Preparations

USP 31: Diethylpropion Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Tenuate; ***Braz.:*** Dualid S; Hipofagin S; Inibex S; ***Canad.:*** Tenuate; ***Chile:*** Sacin; ***Denm.:*** Regenon; ***Ger.:*** Regenon; ***Hong Kong:*** Atractil; Prothin; ***Mex.:*** Ifa Norex; Neobes; ***NZ:*** Tenuate Dospan; ***S.Afr.:*** Tenuate Dospan; ***Switz.:*** Prefamone†; Regenon; ***Thai.:*** Atractil; Dietil; Regenon†; ***USA:*** Tenuate†.

Multi-ingredient: ***Arg.:*** Tratobes; ***Indon.:*** Apisate.

Dimefline Hydrochloride *(BANM, USAN, rINNM)*

Dimépline, Chlorhydrate de; Dimeflini Hydrochloridum; DW-62; Hidrocloruro de dimeflina; NSC-114650; Rec-7/0267. 8-Dimethylaminomethyl-7-methoxy-3-methyl-2-phenylchromen-4-one hydrochloride.

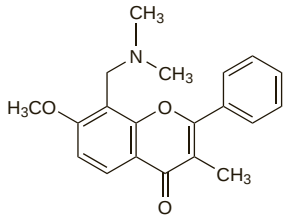
Димефлина Гидрохлорид

$C_{20}H_{21}NO_3,HCl$ = 359.8.

CAS — 1165-48-6 (dimefline); 2740-04-7 (dimefline hydrochloride).

ATC — R07AB08.

ATC Vet — QR07AB08.



(dimefline)

Profile

Dimefline has actions similar to those of doxapram (below) and has been used orally as the hydrochloride and parenterally as a respiratory stimulant.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Remeflin.

Doxapram Hydrochloride *(BANM, USAN, rINNM)*

AHR-619; Doksapraamihydrokloridi; Doksapram Hidroklorür; Doksapramo hidrochloridas; Doxapram, chlorhydrate de; Doxaprám-hidroklorid; Doxapram-hydrochlorid monohydrát; Doxapramhydroklorid; Doxaprami hydrochloridum; Doxaprami Hydrochloridum Monohydricum; Hidrocloruro de doxapram. 1-Ethyl-4-(2-morpholinoethyl)-3,3-diphenyl-2-pyrrolidinone hydrochloride monohydrate.

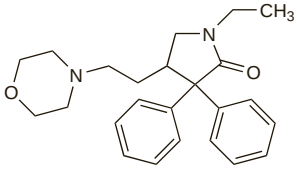
Доксапрама Гидрохлорид

$C_{24}H_{30}N_2O_2,HCl,H_2O$ = 433.0.

CAS — 309-29-5 (doxapram); 113-07-5 (anhydrous doxapram hydrochloride); 7081-53-0 (doxapram hydrochloride monohydrate).

ATC — R07AB01.

ATC Vet — QR07AB01.



(doxapram)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Doxapram Hydrochloride). A white or almost white crystalline powder. Sparingly soluble in water, in alcohol and in dichloromethane. A 1% solution in water has a pH of 3.5 to 5.0.

USP 31 (Doxapram Hydrochloride). A white to off-white, odourless, crystalline powder. Soluble 1 in 50 of water; soluble in chloroform; sparingly soluble in alcohol; practically insoluble in ether. pH of a 1% solution in water is between 3.5 and 5.0. Store in airtight containers.

Incompatibility. The commercial injection of doxapram hydrochloride is reported to be incompatible with alkaline solutions such as aminophylline, furosemide, or thiopental sodium.

Adverse Effects

As with other respiratory stimulants, there is a risk that doxapram will produce adverse effects due to general stimulation of the CNS.

Doxapram may produce dyspnoea and other respiratory problems such as coughing, bronchospasm, laryngospasm, hiccup, hyperventilation, and rebound hypoventilation. Muscle involvement may range from fasciculations to spasticity. Convulsions, headache, dizziness, hyperactivity, and confusion can occur as can sweating, flushing, fever or a sensation of warmth, particularly in the genital or perineal regions. Hallucinations may occur rarely. There may be nausea, vomiting, diarrhoea, and problems with urination. Cardiovascular effects include hypertension and various arrhythmias although sudden hypotension may also occur.

Thrombophlebitis may follow extravasation of doxapram during injection.

Effects on the heart. Second-degree AV block caused by prolongation of the QT interval has been associated with doxapram use in 3 neonates.[1] Although the preparation used contained benzyl alcohol this was not considered to play a role in the adverse effect. A prospective study[2] involving 40 premature infants given doxapram for apnoea of prematurity also found QT interval lengthening at 48 and 72 hours of treatment, even when the drug plasma concentrations were kept within therapeutic ranges. In 6 infants, the QT interval lengthened to a degree considered to be life-threatening. There was also a trend towards moderate increases in blood pressure. The authors recommended heart monitoring when doxapram was given to premature infants.

1. De Villiers GS, *et al.* Second-degree atrioventricular heart block after doxapram administration. *J Pediatr* 1998; **133:** 149–50.
2. Maillard C, *et al.* QT interval lengthening in premature infants treated with doxapram. *Clin Pharmacol Ther* 2001; **70:** 540–5.

Effects on the liver. Acute hepatic necrosis in a patient was attributed to a 24-hour infusion of doxapram.[1] Liver function tests returned to normal over 3 weeks.

1. Fancourt GJ, *et al*. Hepatic necrosis with doxapram hydrochloride. *Postgrad Med J* 1985; **61:** 833–5.

Precautions

Doxapram should not be given to patients with epilepsy or other convulsive disorders, cerebral oedema, cerebrovascular accident, head injury, acute severe asthma, physical obstruction of the airway, severe hypertension, ischaemic heart disease, hyperthyroidism, or phaeochromocytoma. Caution is also advisable if doxapram is used in patients with less severe degrees of hypertension or impaired cardiac reserve. It should be given with care to patients with significant hepatic or renal impairment.

Patients should be carefully supervised during use of doxapram; special attention should be paid to changes in blood gas measurements. Doxapram should be given with oxygen in severe irreversible airways obstruction or severely decreased lung compliance because of the increased work of breathing. A $beta_2$ agonist should also be given to patients with bronchoconstriction.

Interactions

Additive pressor effects may occur when doxapram is used with sympathomimetics or MAOIs. Cardiac arrhythmias may occur when doxapram is given with anaesthetics known to sensitise the myocardium, such as halothane, enflurane, and isoflurane; it has been recommended that doxapram should not be given for at least 10 minutes after stopping these anaesthetics. Doxapram may temporarily mask the residual effects of neuromuscular blockers. The manufacturers have reported that there may be an interaction between doxapram and aminophylline manifested by agitation and increased skeletal muscle activity.

Pharmacokinetics

After intravenous doses doxapram is rapidly distributed into the tissues. Onset of respiratory stimulation usually occurs in 20 to 40 seconds, with a peak effect achieved in 1 to 2 minutes. Duration of effect following a single dose varies from 5 to 12 minutes. Doxapram is extensively metabolised in the liver. The major route of excretion of metabolites and a small amount of unchanged drug is thought to be via bile to the faeces. It is also excreted in the urine.

Some absorption occurs when doxapram is given orally.

◊ References.

1. Robson RH, Prescott LF. A pharmacokinetic study of doxapram in patients and volunteers. *Br J Clin Pharmacol* 1978; **7:** 81–7.
2. Baker JR, *et al*. Normal pharmacokinetics of doxapram in a patient with renal failure and hypothyroidism. *Br J Clin Pharmacol* 1981; **11:** 305–6.

Uses and Administration

Doxapram hydrochloride is a central and respiratory stimulant with a brief duration of action. It acts by stimulation of peripheral chemoreceptors and central respiratory centres; at higher doses, it stimulates other parts of the brain and spinal cord. Doxapram has a pressor action and may also increase catecholamine release.

Doxapram has limited uses in the treatment of acute respiratory failure (for example where this is superimposed on chronic obstructive pulmonary disease), and of postoperative respiratory depression (see Respiratory Failure under Oxygen, p.1691).

Doxapram hydrochloride may be infused at a rate of 1.5 to 4 mg/minute in the treatment of acute respiratory failure.

For postoperative respiratory depression it has been given in a dose of 0.5 to 1.5 mg/kg by intravenous injection over a period of at least 30 seconds. This dose may be repeated at hourly intervals. It may also be given by intravenous infusion, initially at a rate of 2 to 5 mg/minute and then reduced, according to response, to 1 to 3 mg/minute; a recommended maximum total dosage is 4 mg/kg.

Doxapram hydrochloride has also been used to treat respiratory and CNS depression following drug overdose but its use for this indication is no longer recommended.

Chronic obstructive pulmonary disease. Respiratory stimulants such as doxapram have a limited and short-term role in hypercapnic respiratory failure in patients with chronic obstructive pulmonary disease (p.1112). Benefit has been reported in such patients in whom doxapram was used as an alternative to intubation.[1,2] However, a systematic review suggested that despite short-term improvements in blood-gas exchange with doxapram, techniques such as non-invasive ventilation might be more effective.[3]

1. Hirshberg AJ, *et al.* Use of doxapram hydrochloride injection as an alternative to intubation to treat chronic obstructive pulmonary disease patients with hypercapnia. *Ann Emerg Med* 1994; **24:** 701–3.
2. Kerr HD. Doxapram in hypercapnic chronic obstructive pulmonary disease with respiratory failure. *J Emerg Med* 1997; **15:** 513–15.
3. Greenstone M, Lasserson TJ. Doxapram for ventilatory failure due to exacerbations of chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 16/05/05).

Neonatal apnoea. Doxapram is effective in neonatal apnoea (p.1118) and may be considered as an alternative, or in addition, to xanthines in infants with apnoea that does not respond to xanthine therapy alone. However, it is less convenient to use as it must be given by continuous intravenous infusion and blood pressure must be monitored (although it has also been suggested that the oral route may be used after the initial intravenous dose—see *BNFC* doses below). Additionally, some preparations may contain benzyl alcohol as a preservative making them unsuitable for use in neonates. It has been used in intravenous doses of 2.5 mg/kg per hour.[1-3] Adverse CNS effects have been reported.[3] Lower doses of 0.25 or 1.5 mg/kg per hour have been shown to be effective.[4,5] However, use of low doses of 500 micrograms/kg per hour in very low birth-weight premature infants produced higher than expected plasma-doxapram concentrations and a greater increase in systolic blood pressure compared with controls.[6] A systematic review[7] concluded that the place of doxapram in the management of neonatal apnoea had not yet been properly established.

Although unlicensed, the *BNFC* suggests giving neonates doxapram hydrochloride intravenously in an initial dose of 2.5 mg/kg over 5 to 10 minutes followed by 300 micrograms/kg per hour by continuous infusion, adjusted according to response, to a maximum dose of 1.5 mg/kg per hour; alternatively, 6 mg/kg may be given orally 4 times daily after the initial intravenous dose.

1. Sagi E, *et al.* Idiopathic apnoea of prematurity treated with doxapram and aminophylline. *Arch Dis Child* 1984; **59:** 281–3.
2. Eyal F, *et al.* Aminophylline versus doxapram in idiopathic apnea of prematurity: a double-blind controlled study. *Pediatrics* 1985; **75:** 709–13.
3. Dear PRF, Wheeler D. Doxapram and neonatal apnoea. *Arch Dis Child* 1984; **59:** 903–4.
4. Bairam A, Vert P. Low-dose doxapram for apnoea of prematurity. *Lancet* 1986; **i:** 793–4.
5. Peliowski A, Finer NN. A blinded, randomized, placebo-controlled trial to compare theophylline and doxapram for the treatment of apnea of prematurity. *J Pediatr* 1990; **116:** 648–53.
6. Huon C, *et al.* Low-dose doxapram for treatment of apnoea following early weaning in very low birthweight infants: a randomized, double-blind study. *Acta Paediatr* 1998; **87:** 1180–4.
7. Henderson-Smart DJ, Steer PA. Doxapram treatment for apnea in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 23/10/07).

Respiratory depression. References to the use of doxapram in postoperative respiratory depression.

1. Jansen JE, *et al.* Effect of doxapram on postoperative pulmonary complications after upper abdominal surgery in high-risk patients. *Lancet* 1990; **335:** 936–8.
2. Thangathurai D, *et al.* Doxapram for respiratory depression after epidural morphine. *Anaesthesia* 1990; **45:** 64–5.
3. Sajjad T. Comparison of the effects of doxapram or carbon dioxide on ventilatory frequency and tidal volume during induction of anaesthesia with propofol, *Br J Anaesth* 1994; **73:** 266P.
4. Alexander-Williams M, *et al.* Doxapram and the prevention of postoperative hypoxaemia. *Br J Anaesth* 1995; **75:** 233P.

Shivering. Doxapram is one of a number of drugs that have been used in postoperative shivering, see p.1779.

References.

1. Sarma V, Fry ENS. Doxapram after general anaesthesia: its role in stopping shivering during recovery. *Anaesthesia* 1991; **46:** 460–1.
2. Singh P, *et al.* Double-blind comparison between doxapram and pethidine in the treatment of postanaesthetic shivering. *Br J Anaesth* 1993; **71:** 685–8.
3. Wrench IJ, *et al.* The minimum effective doses of pethidine and doxapram in the treatment of post-anaesthetic shivering. *Anaesthesia* 1997; **52:** 32–6.

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.

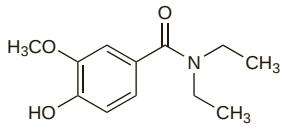
Этамиван

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

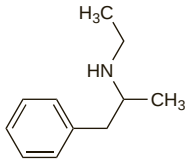
Этиламфетамина Гидрохлорид

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

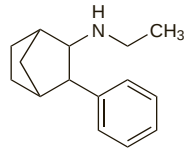
Фенкамфамина Гидрохлорид

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

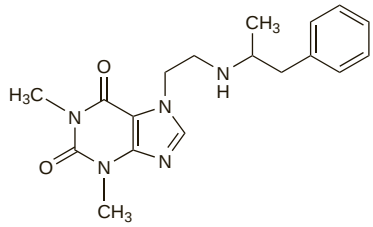
Фенетиллина Гидрохлорид

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

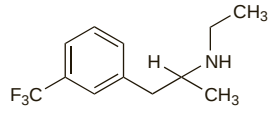
Фенфлюрамина Гидрохлорид

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