UK preparations suggest that these doses be given up to a maximum of 4 times daily, although in other countries higher total doses may be given.

Respiratory disorders. An FDA review of preparations available over-the-counter concluded that guaifenesin was an effective expectorant. The use of expectorants for productive cough is discussed on p.1547. A small study<sup>2</sup> found that guaifenesin also appeared to reduce cough reflex sensitivity in patients with upper respiratory-tract infections, which produce a transient increase in sensitivity, although it had no effect on cough reflex in healthy subjects. The mechanism for this effect was unclear.

Guaifenesin has been given to patients with altered nasal mucociliary clearance associated with HIV infection.

- Chilary Clearaine associated with ITH vinection.
  1. Thomas J. Guaiphenesin—an old drug now found to be effective. Aust J Pharm 1990; 71: 101–3.
  2. Dicpinigaitis PV, Gayle YE. Effect of guaifenesin on cough reflex sensitivity. Chest 2003; 124: 2178–81.
  3. Rosen EJ, Calhoun KH. Alterations of nasal mucociliary clearance in association with HIV infection and the effect of guaifenesin therapy. Laryngoscope 2005; 115: 27–30.

#### **Preparations**

USP 31: Dyphylline and Guaifenesin Elixir; Dyphylline and Guaifenesin Tablets; Guaifenesin and Codeine Phosphate Syrup; Guaifenesin and Pseudoephedrine Hydrochloride Capsules; Guaifenesin Capsules; Guaifenesin Syrup; Guaifenesin Tablets; Guaifenesin, Pseudoephedrine Hydrochloride, and Dextromethorphan Hydrobromide Capsules; Theophylline and

and Dextromethorphan Hydrobromide Capsules; Iheophylline and Guaifenesin Capsules; Theophylline and Guaifenesin Capsules; Theophylline and Guaifenesin Oral Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Guaifen; Omega 100 Bronquial; Plenum; Robitussin†; Vick 44 Exp; Vidkmiel; Australi: Actifed CC Chesty, Robitussin Chesty Cough; Robitussin EX; Strepsils Chesty Cough†; Vicks Cough Syrup for Chesty Coughs†; Austria: Resyl; Waldheim Husten; Belga: Vicks Vaposyrup Expectorant: Braz.: Broncofenil; Dimetapp Expectorante; Transpulmin; Vick Xarope; Canad.: Balminil Expectorant: Berlylin E: Bronchophan Expectorant; Cough Syrup Expectorant; Vicks Expectorant; Expectorant; Expectorant; Vicks Expectorant; Expe Guaifenesin Capsules; Theophylline and Guaifenesin Oral Solution. Proprietary Preparations (details are given in Part 3)

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

# Guaimesal (HNN)

Guaïmésal; Guaimesalum. (±)-2-(o-Methoxyphenoxy)-2-methyl-1,3-benzodioxan-4-one.

Гваймесал  $C_{16}H_{14}O_5 = 286.3.$  CAS - 81674-79-5.

Guaimesal is reported to have expectorant and antipyretic properties and has been given orally as an adjunct in the treatment of respiratory-tract disorders. It has also been given rectally in suppositories

## Helicidine

Helicidina; Helixinum.

Гелицидин

### **Profile**

Helicidine is a mucoglycoprotein from the snail Helix pomatia that has been used as a cough suppressant.

1. Pons F, et al. L'effect bronchorelaxant de l'helicidine, un extrait d'Helix pomatia, fait intervenir une liberation de prostaglandine E2. *Pathol Biol (Paris)* 1999; **47:** 73–80.

## **Preparations**

**Proprietary Preparations** (details are given in Part 3)

Multi-ingredient: Ger.: Original Schneckensirup†.

### Indanazoline Hydrochloride (HNNM) ⊗

Hidrocloruro de indanazolina; Indanazolin Hidroklorür; Indanazoline, Chlorhydrate d'; Indanazolini Hydrochloridum.

Инданазолина Гидрохлорид  $C_{12}H_{15}N_3$ , HCI = 237.7. 56601-85-5.

(indanazoline)

#### **Profile**

Indanazoline is a sympathomimetic with effects similar to those of naphazoline (p.1565). It has been used as the hydrochloride for its vasoconstrictor effect in the management of nasal congestion (p.1548). It has been given as nasal drops, a nasal gel, or a nasal spray in a concentration equivalent to indanazoline 0.1%.

#### Preparations

**Proprietary Preparations** (details are given in Part 3) Ger.: Farial; Turk.: Farial

#### **Iodinated Glycerol** (BAN, USAN)

Glicerol yodado; lodopropylidene Glycerol.

Глицерин Йодированный  $C_6H_{11}IO_3 = 258.1.$ CAS - 5634-39-9

Iodinated glycerol, a methyl derivative of domiodol, is an isomeric mixture of iodinated dimers of glycerol. It has been used as an expectorant. The limitations of iodides as expectorants are discussed in Cough on p.1547. The actions of iodides and iodine compounds are discussed under Iodine p.2169. Prolonged use of iodinated glycerol has been associated with thyroid dysfunction (see Effects on the Thyroid Gland, below) and severe skin eruptions; gastrointestinal disturbances and hypersensitivity reactions have also occurred. Malignant neoplasms have developed in animals given iodinated glycerol.

Chronic obstructive pulmonary disease. Studies<sup>1-3</sup> of the use of iodinated glycerol in patients with chronic bronchitis have produced conflicting results. The use of mucolytics or expectorants in chronic obstructive pulmonary disease (p.1112) is con-

- 1. Petty TL. The National Mucolytic Study: results of a rand-omized, double-blind, placebo-controlled study of iodinated glycerol in chronic obstructive bronchitis. Chest 1990; 97: 75-83
- 2. Repsher LH. Treatment of stable chronic bronchitis with iodinated glycerol: a double-blind, placebo-controlled trial. *J Clin Pharmacol* 1993; **33:** 856–60.
- 3. Rubin BK, et al. Iodinated glycerol has no effect on pulmonary function, symptom score, or sputum properties in patients with stable chronic bronchitis. *Chest* 1996; **109**: 348–52.

Effects on the thyroid gland. Thyroid dysfunction (both hyperthyroidism and hypothyroidism) has developed after giving iodinated glycerol to previously euthyroid patients. It was recommended that baseline thyroid function tests should be carried out before starting treatment with iodinated glycerol;1 it should be withdrawn if abnormal results are obtained during use.

Gittoes NJL, Franklyn JA. Drug-induced thyroid disorders. Drug Safety 1995; 13: 46–55.

# **Preparations**

Proprietary Preparations (details are given in Part 3) USA: lophen; Par Glycerol; R-Gen

# **Ipecacuanha**

Hlavěnkový kořen; lpecac; lpecacuana; lpécacuanha, racine d'; lpecacuanha Root: Ipecacuanhae radix: Ipekakuána-gyökér: Ipekakuananjuuri (ipecacuanha root); Ipekakuanarot (ipecacuanha root); Ipekakuanų šaknys; Korzeń ipekakuany; Raíz de ipecacuana.

Ипекакуана CAS — 8012-96-2. ATC - R05CA04; V03AB01. ATC Vet — QR05CA04; QV03AB01.

Pharmacopoeias. In Eur. (see p.vii), Int., Jpn, and US. Eur., Jpn, and US also include a monograph for Prepared Ipecacuanha or a similar standardised form.

Ph. Eur. 6.2 (Ipecacuanha Root; Ipecacuanha BP 2008). It consists of the fragmented and dried underground organs of Cephaelis ipecacuanha known as Matto Grosso ipecacuanha, or of C. acuminata known as Costa Rica ipecacuanha, or a mixture of both species. It contains not less than 2.0% of total alkaloids, calculated as emetine. It has a slight odour. Store in airtight containers. Protect from light.

The BP 2008 directs that when Ipecacuanha, Ipecacuanha Root, or Powdered Ipecacuanha is prescribed or demanded, Prepared Ipecacuanha shall be dispensed or supplied.

Ph. Eur. 6.2 (Ipecacuanha, Prepared; Ipecacuanhae Pulvis Normatus). It is ipecacuanha root powder adjusted to an alkaloidal content of 1.9 to 2.1% of total alkaloids, calculated as emetine. Store in airtight containers. Protect from light.

USP 31 (Ipecac). The dried rhizome and roots of Cephaelis acuminata or of C. ipecacuanha (Rubiaceae). It yields not less than 2% of ether-soluble alkaloids of which not less than 90% is emetine and cephaeline; the content of cephaeline varies from an amount equal to, to an amount not more than 2.5 times, that of

USP 31 (Powdered Ipecac). It contains 1.9 to 2.1% of ether-soluble alkaloids, with emetine and cephaeline content as for Ipecacuanha. It is pale brown, weak yellow, or light olive-grey powder that should be stored in airtight containers

#### Adverse Effects

Large doses of ipecacuanha have an irritant effect on the gastrointestinal tract, and persistent bloody vomiting or bloody diarrhoea may occur. Mucosal erosions of the entire gastrointestinal tract have been reported. The absorption of emetine, which is most likely if vomiting does not occur after emetic doses of ipecacuanha, may give rise to adverse effects on the heart, such as conduction abnormalities or myocardial infarction. These, combined with dehydration due to vomiting may cause vasomotor collapse followed by death. There have been several reports of chronic abuse of ipecacuanha to induce vomiting in eating disorders; cardiotoxicity and myopathy have occurred and may be a result of accumulation of emetine.

There have also been several reports of ipecacuanha poisoning due to the unwitting substitution of Ipecac Fluidextract (a former USP preparation) for Ipecac Syrup (USP); the fluidextract was about 14 times the strength of the syrup.

◊ References

1. Manno BR, Manno JE. Toxicology of ipecac: a review. *Clin Toxicol* 1977; **10:** 221–42.

Hypersensitivity. Allergy, characterised by rhinitis, conjunctivitis, and chest tightness, has occurred due to inhalation of ipecacuanha dust in packers of ipecacuanha tablets.1

Luczynska CM, et al. Occupational allergy due to inhalation of ipecacuanha dust. Clin Allergy 1984; 14: 169–75.

Vomiting. Prolonged vomiting has been reported in 17% of patients given ipecacuanha in the treatment of poisoning and may lead to gastric rupture, Mallory-Weiss tears of the oesophagogastric junction, cerebrovascular events, and pneumomediastinum and pneumoperitoneum.1

 Bateman DN, Adverse reactions to antidotes, Adverse Drug React Bull 1988; 133: (Dec.): 496–9

### Treatment of Adverse Effects

After acute overdose of ipecacuanha, activated charcoal is given to delay absorption followed if necessary by gastric lavage. Prolonged vomiting may be controlled by the injection of antiemetics. Fluid and electrolyte imbalance should be corrected and facilities should be available to correct any cardiac effects and subsequent shock.

When ipecacuanha is withdrawn after chronic abuse, recovery may be prolonged due to the slow elimination of emetine.

#### **Precautions**

The use of emetics is now rarely favoured; in particular, ipecacuanha should not be used as an emetic in patients who are unconscious or whose condition otherwise increases the risk of aspiration, nor in patients who have taken substances, such as corrosive compounds or petroleum products, that might be especially dangerous if aspirated. Ipecacuanha should not be given to patients in shock or to those at risk from seizures either as a result of their condition or from compounds, such as strychnine, that have been ingested. Patients with cardiovascular disorders are at risk if ipecacuanha is absorbed.

Abuse. Ipecac syrup has been abused by patients with eating disorders to induce vomiting.<sup>1</sup> Adverse effects of repeated vomiting, such as metabolic complications, aspiration pneumonitis, parotid enlargement, dental abnormalities, and oesophagitis or haematemesis due to mucosal lacerations (the Mallory-Weiss syndrome) may be observed. Cardiotoxicity may occur and fatalities have been reported including one patient who had ingested 90 to 120 mL of ipecac syrup daily for 3 months.<sup>2</sup> It has been suggested that cardiac effects and myopathy following the prolonged abuse of ipecac syrup may be due to the long-term accumulation of emetine<sup>3,4</sup> but some have expressed doubts.<sup>5</sup>

Cardiomyopathy has also been reported in children given ipecacuanha to produce factitious illness (Munchausen's syndrome by proxy);6-8 fatalities have occurred.

- Harris RT. Bulimarexia and related serious eating disorders with medical complications. Ann Intern Med 1983; 99: 800–7.
- Adler AG, et al. Death resulting from ipecac syrup poisoning. JAMA 1980; 243: 1927–8.
- 3. Palmer EP, Guay AT. Reversible myopathy secondary to abuse of ipecac in patients with major eating disorders. N Engl J Med 1985; **313:** 1457–9.
- Pope HG, et al. The epidemiology of ipecac abuse. N Engl J Med 1986; 314: 245–6.
- 5. Isner JM. Effects of ipecac on the heart. N Engl J Med 1986; 314:
- 6. Goebel J, et al. Cardiomyopathy from ipecac administration in Munchausen syndrome by proxy. Pediatrics 1993; 92: 601-3. 7. Schneider DJ, et al. Clinical and pathologic aspects of cardiomy-
- opathy from ipecac administration in Munchausen's syndrome by proxy. *Pediatrics* 1996; **97**: 902–6.
- Carter KE, et al. Munchausen syndrome by proxy caused by ipe-cac poisoning. Pediatr Emerg Care 2006; 22: 655–6.

## Interactions

The action of ipecacuanha may be delayed or diminished if it is given with or after charcoal; antiemetics may also reduce its effect.

Food. Milk had been believed to impair the emetic efficacy of ipecacuanha but there was no significant difference in the time to onset of vomiting, the duration of vomiting, or the number of episodes in 250 children who were given ipecac syrup with milk compared with 250 given ipecac syrup with clear fluids.

Klein-Schwartz W, et al. The effect of milk on ipecac-induced emesis. J Toxicol Clin Toxicol 1991; 29: 505–11.

## **Uses and Administration**

Ipecacuanha has been used as an expectorant in productive cough (p.1547) in doses of up to about 1.4 mg of total alkaloids.

Ipecacuanha may also be used in larger doses as an emetic but is of very limited value (see Emesis Induction in Acute Poisoning, below). Vomiting usually occurs within 30 minutes of an oral emetic dose, due to an irritant effect on the gastrointestinal tract and a central action on the chemoreceptor trigger zone. Doses are usually followed by a copious drink of water or fruit juice. Adults have been given doses of about 21 to 42 mg of total alkaloids; each 5 mL of Ipecac Syrup (USP 31) supplies about 7 mg of total alkaloids. Doses may be repeated once only after 20 to 30 minutes if emesis has not occurred. For children's doses, see Administration in Children, below.

**Homoeopathy.** Ipecacuanha has been used in homoeopathic medicines under the following names: Ipeca; Cephaelis ipecacuanha; Ipecac.

Administration in children. Over-the-counter cough and cold preparations containing expectorants (including ipecacuanha) should be used with caution in children and generally avoided in those under 2 years of age (see p.1547).

In the UK, induction of emesis with ipecacuanha is not recommended because there is no evidence that it affects absorption and it may increase the risk of aspiration (see also Emesis Induction in Acute Poisoning, below).

In the USA, children aged 6 months to 1 year have been given about 7 to 14 mg of total alkaloids and older children about 21 mg. Each 5 mL of Ipecac Syrup (USP 31) supplies about 7 mg of total alkaloids. Doses are usually followed by a copious drink of water or fruit juice; in young children this may be given before the dose. Doses may be repeated once only after 20 to 30 minutes if emesis has not occurred.

**Emesis induction in acute poisoning.** Standard practice in the management of acute poisoning (p.1435) has varied widely, with different procedures favoured at different times and in different countries. However, measures to reduce absorption of the toxic substance, such as stomach emptying, have often been advocated

Two techniques of stomach emptying have been very widely used: gastric lavage; and emesis induction, with ipecacuanha as the emetic of choice. Neither technique is without hazard and the dangers of attempting to empty the stomach have to be balanced against the toxicity of the ingested poison. If the patient presents late or the risk of toxicity is small, then gastric emptying is un-

- · Gastric lavage is not recommended in the routine management of poisoned patients1 because there is little evidence from experimental studies that it improves the clinical outcome and it may cause significant morbidity. It should only be considered if a potentially life-threatening amount of toxic substance has been ingested within the preceding hour. There is significant danger of aspiration of stomach contents associated with the procedure and it should only be attempted in fully conscious patients with good airway protective reflexes, unless other means are undertaken to protect the airway. Gastric lavage is also contra-indicated if corrosive or petroleum products have been ingested. Another risk that has been suggested with gastric lavage is that the procedure may propel stomach contents beyond the pylorus and thus enhance absorption,2 but this conclusion has been challenged3 and the evidence appears to be limited.
- · Induction of emesis with ipecacuanha has often been advocated for use in children, in whom gastric lavage may be particularly traumatic; it has also been used in adults. However, like gastric lavage, its routine use is not recommended in the management of poisoned patients4 because there is no clear evidence from clinical studies that it improves the outcome; clinically significant absorption may not be prevented even if it is given within 1 hour of the ingested poison. It may also delay the use or reduce the effectiveness of activated charcoal or oral antidotes. Ipecacuanha should not be given to patients with compromised airway reflexes, nor following ingestion of corrosive or petroleum products. In addition it should be avoided in debilitated or elderly patients, or those with medical conditions that may be compromised by induction of emesis. It may be considered in alert, conscious patients, if a potentially lifethreatening amount of toxic substance has been ingested within the preceding hour, and if gastric lavage or activated charcoal are deemed inappropriate.

Because of the limitations of both methods of gastric emptying, a number of studies have addressed the question of whether either is appropriate. Such studies have indicated that the use of activated charcoal alone to prevent absorption, without gastric emptying, is as effective as a combination of both methods.

- 1. American Academy of Clinical Toxicology, European Association of Poisons Centres and Clinical Toxicologists. Position paper: gastric lavage. *J Toxicol Clin Toxicol* 2004; **42:** 933–43. Also available at: http://www.clintox.org/Pos\_Statements/GastricLavage.pdf (accessed 5/12/06)
- Saetta JP, et al. Gastric emptying procedures in the self-poisoned patient: are we forcing gastric content beyond the pylorus? J R Soc Med 1991; 84: 274-6.
- 3. Eddleston M, et al. Does gastric lavage really push poisons beyond the pylorus? A systematic review of the evidence. *Ann Emerg Med* 2003; **42:** 359–64.
- American Academy of Clinical Toxicology, European Association of Poisons Centres and Clinical Toxicologists. Position statement: ipecac syrup. *J Toxicol Clin Toxicol* 2004; **42:** 133–43. Also available at: http://www.clintox.org/ Pos\_Statements/IpecacSyrup.pdf (accessed 5/12/06)
- Albertson TE, et al. Superiority of activated charcoal alone compared with ipecae and activated charcoal in the treatment of acute toxic ingestions. Ann Emerg Med 1989; 18: 56–9.
- Merigian KS, et al. Prospective evaluation of gastric emptying in the self-poisoned patient. Am J Emerg Med 1990; 8: 479–83.
- Pond SM, et al. Gastric emptying in acute overdose: a prospective randomised controlled trial. Med J Aust 1995; 163: 345–9.

# **Preparations**

**BP 2008:** Paediatric Ipecacuanha Emetic Mixture; **Ph. Eur.:** [pecacuanha Liquid Extract, Standardised; Ipecacuanha Tincture, Standardised; USP 31: Ipecac Syrup.

Proprietary Preparations (details are given in Part 3) Fin.: Ipeca†; Gr.: Ipecavom; UK: Fennings Little Healers

Multi-ingredient: Arg.: Cobenzil Compuesto†; No-Tos Infantil; Braz.: Agrimel†; Expec; Expectomel; Fenergan Expectorante; Iodesin; Iodopulmin†; Ipecol†; KI-Expectorante; Melagriao; Pilulas Ross; Iussol†; Tussucalman†; Fr.: Humex; Hong Kong; Pectoral†; Hung.: Artin†; Infano.: Andonex; Koffex for Children; Prome; Promedex; Promethazine Ikapharmindo; Inl.: Venos Honge & Lemon; Israel: Doveri, Laxative Comp. Promethazine Expectorant; Neth.: Buckleys Kinderhoestsiroop; Rus.: Prothiazine Expectorant (Противанн Экспекторант); S.Afr.: Chamberlains Cough Remedy Regular; Cough

Elixir; Linctus Tussi Infans; SB Cirogin Cough Mixture; **Singapore**: Beacons Cough; **Spain**: Alofedina; Buco Regis; Encialina†; Fenergan Expectorante; **Switz**: Bromocod N; Demo Elixir pectoral N; Gouttes contre la toux "5"; Neo-Codion N; Pastilles pectorales Demo N; **UK**: Allens Dry Tickly Cough; Allens Pine & Honey, Asthma & Catarrh Relief, Beehive Balsam; Buttercup Infant Cough Syrup; Buttercup Syrup (Blackcurrant flavour); Buttersus Signi, Valence Park, Cauche Cataly, Cauche State Calledon (Cataly Cataly Buttercup Jinant Cough Syrup; Suttercup Syrup; Blackcurrant havour); Buttercup Syrup; Hill's Balsam Chesty Cough for Children; Hill's Balsam Chesty Cough Pastilles; Hill's Balsam Extra Strong; Honey & Molasses; Jackson's Troublesome Coughs; Kilkof, Lockets Medicated Linctus; Modern Herbals Cough Mixture; Potters Children's Cough Pastilles; Vegetable Cough Remover; USA: Poison Antidote Kit; Quelidrine; Venez.: Tabonuco; Tessamag con Coddina.

#### **Isoaminile** (BAN, rINN)

Isoaminiili; Isoaminilo; Isoaminilum. 4-Dimethylamino-2-isopropyl-2-phenylpentanonitrile.

Изоаминил

 $C_{16}H_{24}N_2 = 244.4.$ CAS — 77-51-0. ATC — R05DB04. ATC Vet - QR05DB04

## Isoaminile Citrate (BANM, rINNM)

Citrato de isoaminilo: Isoaminile. Citrate d': Isoaminili Citras. 4-Dimethylamino-2-isopropyl-2-phenylvaleronitrile dihydrogen cit-

Изоаминила Цитрат  $C_{16}H_{24}N_{2}$ ,  $C_{6}H_{8}O_{7} = 436.5$ . CAS - 126-10-3; 28416-66-2. ATC - R05DB04.

ATC Vet — QR05DB04.

# Isoaminile Cyclamate (HNNM)

Ciclamato de isoaminilo; Isoaminile, Cyclamate d'; Isoaminili Cyclamas. 4-Dimethylamino-2-isopropyl-2-phenylvaleronitrile cyclohexanesulfamate.

Изоаминила Цикламат  $C_{16}H_{24}N_2$ ,  $C_6H_{13}NO_3S = 423.6$ . CAS - 10075-36-2. ATC - R05DB04. ATC Vet - QR05DB04.

### **Profile**

Isoaminile is a centrally acting cough suppressant, Isoaminile cyclamate has been given orally in doses of 40 to 80 mg up to 5 times daily. For children's doses, see Administration in Children, below. The citrate has also been used.

Administration in children. Isoaminile cyclamate has been given orally in the following doses:

· 1 to 6 years: 20 mg 2 or 3 times daily

· over 6 years: 40 mg 2 or 3 times daily

## **Preparations**

**Proprietary Preparations** (details are given in Part 3) **Gr.:** Peracon†, **Indon.:** Peracon, **S.Afr.:** Peracon†.

Multi-ingredient: S.Afr.: Peracon Expectorant †.

### Letosteine (pINN)

Letosteína; Létostéine; Letosteinum. 2-[2-(Ethoxycarbonylmethylthio)ethyl]thiazolidine-4-carboxylic acid.

Летостеин

 $C_{10}H_{17}NO_4S_2 = 279.4.$  CAS - 53943-88-7. ATC - R05CB09.ATC Vet - QR05CB09.

Letosteine is a mucolytic that has been used in the treatment of respiratory disorders associated with productive cough (p.1547).

### **Preparations**

Proprietary Preparations (details are given in Part 3) Fr.: Viscotiol†; Spain: Broluidan†.