

of a link between UK products containing phenylpropranolamine and haemorrhagic stroke was weak (phenylpropranolamine is not licensed as an appetite suppressant in the UK and the maximum recommended dose of 100 mg daily was lower than the 150 mg daily recommended in the USA). It was therefore suggested by UK commentators that use of licensed doses, with appropriate precautions, posed no additional risk.² However, subsequently, UK preparations containing phenylpropranolamine have either been reformulated (mainly with pseudoephedrine) or withdrawn by the manufacturers.

1. Lake CR, et al. Adverse drug effects attributed to phenylpropranolamine: a review of 142 case reports. *Am J Med* 1990; **89**: 195–208.
2. Moffatt T, et al. Phenylpropranolamine: putting the record straight. *Pharm J* 2000; **265**: 817.
3. Kernan WN, et al. Phenylpropranolamine and the risk of hemorrhagic stroke. *N Engl J Med* 2000; **343**: 1826–32.
4. Ernst ME, Hartz A. Phenylpropranolamine and hemorrhagic stroke. *N Engl J Med* 2001; **344**: 1094.
5. Wolowich WR, et al. Phenylpropranolamine and hemorrhagic stroke. *N Engl J Med* 2001; **344**: 1094–5.
6. Stier BG, Hennekens CH. Phenylpropranolamine and hemorrhagic stroke in the Hemorrhagic Stroke Project: a reappraisal in the context of science, the Food and Drug Administration, and the law. *Ann Epidemiol* 2006; **16**: 49–52.
7. Committee on Safety of Medicines/Medicines Control Agency. Phenylpropranolamine and haemorrhagic stroke. *Current Problems* 2001; **27**: 5–6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007458&RevisionSelectionMethod=LatestReleased (accessed 04/01/07)

Interactions

As for Sympathomimetics, p.1407. For a comment that drug interactions were likely to have been involved in many adverse events associated with phenylpropranolamine see under Adverse Effects and Precautions, above. Due to its indirect action, hypertensive crisis is a particular risk in patients receiving MAOIs.

Amantadine. Severe psychosis has been reported¹ in a woman taking amantadine with phenylpropranolamine. In another report,² a 39-year-old man had intense and recurrent *déjà vu* experiences after taking amantadine with phenylpropranolamine for viral influenza. The effect ceased when he stopped both drugs. The authors suggested that his symptoms were due to increased dopamine activity caused by the combination.

1. Stroe AE, et al. Psychotic episode related to phenylpropranolamine and amantadine in a healthy female. *Gen Hosp Psychiatry* 1995; **17**: 457–8.
2. Taiminen T, Jääskeläinen SK. Intense and recurrent *déjà vu* experiences related to amantadine and phenylpropranolamine in a healthy male. *J Clin Neurosci* 2001; **8**: 460–2.

Antipsychotics. A 27-year-old woman with schizophrenia and T-wave abnormality of the heart, who had responded to *thioridazine* 100 mg daily with procyclidine 2.5 mg twice daily, died from ventricular fibrillation within 2 hours of taking a single dose of a preparation reported to contain chlorphenamine maleate 4 mg with phenylpropranolamine hydrochloride 50 mg (*Contac C*), concurrently with thioridazine.¹

1. Chouinard G, et al. Death attributed to ventricular arrhythmia induced by thioridazine in combination with a single *Contac C* capsule. *Can Med Assoc J* 1978; **119**: 729–31.

Antivirals. A patient taking an over-the-counter nasal decongestant preparation containing phenylpropranolamine and clemastine as well as a triple-drug HIV prophylactic regimen, had a hypertensive crisis 3 days after *stavudine* was substituted for *zidovudine*;¹ the other antivirals in the regimen were *indinavir* and *lamivudine*.

1. Khurana V, et al. Hypertensive crisis secondary to phenylpropranolamine interacting with triple-drug therapy for HIV prophylaxis. *Am J Med* 1999; **106**: 118–19.

Bromocriptine. For a report of hypertension and life-threatening complications after use of phenylpropranolamine with bromocriptine, see Sympathomimetics, p.800.

NSAIDs. A 27-year-old woman who had been taking d-phenylpropranolamine [sic] 85 mg daily for some months, experienced severe hypertension when she also took *indometacin* 25 mg. It was considered that the inhibition of prostaglandin synthesis by indometacin might have caused enhancement of the sympathomimetic effect of phenylpropranolamine.¹

1. Lee KY, et al. Severe hypertension after ingestion of an appetite suppressant (phenylpropranolamine) with indomethacin. *Lancet* 1979; **i**: 1110–11.

Pharmacokinetics

Phenylpropranolamine is readily and completely absorbed from the gastrointestinal tract, peak plasma concentrations being achieved about 1 or 2 hours after oral doses. It undergoes some metabolism in the liver, to an active hydroxylated metabolite, but up to 80 to

90% of a dose is excreted unchanged in the urine within 24 hours. The half-life has been reported to be about 3 to 5 hours.

References

1. Simons FER, et al. Pharmacokinetics of the orally administered decongestants pseudoephedrine and phenylpropranolamine in children. *J Pediatr* 1996; **129**: 729–34.
2. Chester N, et al. Elimination of ephedrine in urine following multiple dosing: the consequences for athletes, in relation to doping control. *Br J Clin Pharmacol* 2004; **57**: 62–7.

Uses and Administration

Phenylpropranolamine is a mainly indirect-acting sympathomimetic (p.1408) with an action similar to that of ephedrine (p.1559) but less active as a CNS stimulant.

Phenylpropranolamine has been given orally as the hydrochloride for the symptomatic treatment of **nasal congestion** (p.1548). It has frequently been used in combination preparations for the relief of cough and cold symptoms.

In the management of nasal congestion, phenylpropranolamine hydrochloride has been given in oral doses of up to 50 mg twice daily as modified-release preparations.

Other uses of phenylpropranolamine have included the control of urinary incontinence in some patients (see p.2180). It has also been given in the management of some forms of priapism (see under Metaraminol, p.1333). Phenylpropranolamine has been used to suppress appetite in the management of obesity (p.2149) but the use of stimulants is no longer recommended.

Phenylpropranolamine polistirex (a phenylpropranolamine and sulfonated diethylenbenzene-ethylenbenzene copolymer complex) has also been used, as have phenylpropranolamine bitartrate, phenylpropranolamine maleate, and phenylpropranolamine sulfate.

Preparations

USP 31: Chlorpheniramine Maleate and Phenylpropranolamine Hydrochloride Extended-release Capsules; Chlorpheniramine Maleate and Phenylpropranolamine Hydrochloride Extended-release Tablets; Phenylpropranolamine Hydrochloride Capsules; Phenylpropranolamine Hydrochloride Extended-release Capsules; Phenylpropranolamine Hydrochloride Extended-release Tablets; Phenylpropranolamine Hydrochloride Oral Solution; Phenylpropranolamine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Fin.: Rinexin; **Ger.:** Boxogetten S; Recatal mono; **Norw.:** Rinexin; **Philipp.:** Decolgen; Desotap; Disudrin; Naldec; Nasadec; Nasaphen; Nasatera P; Neo-Coldan; **S.Afr.:** Restaslim†; **Swed.:** Rinexin; **Switz.:** Kontexin†; Merex†; Slim Caps.

Multi-ingredient: numerous preparations are listed in Part 3.

Pholcodine (BAN, rINN)

Folcodina; Folkodiini; Folkodin; Folkodin monohydrát; Folkodinas; Pholcodinum; Pholcodinum Monohydricum. 3-O-(2-Morpholinoethyl)morphine monohydrate.

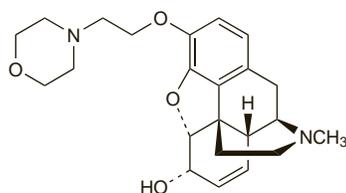
ФОЛКОДИН

$C_{23}H_{30}N_2O_4 \cdot H_2O = 416.5$.

CAS — 509-67-1 (anhydrous pholcodine).

ATC — R05DA08.

ATC Vet — QR05DA08.



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

Ph. Eur. 6.2 (Pholcodine). A white or almost white crystalline powder or colourless crystals. Sparingly soluble in water; freely soluble in alcohol and in acetone; dissolves in dilute mineral acids.

Adverse Effects and Precautions

As for Dextromethorphan, p.1555. Constipation, drowsiness, and skin rashes have been reported occasionally.

Interactions

Use of pholcodine with alcohol or other CNS depressants may increase the effects on the CNS.

Uses and Administration

Pholcodine is a centrally acting cough suppressant that has actions and uses similar to those of dextromethorphan (p.1556). It is given orally in a usual dose of 5 to 10 mg three or four times daily. For children's doses, see Administration in Children, below. The citrate has also been used. Pholcodine polistirex (a pholcodine and sulfonated diethylenbenzene-ethylenbenzene copolymer complex) has been used in modified-release preparations.

Administration in children. Although pholcodine is licensed for use in children, over-the-counter cough and cold preparations containing cough suppressants (including pholcodine) should be used with caution and generally avoided in those under 2 years of age (see p.1547). The following oral doses of pholcodine are given in the *BNFC* for use in children:

- 2 to 5 years: 2 mg three times daily
- 5 to 12 years: 2 to 5 mg three or four times daily

Preparations

BP 2008: Pholcodine Linctus; Strong Pholcodine Linctus.

Proprietary Preparations (details are given in Part 3)

Austral.: Actified CC Dry†; Actuss†; Duro-Tuss; Logicin Cough Suppressant†; Nyal Plus† Dry Cough†; Ordov Dry Tickly Cough†; Pholtrate†; Tussinol; **Cz.:** Neocodinj; **Fin.:** Tuxi; **Fr.:** Biocalyptol; Broncorinol toux sèche†; Codotussyl Toux Seche; Dimetane; Humex; Pharmakod toux sèche; Respitene; Rhinathiol Toux Seche Pholcodine; Sirop des Vosges Toux Seche; **Hong Kong:** Duro-Tuss; Uni-Pholco; **Ind.:** Expulin Dry Cough; Pholcodex; Pholcolin; **Malaysia:** Dhacodine; Duro-Tuss; **Norw.:** Tuxi; **NZ:** Actified CC Dry†; Duro-Tuss; **S.Afr.:** Pholcolint; Pholtec; **Singapore:** Duro-Tuss; **Spain:** Trophires†; **UK:** Berylin Childrens Dry Coughs; Boots Dry Cough Syrup 1 Year Plus; Galenphol; Hill's Balsam Dry Cough; Pavacol-D; Tixilyx Daytime.

Multi-ingredient: **Austral.:** Chemists Own Kiddico; Demazin Cough & Cold; Diffiam Anti-inflammatory Lozenges with Cough Suppressant; Duro-Tuss Cough Lozenges; Duro-Tuss Decongestant; Duro-Tuss Dry Cough Plus Nasal Decongestant; Duro-Tuss Expectorant; Phensedyl†; Tixilyx Night-time; **Belg.:** Broncho-pectorals Pholcodine; Eucalyptine Pholcodine; Eucalyptine Pholcodine Le Brun†; Folex†; Norhitis; Pectorhiny†; Pholco-Merprine; **Cz.:** Biocalyptol S†; **Fr.:** Atoux; Broncalene; Clarix; Denoral†; Hexapneumine; Isomyrtine†; Polery; Trophires; **Hong Kong:** Biocalyptol†; Duro-Tuss Decongestant; Duro-Tuss Expectorant; Hexapneumine; Tripe P; **India:** Tixilyx; **Ind.:** Day Nurse; Expulin; Expulin Childrens Cough; **Malaysia:** Diffiam Anti-inflammatory Lozenges (with cough suppressant); Duro-Tuss Expectorant; Phensedyl Dry Cough; Promedy† Plus; Rhynacol; Russedyl Plus; Tixilyx†; **NZ:** Diffiam Cough; Duro-Tuss Cough; Duro-Tuss Expectorant; Duro-Tuss Lozenges; Phensedyl Dry Family Cough†; Tixilyx; **S.Afr.:** Contra-Coff; Docsed; Folcofen; Pholtec Linctus; Procof; Respinol Compound; Tixilyx; **Singapore:** 3P†; Duro-Tuss Cough Lozenges; Duro-Tuss Decongestant; Duro-Tuss Expectorant; **Spain:** Caltoson Balsamico; **Switz.:** Pecto-Baby; Phol-Tussil; Phol-Tuss; Tussiplex†; **UK:** Boots Nighttime Cough Syrup 1 Year Plus; Cough Nurse; Day & Night Nurse; Day Nurse; Expulin Childrens Cough†; Nirolex Day Cold & Flu; Nirolex Night Cold & Flu; Tixilyx Cough & Cold; Tixilyx Night-Time.

Pipazetate (BAN, rINN)

D-254; Pipazétate; Pipazetato; Pipazetato; Pipazetate (USAN); SKF-70230-A; SQ-15874. 2-(2-Piperidinoethoxy)ethyl pyrido[3,2-b][1,4]benzothiazine-10-carboxylate.

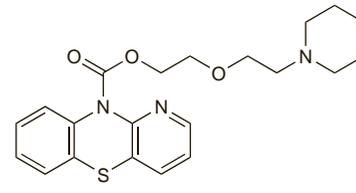
Пипазетат

$C_{21}H_{25}N_3O_3S = 399.5$.

CAS — 2167-85-3.

ATC — R05DB11.

ATC Vet — QR05DB11.



Pipazetate Hydrochloride (BANM, rINNM)

Hydrocloruro de pipazetato; Pipazétate, Chlorhydrate de; Pipazetati Hydrochloridum; Pipazetate Hydrochloride; Piperestazine Hydrochloride.

Пипазетата Гидрохлорид

$C_{21}H_{25}N_3O_3S \cdot HCl = 436.0$.

CAS — 6056-11-7.

ATC — R05DB11.

ATC Vet — QR05DB11.

Profile

Pipazetate hydrochloride is a centrally acting cough suppressant that also has some peripheral actions in non-productive cough (p.1547). It has been given by mouth and rectally.

Overdosage. A healthy 4-year-old child became somnolent and agitated, with convulsions, followed by coma, after swallowing an unknown number of tablets containing pipazetate; cardiac arrhythmias also developed.¹ Fatal toxicity has also been reported in children.^{2,3}

1. da Silva OA, Lopez M. Pipazetate—acute childhood poisoning. *Clin Toxicol* 1977; **11**: 455–8.
2. Bonavita V, et al. Accidental lethal pipazetate poisoning in a child. *Z Rechtsmed* 1982; **89**: 145–8.
3. Soto E, et al. Pipazetate lethality in a baby. *Vet Hum Toxicol* 1993; **35**: 41.

Preparations

Proprietary Preparations (details are given in Part 3)

Braz.: Selvigon; **Ital.:** Selvigon; **Mex.:** Selvigon; **Thai.:** Transpulmin†.

Poppy Capsule

Dormideiras; Fruit du Pavot; Fruto de adormidera; Mohnfrucht; Papaveris Capsula; Poppy Heads.

Маковая Коробочка

Pharmacopoeias. In *Chin.*

Profile

Poppy capsule consists of dried fruits of *Papaver somniferum* (Papaveraceae), collected before dehiscence has occurred, containing very small amounts of morphine with traces of other opium alkaloids. It is mildly sedative and has been used as a liquid extract or syrup in cough mixtures.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: **Belg.:** Sedemol; Sulfa-Sedemol; **Braz.:** Malvodon.

Prenoxdiazine Hydrochloride (rINN)

Hydrocloruro de prenoxidiazina; HK-256; Prenoxdiazin Hydrochloride; Prénoxidiazine, Chlorhydrate de; Prenoxdiazini Hydrochloridum. 3-(2,2-Diphenylethyl)-5-(2-piperidinoethyl)-1,2,4-oxadiazole hydrochloride.

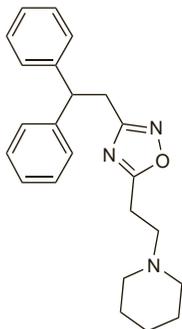
Преноксидиазина Гидрохлорид

$C_{23}H_{27}N_3O.HCl = 397.9$.

CAS — 47543-65-7 (prenoxdiazine); 37671-82-2 (prenoxdiazine hibenazate); 982-43-4 (prenoxdiazine hydrochloride).

ATC — R05DB18.

ATC Vet — QR05DB18.



(prenoxdiazine)

Profile

Prenoxdiazine hydrochloride is a peripherally acting cough suppressant for non-productive cough (p.1547) that has been given orally. Prenoxdiazine hibenazate has also been used.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Libexin†; **Hung.:** Libexin; Rhinathiol Tusso; **India:** Libexin; **Rus.:** Libexin (Либексин).

Multi-ingredient: **Ital.:** Broncofluid; Libexin Mucolitico.

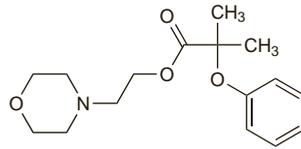
Promolate (rINN)

Morphethylbutyne; Promolato; Promolatum. 2-Morpholinoethyl 2-methyl-2-phenoxypropionate.

Промолат

$C_{16}H_{23}NO_4 = 293.4$.

CAS — 3615-74-5.

**Profile**

Promolate is a cough suppressant that has been given rectally to infants.

Preparations

Proprietary Preparations (details are given in Part 3)

Chile: Atusil.

Pseudoephedrine (BAN, rINN)

d-Ψ-Ephedrine; d-Isoephedrine; Pseudoefedriini; Pseudoefedrin; Pseudoefedrina; Pseudoéphédrine; Pseudoephedrinum. (+)-(1S,2S)-2-Methylamino-1-phenylpropan-1-ol.

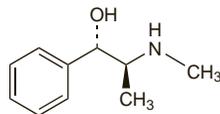
Псевдоэфедрин

$C_{10}H_{15}NO = 165.2$.

CAS — 90-82-4.

ATC — R01BA02.

ATC Vet — QR01BA02.



Description. Pseudoephedrine is an alkaloid obtained from *Ephedra* spp.

Pseudoephedrine Hydrochloride

(BANM, USAN, rINN)

Hydrocloruro de pseudoefedrina; Pseudoefedriinihydrokloridi; Pseudoefedrin-hydrochlorid; Pseudoefedrinhydroklorid; Pseudoefedrinohydrochlorid; Pseudoéphédrine, chlorhydrate de; Pseudoephedrini hydrochloridum; Psödoefedrin Hydroklörür; Pszeudoefedrin-hidroklorid.

Псевдоэфедрина Гидрохлорид

$C_{10}H_{15}NO.HCl = 201.7$.

CAS — 345-78-8.

ATC — R01BA02.

ATC Vet — QR01BA02.

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

Ph. Eur. 6.2 (Pseudoephedrine Hydrochloride). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water and in alcohol; sparingly soluble in dichloromethane. Protect from light.

USP 31 (Pseudoephedrine Hydrochloride). A fine, white to off-white crystalline powder, having a faint characteristic odour. Soluble 1 in 0.5 of water, 1 in 3.6 of alcohol, 1 in 91 of chloroform, and 1 in 7000 of ether. pH of a 5% solution in water is between 4.6 and 6.0. Store in airtight containers. Protect from light.

Pseudoephedrine Sulfate (USAN, rINN)

Pseudoéphédrine, Sulfate de; Pseudoephedrine Sulphate (BANM); Pseudoephedrini Sulfas; Sch-4855; Sulfate de pseudoefedrina.

Псевдоэфедрина Сульфат

$(C_{10}H_{15}NO)_2.H_2SO_4 = 428.5$.

CAS — 7460-12-0.

ATC — R01BA02.

ATC Vet — QR01BA02.

Pharmacopoeias. In *US*.

USP 31 (Pseudoephedrine Sulfate). Odourless, white crystals or crystalline powder. Freely soluble in alcohol. pH of a 5% solution in water is between 5.0 and 6.5. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for Ephedrine, p.1558. The commonest adverse effects of pseudoephedrine include tachycardia, anxiety,

restlessness, and insomnia; skin rashes and urinary retention have occasionally occurred. Hallucinations have been reported rarely, particularly in children.

◊ In response to reports in the USA of overdoses associated with cough and cold medications, the CDC and the National Association of Medical Examiners investigated deaths in infants aged under 12 months associated with such use; 3 cases were identified. All 3 infants had high concentrations of pseudoephedrine in postmortem blood samples, 2 had detectable blood concentrations of dextromethorphan and paracetamol, and 1 was also found to have detectable concentrations of doxylamine. None of the deaths were determined to be intentional. Two infants had evidence of respiratory infection upon autopsy; no cardiac abnormalities were found in any of the infants.¹

1. CDC. Infant deaths associated with cough and cold medications—two States, 2005. *MMWR* 2007; **56**: 1–4. Also available at: <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm> (accessed 19/04/07)

Abuse. Acute psychosis and visual and tactile hallucinations have been reported¹ in an 18-year-old male after intravenous misuse of pseudoephedrine hydrochloride. Pseudoephedrine has also been used for the illicit manufacture of street stimulants such as metamfetamine (p.2158).

For reference to toxic effects after long-term use of over-the-counter preparations containing sympathomimetics, such as pseudoephedrine, see under Ephedrine, p.1558.

1. Sullivan G. Acute psychosis following intravenous abuse of pseudoephedrine: a case report. *J Psychopharmacol* 1996; **10**: 324–5.

Breast feeding. The American Academy of Pediatrics¹ states that, although usually compatible with breast feeding, preparations used by breast-feeding mothers that contain pseudoephedrine with dexbrompheniramine maleate have resulted in crying, irritability, and poor sleep patterns in the infant.

The concentrations of pseudoephedrine and triprolidine in plasma and breast milk of 3 mothers for up to 48 hours after ingestion of a preparation containing pseudoephedrine hydrochloride 60 mg with triprolidine hydrochloride 2.5 mg have been studied.² Concentrations of pseudoephedrine in milk were consistently higher than in plasma; the half-life in both fluids was between 4.2 and 7.0 hours. Assuming a generous milk secretion of 500 mL over 12 hours it was calculated that the excreted dose was the equivalent of 250 to 330 micrograms of pseudoephedrine base, or 0.5 to 0.7% of the dose ingested by the mothers. Triprolidine did not appear to be concentrated in breast milk. The amounts of pseudoephedrine and triprolidine distributed into breast milk were probably not high enough to warrant cessation of breast feeding.

A small, randomised, crossover study concluded that a single dose of 60 mg pseudoephedrine hydrochloride decreased 24-hour milk production by 24%. The authors of the study suggested that pseudoephedrine might be of benefit for suppressing excess milk production.³

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. Correction. *ibid.*: 1029. Also available at: <http://aapolicy.aapublications.org/cgi/content/full/pediatrics%3b108/3/776> (accessed 05/01/07)
2. Findlay JWA, et al. Pseudoephedrine and triprolidine in plasma and breast milk of nursing mothers. *Br J Clin Pharmacol* 1984; **18**: 901–6.
3. Aljazaf K, et al. Pseudoephedrine: effects on milk production in women and estimation of infant exposure via breastmilk. *Br J Clin Pharmacol* 2003; **56**: 18–24.

Convulsions. A child who suffered a generalised seizure after ingesting a large quantity of pseudoephedrine hydrochloride tablets was believed to be the first report of convulsions associated with overdose of a preparation containing the drug as a single ingredient.¹

1. Clark RF, Curry SC. Pseudoephedrine dangers. *Pediatrics* 1990; **85**: 389–90.

Effects on the gastrointestinal tract. Ischaemic colitis has been reported¹⁻³ after acute or chronic use of pseudoephedrine in combination cold and allergy preparations. In one case³ the authors suggested that use with tramadol may have contributed to adrenergic vasoconstriction by inhibition of noradrenaline reuptake.

1. Dowd J, et al. Ischemic colitis associated with pseudoephedrine: four cases. *Am J Gastroenterol* 1999; **94**: 2430–4.
2. Lichtenstein GR, Yee NS. Ischemic colitis associated with decongestant use. *Ann Intern Med* 2000; **132**: 682.
3. Traino AA, et al. Probable ischemic colitis caused by pseudoephedrine with tramadol as a possible contributing factor. *Ann Pharmacother* 2004; **38**: 2068–70.

Effects on mental function. Adverse mental effects (particularly in children) have been associated with combination preparations containing pseudoephedrine.¹⁻⁵ See also Abuse, above.

1. Leighton KM. Paranoid psychosis after abuse of Actifed. *BMJ* 1982; **284**: 789–90.
2. Sankey RJ, et al. Visual hallucinations in children receiving decongestants. *BMJ* 1984; **288**: 1369.
3. Stokes MA. Visual hallucinations in children receiving decongestants. *BMJ* 1984; **288**: 1540.