Preparations

BP 2008: Doxapram Injection;
USP 31: Doxapram Hydrochloride Injection.

Proprietary Preparations (details are given in Part 3)

Austral.: Dopram†; ***Austria:*** Dopram; ***Belg.:*** Dopram; ***Denm.:*** Dopram; ***Fin.:*** Dopram; ***Fr.:*** Dopram; ***Ger.:*** Dopram; ***Gr.:*** Dopram; ***Hong Kong:*** Dopram†; ***Irl.:*** Dopram; ***Neth.:*** Dopram; ***Norw.:*** Dopram; ***NZ:*** Dopram†; ***S.Afr.:*** Dopram; ***Spain:*** Docatone†; ***Switz.:*** Dopram†; ***UK:*** Dopram; ***USA:*** Dopram.

Etamivan *(BAN, rINN)* ⊗

Etamivaani; Étamivan; Etamiván; Etamivanum; Ethamivan *(USAN)*; NSC-406087; Vanillic Acid Diethylamide; Vanillic Diethylamide. *N,N*-Diethylvanillamide.

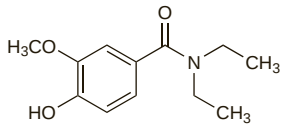
Этамиван

$C_{12}H_{17}NO_3$ = 223.3.

CAS — 304-84-7.

ATC — R07AB04.

ATC Vet — QR07AB04.



Profile

Etamivan has actions similar to those of doxapram (above). It was formerly used as a respiratory stimulant, but the risk of toxicity associated with effective doses is now considered to be unacceptable.

Etamivan is available in oral compound preparations for cerebrovascular and circulatory disorders and hypotension, but such use is not recommended.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Dosulfin Bronquial; ***Austria:*** Cinnarplus; Instenon; ***Ger.:*** Normotin-R†; ***Hong Kong:*** Instenon; ***Rus.:*** Instenon (Инстенон); ***Thai.:*** Instenon†.

Etilamfetamine Hydrochloride *(rINNM)* ⊗

Ethylamphetamine Hydrochloride; Étilamfétamine, Chlorhydrate d'; Etilamfetamini Hydrochloridum; Hidrocloruro de etilanfetamina. *N*-Ethyl-α-methylphenethylamine hydrochloride.

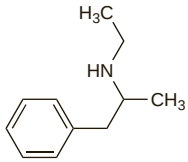
Этиламфетамина Гидрохлорид

$C_{11}H_{17}N,HCl$ = 199.7.

CAS — 457-87-4 (etilamfetamine); 1858-47-5 (etilamfetamine hydrochloride).

ATC — A08AA06.

ATC Vet — QA08AA06.



(etilamfetamine)

Profile

Etilamfetamine hydrochloride is a central stimulant with properties similar to those of dexamfetamine (p.2153). It has been used as an anorectic in the treatment of obesity.

Fencamfamin Hydrochloride *(BANM, rINNM)* ⊗

Fencamfamine, Chlorhydrate de; Fencamfamini Hydrochloridum; H-610; Hidrocloruro de fencanfamina. *N*-Ethyl-3-phenylbicyclo[2.2.1]hept-2-ylamine hydrochloride.

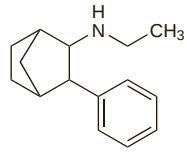
Фенкамфамина Гидрохлорид

$C_{15}H_{21}N,HCl$ = 251.8.

CAS — 1209-98-9 (fencamfamin); 2240-14-4 (fencamfamin hydrochloride).

ATC — N06BA06.

ATC Vet — QN06BA06.



(fencamfamin)

Profile

Fencamfamin hydrochloride has been given orally as a central stimulant.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***S.Afr.:*** Reactivan.

Fenetylline Hydrochloride *(BANM, rINNM)* ⊗

Amfetyline Hydrochloride; 7-Ethyltheophylline Amphetamine Hydrochloride; Fenethylline Hydrochloride *(USAN)*; Fénétylline, Chlorhydrate de; Fenetyllini Hydrochloridum; H-814; Hidrocloruro de fenetilina; R-720-11. 7-[2-(α-Methylphenethylamino)ethyl]theophylline hydrochloride.

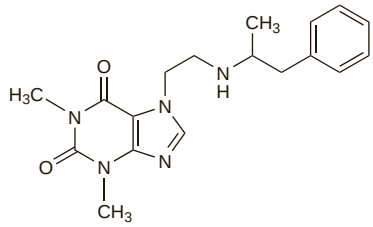
Фенетиллина Гидрохлорид

$C_{18}H_{23}N_5O_2,HCl$ = 377.9.

CAS — 3736-08-1 (fenetylline); 1892-80-4 (fenetylline hydrochloride).

ATC — N06BA10.

ATC Vet — QN06BA10.



(fenetylline)

Profile

Fenetylline is a theophylline derivative of amfetamine with properties similar to those of dexamfetamine (p.2153). It is given orally in the management of narcolepsy in an initial dose of 25 mg daily, increased to usual maintenance doses of 50 to 100 mg daily in 2 divided doses; no more than 150 mg daily should be used. It has also been used in the management of hyperactivity disorders. Fenetylline is subject to abuse.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Captagon; ***Ger.:*** Captagon†.

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

AHR-3002; Fenfluramine, Chlorhydrate de; Fenfluramini Hydrochloridum; Hidrocloruro de fenfluramina; S-768. *N*-Ethyl-α-methyl-3-trifluoromethylphenethylamine hydrochloride.

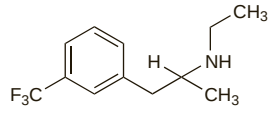
Фенфлюрамина Гидрохлорид

$C_{12}H_{16}F_3N,HCl$ = 267.7.

CAS — 458-24-2 (fenfluramine); 404-82-0 (fenfluramine hydrochloride).

ATC — A08AA02.

ATC Vet — QA08AA02.



(fenfluramine)

Adverse Effects and Precautions

As for Dexamfetamine, p.2153, but fenfluramine usually depresses rather than stimulates the CNS. Fenfluramine has been associated with serious cardiovascular toxicity. Pulmonary hypertension led to certain precautions being imposed upon its use and subsequent reports of valvular heart defects led to its general withdrawal worldwide.

Effects on the cardiovascular system. The association of primary *pulmonary hypertension* with the use of anorectics including fenfluramine, dexfenfluramine, and phentermine is well recognised.[1-3] Both reversible and irreversible cases have been reported and in some cases it has proved fatal.[1,4-9] The condition appears to be linked to prolonged or repeated therapy.[1,10] In 1992 the UK CSM advised that treatment should not exceed 3 months[1] but later in 1997 it revised its recommendations for fenfluramine and dexfenfluramine allowing treatment for up to 12 months under certain conditions.[2] The CSM stated that treatment could be continued beyond 3 months only if there had been a satisfactory response (more than 10% weight loss) and that this loss was maintained. Patients should also be monitored for symptoms of pulmonary hypertension. For other anorectics such as phentermine the maximum duration of treatment remained 3 months.

However, shortly after this, a report was published[11] that outlined an association between the use of a fenfluramine-phentermine combination and the development of *valvular heart disease* in 24 patients. Initially, the response by the CSM was to advise against the use of combinations of anorectics[12] although subsequently fenfluramine, along with dexfenfluramine, was withdrawn from the world market after more cases became known.[13,14] By September 1997 the FDA in the USA[14] had received 144 reports of valvulopathy, including the original 24, associated with fenfluramine or dexfenfluramine, with or without phentermine; none were associated with phentermine treatment alone. As a consequence the US authorities made recommendations[14] for the screening of all patients who had previously received fenfluramine or dexfenfluramine in order to detect heart valve lesions and to provide optimal care. Further studies[15-20] have supported the association with valvular abnormalities, and suggested that prolonged exposure or exposure to high doses of dexfenfluramine or fenfluramine increased the risk; clinically important disease would probably not develop in most patients with only short-term exposure.[21]

In 2000, the European Commission called for the withdrawal of all anorectics from the European market. Those anorectics involved in the decision included clobenzorex, diethylpropion, fenproporex, mazindol, mefenorex, phendimetrazine, phenmetrazine, and phentermine. However in 2002, after an appeal by some manufacturers, the European Court ruled that the Commission did not have the authority to withdraw marketing authorisations. Subsequently, some anorectics have been allowed back onto the European market.

1. CSM. Fenfluramine (Ponderax Pacaps), dexfenfluramine (Adifax) and pulmonary hypertension. *Current Problems 34* 1992. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService= GET_FILE&dDocName=CON2024452&RevisionSelectionMethod=LatestReleased (accessed 11/08/08)
2. CSM/MCA. Anorectic agents: risks and benefits. *Current Problems* 1997; **23:** 1–2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015623&RevisionSelectionMethod=LatestReleased (accessed 11/08/08)
3. Abenhaim L, *et al.* Appetite-suppressant drugs and the risk of primary pulmonary hypertension. *N Engl J Med* 1996; **335:** 609–16.
4. Douglas JG, *et al.* Pulmonary hypertension and fenfluramine. *BMJ* 1981; **283:** 881–3.
5. McMurray J, *et al.* Irreversible pulmonary hypertension after treatment with fenfluramine. *BMJ* 1986; **292:** 239–40.
6. Fotiadis I, *et al.* Fenfluramine-induced irreversible pulmonary hypertension. *Postgrad Med J* 1991; **67:** 776–7.
7. Atanassoff PG, *et al.* Pulmonary hypertension and dexfenfluramine. *Lancet* 1992; **339:** 436.
8. Cacoub P, *et al.* Pulmonary hypertension and dexfenfluramine. *Eur J Clin Pharmacol* 1995; **48:** 81–3.
9. Roche N, *et al.* Pulmonary hypertension and dexfenfluramine. *Lancet* 1992; **339:** 436–7.
10. Thomas SHL, *et al.* Appetite suppressants and primary pulmonary hypertension in the United Kingdom. *Br Heart J* 1995; **74:** 600–63.
11. Connolly HM, *et al.* Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med* 1997; **337:** 581–8. Correction. *ibid.*; 1783.
12. CSM/MCA. Anorectic agents and valvular heart disease. *Current Problems* 1997; **23:** 12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023240&RevisionSelectionMethod=LatestReleased (accessed 23/05/06)
13. CSM/MCA. Fenfluramine and dexfenfluramine withdrawn. *Current Problems* 1997; **23:** 13–14. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023238&RevisionSelectionMethod=LatestReleased (accessed 11/08/08)
14. Anonymous. Cardiac valvulopathy associated with exposure to fenfluramine or dexfenfluramine: US Department of Health and Human Services interim public health recommendations, November 1997. *MMWR* 1997; **46:** 1061–6.
15. Khan MA, *et al.* The prevalence of cardiac valvular insufficiency assessed by transthoracic echocardiography in obese patients treated with appetite-suppressant drugs. *N Engl J Med* 1998; **339:** 713–18.
16. Jick H, *et al.* A population-based study of appetite-suppressant drugs and the risk of cardiac-valve regurgitation. *N Engl J Med* 1998; **339:** 719–24.
17. Weissman NJ, *et al.* An assessment of heart-valve abnormalities in obese patients taking dexfenfluramine, sustained-release dexfenfluramine, or placebo. *N Engl J Med* 1998; **339:** 725–32.
18. Gardin JM, *et al.* Valvular abnormalities and cardiovascular status following exposure to dexfenfluramine or phentermine/fenfluramine. *JAMA* 2000; **283:** 1703–9.
19. Lepor NE, *et al.* Dose and duration of fenfluramine-phentermine therapy impacts the risk of significant valvular heart disease. *Am J Cardiol* 2000; **86:** 107–10.
20. Jollis JG, *et al.* Fenfluramine and phentermine and cardiovascular findings: effect of treatment duration on prevalence of valve abnormalities. *Circulation* 2000; **101:** 2071–7.
21. Devereux RB. Appetite suppressants and valvular heart disease. *N Engl J Med* 1998; **339:** 765–6.

Effects on the liver. The UK MHRA had warned[1] that there had been cases of hepatotoxicity associated with adulteration of traditional Chinese slimming medicines with fenfluramine and/or nitrosofenfluramine. Nitrosofenfluramine was known to be hepatotoxic.

1. Medicines and Healthcare products Regulatory Agency (MHRA). Shubao slimming capsules containing fenfluramine and nitrosofenfluramine (issued 28th April, 2004). Available at: http://www.mhra.gov.uk/home/groups/es-herbal/documents/websiteresources/con009291.pdf (accessed 11/08/08)

Porphyria. Fenfluramine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Uses and Administration

Fenfluramine is an indirect-acting sympathomimetic related to amfetamine, but at standard doses it usually depresses rather than stimulates the CNS. It appears to stimulate the release of serotonin and selectively inhibits its reuptake resulting in increased CNS serotonin concentrations. It may also increase glucose utilisation and lower blood-glucose concentrations.

Fenfluramine was formerly given by mouth as the hydrochloride in the treatment of obesity (p.2149) but was generally withdrawn worldwide after reports of valvular heart defects.

Preparations

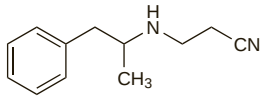
Proprietary Preparations (details are given in Part 3)
Chile: Megaval†.

Fenproporex Hydrochloride *(rINNM)* ⊗

N-2-Cyanoethylamphetamine Hydrochloride; Fenproporex, Chlorhydrate de; Fenproporexi Hydrochloridum; Hidrocloruro de fenproporex. (±)-3-(α-Methylphenethylamino)propionitrile hydrochloride.

Фенпропорекса Гидрохлорид

$C_{12}H_{16}N_2$,HCl = 224.7.
CAS — 15686-61-0 (fenproporex); 18305-29-8 (fenproporex hydrochloride).



(fenproporex)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of fenproporex:
Pasexes.

Profile

Fenproporex is a central stimulant and indirect-acting sympathomimetic with actions similar to those of dexamfetamine (p.2153). After oral doses it is reported to be metabolised to amfetamine. Fenproporex has been given as the hydrochloride, the diphenylacetate, and as a resinate.

Fenproporex hydrochloride has been used as an anorectic in the treatment of obesity (p.2149) although the use of stimulants in this way is no longer recommended. Regulatory authorities in the EU have called for the withdrawal of all anorectics from the market (see under Effects on the Cardiovascular System in Fenfluramine, p.2156).

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Desobesi-M; Lipomax†; ***Chile:*** Salcal; Sinapet†; ***Mex.:*** Feprorex; Ifa-Diety.

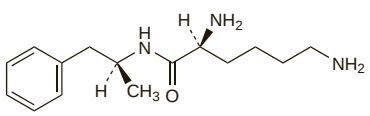
Multi-ingredient: ***Arg.:*** Tratobes; ***Mex.:*** Esbelcaps.

Lisdexamfetamine Mesilate *(rINNM)* ⊗

Lisdexamfetamine Dimesylate *(USAN)*; Lisdexamfétamine, Mésilate de; Lisdexamfetamini Mesilas; Mesilato de lisdexanfetamina; NRP-104. (2*S*)-2,6-Diamino-*N*-[(1*S*)-1-methyl-2-phenylethyl]hexanamide dimethanesulfonate.

Лисдексамфетамина Мезилат

$C_{15}H_{25}N_3O$,$(CH_4O_3S)_2$ = 455.6.
CAS — 608137-32-2 (lisdexamfetamine); 608137-33-3 (lisdexamfetamine mesilate).



(lisdexamfetamine)

Profile

Lisdexamfetamine is a prodrug of dexamfetamine (p.2153). It is used as a central stimulant in the treatment of attention deficit hyperactivity disorders (p.2148).

Lisdexamfetamine is given orally as the mesilate and doses are expressed in terms of this salt. For adults, and children between 6 and 12 years of age, the starting dose is 30 mg once daily in the morning, increased if necessary in increments of 10 or 20 mg daily at approximately weekly intervals, up to a total maximum dose of 70 mg daily. If therapy is continued for longer than 4 weeks, use of lisdexamfetamine should be periodically stopped to evaluate the necessity for continued administration.

◊ References.

1. Blick SK, Keating GM. Lisdexamfetamine. *Paediatr Drugs* 2007; **9:** 129–35.
2. Biederman J, *et al*. Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: a phase III, multicenter, randomized, double-blind, forced-dose, parallel-group study. *Clin Ther* 2007; **29:** 450–63.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Vyvanse.

Lobelia

Indian Tobacco.

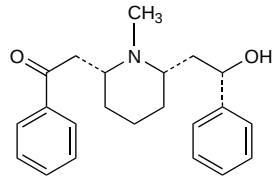
Description. Lobelia consists of the dried aerial parts of *Lobelia inflata* (Lobeliaceae). Lobeline is the main alkaloidal constituent.

Lobeline Hydrochloride *(BANM, rINNM)* ⊗

Alpha-lobeline Hydrochloride; Hidrocloruro de lobelina; Lobeliinihydrokloridi; Lobéline, chlorhydrate de; Lobelin-hidroklorid; Lobelin-hydrochlorid; Lobelinhydroklorid; Lobelini hydrochloridum; Lobelino hidrochloridas. 2-[6-(β-Hydroxyphenethyl)-1-methyl-2-piperidyl]acetophenone hydrochloride.

Лобелина Гидрохлорид

$C_{22}H_{27}NO_2$,HCl = 373.9.
CAS — 90-69-7 (lobeline); 134-63-4 (lobeline hydrochloride).



(lobeline)

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).
Ph. Eur. 6.2 (Lobeline Hydrochloride). A white or almost white microcrystalline powder. Sparingly soluble in water; freely soluble in alcohol; soluble in dichloromethane. A 1% solution in water has a pH of 4.6 to 6.4. Protect from light.

Lobeline Sulfate *(rINNM)* ⊗

Lobéline, Sulfate de; Lobeline Sulphate *(BANM)*; Lobelini Sulfas; Sulfato de lobelina.

Лобелина Сульфат

$(C_{22}H_{27}NO_2)_2$,H_2SO_4 = 773.0.
CAS — 134-64-5.

Adverse Effects

Adverse effects of lobelia and lobeline include nausea and vomiting, coughing, tremor, and dizziness. Symptoms of overdosage include profuse diaphoresis, paresis, tachycardia, hypothermia, hypotension, and coma; fatalities have occurred.

Uses and Administration

Lobelia is the dried aerial parts of *Lobelia inflata* (Lobeliaceae). Lobeline is the main alkaloidal constituent and has peripheral and central effects similar to those of nicotine (p.2352).

Lobelia has been used mainly in preparations aimed at relieving respiratory-tract disorders. Lobeline has been given by mouth as the hydrochloride or sulfate as a smoking deterrent (see Smoking Cessation, p.2354). Lobelia has been used similarly given either orally or incorporated into herbal cigarettes.

Smoking cessation. Reviews of smoking cessation therapy generally consider lobeline to have little benefit compared with placebo.[1-3]

1. Nunn-Thompson CL, Simon PA. Pharmacotherapy for smoking cessation. *Clin Pharm* 1989; **8:** 710–20.
2. Gourlay SG, McNeil JJ. Antismoking products. *Med J Aust* 1990; **153:** 699–707.
3. Stead LF, Hughes JR. Lobeline for smoking cessation. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1997 (accessed 16/05/05).

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Cig-Ridettes†; ***Canad.:*** Butt-Out; ***Spain:*** Smokeless.

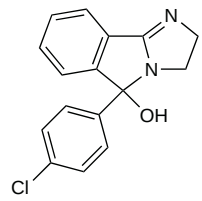
Multi-ingredient: ***Austral.:*** Potassium Iodide and Stramonium Compound†; ***Belg.:*** Kamfeine†; ***Braz.:*** Asmatiron†; Bronquidex; Brontoss; Expectobron†; Expectol†; Iodeto de Potassio†; Iol†; Iolin†; MM Expectorante; Pulmoforte†; Sedatux†; Xarope Peitoral de Ameixa Composto†; ***Chile:*** Paltomiel Plus; Pulmagol; Ramistos; ***Spain:*** Pazbronquial; ***UK:*** Antibron; Asthma & Catarrh Relief; Balm of Gilead; Chest Mixture; Herbelix; Horehound and Aniseed Cough Mixture; Modern Herbals Cold & Congestion; Vegetable Cough Remover; ***Venez.:*** Novacodin.

Mazindol *(BAN, USAN, rINN)* ⊗

42-548; AN-448; Matsindoli; Mazindolum; SaH-42548. 5-(4-Chlorophenyl)-2,5-dihydro-3*H*-imidazo[2,1-*a*]isoindol-5-ol.

Мазиндол

$C_{16}H_{13}ClN_2O$ = 284.7.
CAS — 22232-71-9.
ATC — A08AA05.
ATC Vet — QA08AA05.



Pharmacopoeias. In *US*.
USP 31 (Mazindol). A white to off-white crystalline powder, having not more than a faint odour. Insoluble in water; slightly soluble in chloroform and in methyl alcohol. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Dexamfetamine Sulfate, p.2153.

Effects on the testes. Testicular pain developed in 8 men after taking mazindol.[1]

1. McEwen J, Meyboom RHB. Testicular pain caused by mazindol. *BMJ* 1983; **287:** 1763–4.

Interactions

As for Dexamfetamine Sulfate, p.2153.

Lithium. For a report of mazindol interacting with lithium to cause lithium toxicity, see Central Stimulants, p.405.

Pharmacokinetics

Mazindol is readily absorbed from the gastrointestinal tract and is excreted in the urine, partly unchanged and partly as metabolites.

Uses and Administration

Mazindol is a central stimulant with actions similar to those of dexamfetamine (p.2154), although structurally the two compounds are unrelated. It appears to inhibit reuptake of dopamine and noradrenaline. It has been used as an anorectic, given orally in the treatment of obesity (p.2149), although stimulants are no longer recommended for this indication. Regulatory authorities in the EU have called for the withdrawal of all anorectics from the market (see under Effects on the Cardiovascular System in Fenfluramine, p.2156).

Mazindol has been investigated in the treatment of Duchenne muscular dystrophy.

Narcolepsy. Mazindol has been reported[1-4] to be beneficial in patients with narcolepsy and associated cataplexy (p.2148). A wide range of doses has been used: 3 to 8 mg daily in one study,[1] 1 mg weekly to 16 mg daily in another;[3] children have been given 1 to 2 mg daily.[4]

1. Parkes JD, Schachter M. Mazindol in the treatment of narcolepsy. *Acta Neurol Scand* 1979; **60:** 250–4.
2. Shindler J, *et al*. Amphetamine, mazindol, and fencamfamin in narcolepsy. *BMJ* 1985; **290:** 1167–70.
3. Alvarez B, *et al*. Mazindol in long-term treatment of narcolepsy. *Lancet* 1991; **337:** 1293–4.
4. Allsopp MR, Zaiwalla Z. Narcolepsy. *Arch Dis Child* 1992; **67:** 302–6.

Preparations

USP 31: Mazindol Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Afilan; Dimagrir; Dimagrir Triac†; Fagolip Plus; Samonter; ***Braz.:*** Absten S; Fagolipo; ***Canad.:*** Sanorex†; ***Hong Kong:*** Qualizindol; ***Hung.:*** Teronac†; ***Indon.:*** Teronac; ***Mex.:*** Diestet; Ifa Lose; Ilezol; Liofindol†; Obendol; Sanorex†; Solucaps; ***Singapore:*** Teronac; ***Switz.:*** Teronac†.

Multi-ingredient: ***Arg.:*** Maxitratobes; ***Braz.:*** Dobesix†; Moderine.