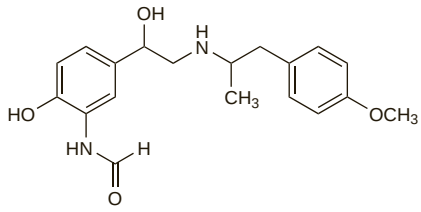
Формотерола Фумарат

$(C_{19}H_{24}N_2O_4)_2.C_4H_4O_4$ = 804.9.

CAS — 73573-87-2 (formoterol); 43229-80-7 (formoterol fumarate).

ATC — R03AC13.

ATC Vet — QR03AC13.



(formoterol)

Pharmacopoeias. In *Jpn. Eur.* (see p.vii) includes the dihydrate.

Ph. Eur. 6.2 (Formoterol Fumarate Dihydrate; Formoteroli Fumaras Dihydricus). A white or almost white or slightly yellow powder. Slightly soluble in water and in isopropyl alcohol; practically insoluble in acetonitrile; soluble in methyl alcohol. A 0.1% solution in water has a pH of 5.5 to 6.5. Protect from light.

Adverse Effects and Precautions

As for Salbutamol, p.1131. Inhalation of formoterol may be associated with paradoxical bronchospasm, and high doses have been associated with an increase in severe exacerbations of asthma. It should not be used in patients who are not also receiving an inhaled corticosteroid.

Long-acting $beta_2$ agonists such as formoterol are not appropriate for the treatment of acute bronchospasm.

Conjunctival irritation and eyelid oedema have been reported in isolated cases.

◊ References.

1. Wilton LV, Shakir SA. A post-marketing surveillance study of formoterol (Foradil): its use in general practice in England. *Drug Safety* 2002; **25:** 213–23.
2. Pauwels RA, *et al.* Formoterol as relief medication in asthma: a worldwide safety and effectiveness trial. *Eur Respir J* 2003; **22:** 787–94.

Asthma. A review of 3 controlled studies comparing inhaled formoterol with placebo, concluded that regular use of high-dose formoterol (48 micrograms daily) may be associated with more frequent serious asthma exacerbations.[1] The concomitant use of inhaled corticosteroids was allowed but not mandatory, and was not reported in the review, which led to debate on whether the results of the study would be applicable when current prescribing guidelines for asthma were followed.[2,3]

In contrast to this, a subsequent study,[4] designed to test the hypothesis of a dose-related increase in serious asthma exacerbations with formoterol therapy, did not show any increase in serious asthma exacerbations between different formoterol doses and placebo. Again, inhaled corticosteroid use was allowed but not mandatory, with 62.4% of patients reported as receiving regular anti-inflammatory therapy.

A systematic review[5] firmly concluded that the addition of a long-acting $beta_2$ agonist (such as formoterol) to low or high doses of inhaled corticosteroids reduced the risk of asthma exacerbations compared with ongoing treatment with similar doses of inhaled corticosteroids alone. The addition of a long-acting $beta_2$ agonist reduced by 19% the relative risk and by 5% the absolute risk of patients requiring systemic corticosteroids for an asthma exacerbation, over 4 to 54 weeks.

For discussion of serious adverse effects associated with long-acting $beta_2$ agonists in asthma, see Increased Mortality, under Salmeterol p.1135.

1. Mann M, *et al.* Serious asthma exacerbations in asthmatics treated with high-dose formoterol. *Chest* 2003; **124:** 70–4.
2. Rissmiller RW, *et al.* Asthma exacerbations and formoterol. *Chest* 2004; **125:** 1590–1.
3. van der Molen T. Formoterol and asthma exacerbations. *Chest* 2004; **125:** 1591.
4. Wolfe J, *et al.* Formoterol, 24μg bid, and serious asthma exacerbations: similar rates compared with formoterol, 12μg bid, with and without extra doses taken on demand, and placebo. *Chest* 2006; **129:** 27–38.
5. Ni Chroinin M, *et al.* Long-acting beta2-agonists versus placebo in addition to inhaled corticosteroids in children and adults with chronic asthma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 15/01/08).

Effects on skeletal muscle. Myalgia and muscle weakness associated with elevated creatine kinase has been reported during formoterol therapy.[1] Subsequent muscle biopsy suggested mitochondrial dysfunction. No inflammatory changes were seen and symptoms resolved on withdrawal of formoterol.

1. Kiernan MC, *et al.* Mitochondrial dysfunction and rod-like lesions associated with administration of β2 adrenoceptor agonist formoterol. *Neuromuscul Disord* 2004; **14:** 375–7.

Tolerance. Regular use of formoterol produced bronchodilator desensitisation,[1-3] and tachyphylaxis to bronchoprotection against methacholine, effects that have been noted with other long-acting $beta_2$ agonists (see Salmeterol, p.1135) and short-acting $beta_2$ agonists (see Salbutamol, p.1132).

1. van der Woude HJ, *et al.* Decreased bronchodilating effect of salbutamol in relieving methacholine induced moderate to severe bronchoconstriction during high dose treatment with long acting β agonists. *Thorax* 2001; **56:** 529–35.
2. Jones SL, *et al.* Reversing acute bronchoconstriction in asthma: the effect of bronchodilator tolerance after treatment with formoterol. *Eur Respir J* 2001; **17:** 368–73.
3. Haney S, Hancox RJ. Tolerance to bronchodilation during treatment with long-acting beta-agonists, a randomised controlled trial. *Respir Res* 2005; **6:** 107. Also available at: http://respiratory-research.com/content/pdf/1465-9921-6-107.pdf (accessed 15/01/08)

Interactions

As for Salbutamol, p.1132.

Pharmacokinetics

Inhaled formoterol is rapidly absorbed. It is largely metabolised by glucuronidation and *O*-demethylation, with about 10% being excreted in the urine as unchanged drug. The mean terminal elimination half-life after inhalation is estimated to be 10 hours.

Stereoselectivity. Formoterol occurs as a racemic mixture, of which arformoterol (p.1115) is the *R,R*-enantiomer. Only the *R,R*-enantiomer is active.[1,2] It has been suggested that stereoselective metabolism and excretion may account for the individual variation in duration of effect seen with formoterol, although the exact mechanism remains unclear.[1,3]

1. Zhang M, *et al.* Stereoselective glucuronidation of formoterol by human liver microsomes. *Br J Clin Pharmacol* 2000; **49:** 152–7.
2. Lötvall J, *et al.* The effect of formoterol over 24 h in patients with asthma: the role of enantiomers. *Pulm Pharmacol Ther* 2005; **18:** 109–13.
3. Zhang M, *et al.* Stereoselective urinary excretion of formoterol and its glucuronide conjugate in human. *Br J Clin Pharmacol* 2002; **54:** 246–50.

Uses and Administration

Formoterol is a direct-acting sympathomimetic with mainly beta-adrenoceptor stimulant activity specific to $beta_2$ receptors (a $beta_2$ agonist). It has properties similar to those of salbutamol (p.1133), but like salmeterol (p.1135) it has a prolonged duration of action of up to 12 hours; it is therefore not considered suitable for the symptomatic relief of acute attacks of bronchospasm. It is used when the regular use of a long-acting $beta_2$ agonist is needed for management of reversible airways obstruction, as in chronic asthma (p.1108) or in some patients with chronic obstructive pulmonary disease (p.1112).

Formoterol is given by inhalation as the fumarate but how the dose is expressed may depend on the formulation.

- A usual dose is 12 micrograms of formoterol fumarate twice daily from inhalational capsules, increased to 24 micrograms twice daily if necessary in severe disease.
- Metered doses from a dry powder inhaler may be expressed as the amount delivered *into* the mouthpiece (multiples of 6 micrograms per inhalation) or the amount delivered *from* the mouthpiece (corresponding to multiples of 4.5 micrograms per inhalation). Usual doses, expressed as the amount delivered *into* the mouthpiece, are 6 or 12 micrograms once or twice daily, increased if necessary in severe disease to 24 micrograms twice daily.
- Metered doses from an aerosol inhaler may also be expressed as the amount delivered *into* the mouthpiece (12 micrograms per inhalation) or the amount delivered *from* the mouthpiece (corresponding to 10.1 micrograms per inhalation). Usual doses are 1 or 2 inhalations twice daily.

Treatment should be reassessed if this proves inadequate; in the UK, some preparations are licensed for additional short-term symptom relief, but such use is contrary to current asthma guidelines (see p.1108).

Formoterol fumarate may also be inhaled via a nebuliser in a dose of 20 micrograms twice daily. Oral doses of 80 micrograms have been given twice daily in adults.

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