

for up to 12 weeks. For maintenance, 1.5 g twice daily is recommended, adjusted according to response up to a maximum of 6 g daily.

In the USA, licensed doses in children aged 5 to 17 years are 750 mg three times daily by mouth, or 2.25 g three times daily; treatment may be continued for up to 8 weeks.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Benoquin; **Austral.:** Colazide; **Cz.:** Colazide†; **Denm.:** Premid; **Ital.:** Balzide; **Norw.:** Colazid; **UK:** Colazide; **USA:** Colazal.

Multi-ingredient: **Swed.:** Colazid.

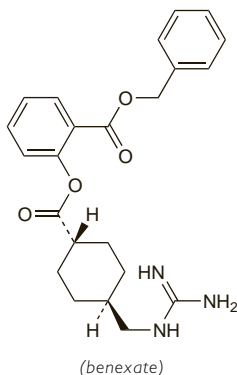
Benexate Hydrochloride (rINN)

Bénexate, Chlorhydrate de; Benexati Hydrochloridum; Hidrocloruro de benexato. Benzyl salicylate *trans*-4-(guanidinomethyl)cyclohexanecarboxylate hydrochloride.

Бенексат Гидрохлорид

$C_{22}H_{27}N_3O_4 \cdot HCl = 445.9$.

CAS — 78718-52-2 (benexate); 78718-25-9 (benexate hydrochloride); 91574-91-3 (benexate hydrochloride betadex).



Profile

Benexate hydrochloride is a mucosal protectant that has been used in the management of peptic ulcer disease. The β -cyclodextrin clathrate, benexate hydrochloride betadex, has been given in an oral dose of 400 mg twice daily.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Uligut.

Bisacodyl (BAN, rINN)

Bisacodilo; Bisacodylum; Bisakodil; Bisakodilisi; Bisakodyl; Bisakodyli; Bisakodil. 4,4'-(2-Pyridylmethylene)di(phenyl acetate).

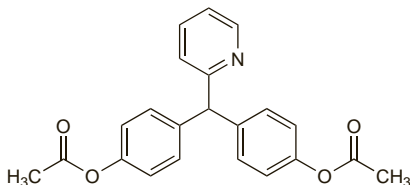
Бисакодил

$C_{22}H_{19}NO_4 = 361.4$.

CAS — 603-50-9.

ATC — A06AB02; A06AG02.

ATC Vet — QA06AB02; QA06AG02.



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

Ph. Eur. 6.2 (Bisacodyl). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in acetone. It dissolves in dilute mineral acids. Protect from light.

USP 31 (Bisacodyl). A white to off-white crystalline powder. Practically insoluble in water; soluble in benzene; soluble 1 in 210 of alcohol, 1 in 2.5 of chloroform, and 1 in 275 of ether; sparingly soluble in methyl alcohol.

Bisacodyl Tannex (BANM, USAN, rINN)

CAS — 1336-29-4.

ATC — A06AB02; A06AG02.

ATC Vet — QA06AB02; QA06AG02.

Adverse Effects

Bisacodyl and other stimulant laxatives may cause abdominal discomfort such as colic or cramps. Prolonged use or overdosage can result in diarrhoea with excessive loss of water and electrolytes, particularly potassium; there is also the possibility of developing an atonic non-functioning colon. Hypersensitivity reactions, including angioedema and anaphylactoid reactions, have been reported rarely. When given rectally, bisacodyl sometimes causes irritation and may cause proctitis or sloughing of the epithelium. To avoid gastric irritation bisacodyl tablets are enteric-coated.

Precautions

As with other laxatives, prolonged use should be avoided. Bisacodyl should not be given to patients with intestinal obstruction or acute abdominal conditions such as appendicitis; care should also be taken in patients with inflammatory bowel disease. It should not be used in patients with severe dehydration. The suppositories should preferably be avoided in patients with anal fissures, proctitis, or ulcerated haemorrhoids.

Handling. Inhalation of bisacodyl powder and contact with eyes, skin, and mucous membranes should be avoided.

Pharmacokinetics

On oral or rectal use bisacodyl is converted to the active desacetyl metabolite bis(*p*-hydroxyphenyl)-pyridyl-2-methane by intestinal and bacterial enzymes. Absorption from the gastrointestinal tract is minimal with enteric-coated tablets or suppositories; the small amount absorbed is excreted in the urine as the glucuronide. Bisacodyl is mainly excreted in the faeces.

Uses and Administration

Bisacodyl is a diphenylmethane stimulant laxative (p.1693) used for the treatment of constipation (p.1693) and for bowel evacuation before investigational procedures or surgery. Its action is mainly in the large intestine and it is usually effective within 6 to 12 hours after oral doses, within 15 to 60 minutes after rectal use by suppository, and within 5 to 20 minutes when given as an enema. Bisacodyl tablets should be swallowed whole and should not be taken within 1 hour of milk or antacids.

For constipation, bisacodyl is given in usual doses of 5 to 10 mg daily as enteric-coated tablets given at night or 10 mg as a suppository or enema given in the morning. Oral doses of 10 to 20 mg are given for complete bowel evacuation, followed by 10 mg as a suppository the next morning. For doses in children, see below.

A complex of bisacodyl with tannic acid (bisacodyl tannex) has been given with a barium sulfate enema before radiographic examination of the colon.

Administration in children. For constipation, the following oral doses of bisacodyl are recommended for children, to be taken at night:

- 4 to 10 years: 5 mg
- over 10 years: 5 to 10 mg

Alternatively, the following rectal doses are recommended, to be inserted in the morning:

- under 10 years: 5 mg
- over 10 years: 10 mg

The *BNFC* gives similar doses, but limits the use of suppositories in children to those aged over 2 years.

For bowel clearance before surgery or radiological investigation, the following doses are recommended:

- 4 to 10 years: 5 mg orally the night before, followed by 5 mg as a suppository the next morning
- over 10 years: 10 to 20 mg orally the night before, followed by 10 mg as a suppository the next morning

The *BNFC* gives similar doses but allows for the use of oral doses for 2 nights before the procedure, followed, if necessary, by the rectal dose 1 hour before the procedure.

Preparations

BP 2008: Bisacodyl Suppositories; Gastro-resistant Bisacodyl Tablets;

USP 31: Bisacodyl Delayed-release Tablets; Bisacodyl Rectal Suspension; Bisacodyl Suppositories.

Proprietary Preparations (details are given in Part 3)

Arg.: Dulcolax; Laxamin; Modaton; Tractoduo; **Austral.:** Bisalax; Dulcolax; **Austria:** Dulcolax; Laxbene; **Belg.:** Carters; Dulcolax; Henafurine; Muci-

num; Nosik-Lax; Purgo-Pil; **Braz.:** Bisalax; Cronoplex; Dislax†; Dulcolax; Fi-deine; Islax; Plesonax; **Canad.:** Alophen; Bisacolax; Carters Little Pills; Correctol; Dulcolax; Feen-A-Mint†; Gentlax; Laxcodyl†; Soflax; **Ex.:** **Chile:** Alysax; **Cz.:** Fenolax; **Fr.:** Xylax†; Stadalax; **Denm.:** Dulcolax; Penilax; Toilax; **Fin.:** Metalax; Toilax; **Gr.:** Contalax; Dulcolax; **Ger.:** Agaroletten; Bekunis Bisacodyl; Bisco-Zitron; Drix Bisacodyl; Dulcolax; Flonsan N; Laxagetten; Laxamin N†; Laxans-ratiopharm; Laxbene†; Laxoberal Bisa; Laxysat Burger; Marienbader Pillen N; Mediolax; Pynlax; Stadalax†; Tempolax; Tirgon; Vinco-Abfuhr-Perlen†; **Gr.:** Dulcolax; Flonsan N; **Hong Kong:** Dulcolax; Mar-cholax; **Hung.:** Dulcolax; Stadalax; **India:** Bo-Lax; Dulcolax; Julax; Julax-M†; **Indon.:** Bicolax; Dulcolax; Laxacol; Laxamex; Stolas; Dulcolax; Toilax; **Israel:** Atzirut X; Contalax; Laxadin; **Ital.:** Alaxa; Conifetto CM†; Dulcolax; Normalene; Stixenil; Vercolene CM†; **Malaysia:** Beacolux†; Dulcolax; **Mex.:** Dulcolax; **Neth.:** Bekunis Bisacodyl; Dulcolax; Kruidvat Laxeert-abletten; Nounilax; Toilax; Trekpleister Laxeerdagees†; **Norw.:** Dulcolax; Toilax; **NZ:** Dulcolax; Fleet Laxative; **Philipp.:** Dulcolax; Vesilax; **Port.:** Dulcolax; Modierax; **Rus.:** Dulcolax (Дульколак); **S.Afr.:** Dulcolax; Megalax†; **Spain:** Singolax; Dulcolax; **Spain:** Dulco Laxo; **Swed.:** Dulcolax; Toilax; **Switz.:** Bekunis Dragees; Demolaxin; Dulcolax; Muxol; Prontolax; Tavolax nouvelle formule; **Thail.:** Conlax; Dulcolax; Emulax; Gencolax; Kadolax; Laxcodyl; Laxitab; Vacolax; **Turk.:** Bisakol; Sekolax; **UAE:** Laxocodyl; **UK:** Biolax; Dulcolax; Entrolax; **USA:** Alophen; Bisa-Lax; Correctol; Doxidan; Dulcolax; Evac-Q-Tabs; Ex-Lax Ultra; Feen-A-Mint; Fleet Bisacodyl; Fleet Laxative; Gentlax; Modane; **Venez.:** Dulcolan.

Multi-ingredient: **Arg.:** En-Ga-Lax; Laxicon; Nigalax; **Austral.:** Coloxyl; Durolax X-Pack†; Go Kit; Go Kit Plus†; **Austria:** Laxbene; Prepacol; Purgazen; Purgat†; **Belg.:** Prepacol; Softene; **Canad.:** Bicholate; Extra Strong Formula 12†; Fruitatives†; Gentlax S; Royvac; **Chile:** Laxogeno; **Cz.:** Prepacol; **Fr.:** Prepacol; **Ger.:** Potsilo N; Prepacol; **Gr.:** Florsan; **Hung.:** Laxbene; **NZ:** Coloxyl; **Port.:** Bekunis; **Spain:** Bekunis Complex; Boldolax-in†; **Thail.:** Bisolax; **Turk.:** Bekunis; **USA:** Dulcolax Bowel Prep Kit; Fleet Prep Kit No. 1; Fleet Prep Kit No. 2; Fleet Prep Kit No. 3; HalfLytely; X-Prep Bowel Evacuant Kit-1.

Bismuth Compounds

Bismuto, compuestos de.

Висмут Соединения

Bismuth compounds have been used for their astringent and antidiarrhoeal properties in a variety of gastrointestinal disorders, and have been applied topically in skin disorders and anorectal disorders such as haemorrhoids. Certain salts are active against *Helicobacter pylori* and are used in the treatment of peptic ulcer disease.

Bismuth Aluminate (USAN)

Aluminato de bismuto; Aluminum Bismuth Oxide.

Алюминат Висмута

$Bi_2(Al_2O_4)_3 \cdot 10H_2O = 952.0$.

CAS — 12284-76-3 (anhydrous bismuth aluminate).

Pharmacopoeias. In *Chin.* and *Fr.*

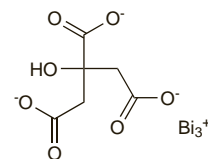
Bismuth Citrate

Citrato de bismuto.

Цитрат Висмута

$Bi_2C_6H_5O_7 = 398.1$.

CAS — 813-93-4.



NOTE. Do not confuse with bismuth subcitrate potassium (p.1711) or tripotassium dicitratobismuthate (colloidal bismuth subcitrate, p.1711).

Pharmacopoeias. In *US*.

USP 31 (Bismuth Citrate). A white, amorphous or crystalline powder. Insoluble in water and in alcohol; soluble in dilute ammonia solution and in solutions of alkali citrates. Store in airtight containers. Protect from light. Prevent exposure to temperatures above 40°.

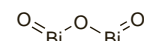
Bismuth Oxide

Bismuth Trioxide; Óxido de bismuto.

Оксид Висмута

$Bi_2O_3 = 466.0$.

CAS — 1304-76-3.



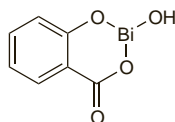
Bismuth Salicylate

Basic Bismuth Salicylate; Bázisos bizmut-szalicilát; Bismuth Oxy-salicylate; Bismuth, sous-salicylate de; Bismuth Subsalicylate (USAN); Bismuthi subsalicylas; Bismuto subsalicylatas; Salicilato de bismuto; Salicylan bismutitű zásaditű; Vismutsalsalicylat; Vismut-tisalsalicylaatti.

Салицилат Висмута

$C_7H_5BiO_4 = 362.1$.

CAS — 14882-18-9.



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

Ph. Eur. 6.2 (Bismuth Subsalicylate). A complex of bismuth and salicylic acid. It contains not less than 56% and not more than 59.4% of Bi, calculated with reference to the dried substance. A white or almost white powder. Practically insoluble in water and in alcohol; dissolves in mineral acids with decomposition. Protect from light.

USP 31 (Bismuth Subsalicylate). A basic salt corresponding to $C_7H_5BiO_4$ and containing not less than 56.0% and not more than 59.4% of Bi and not less than 36.5% and not more than 39.3% of total salicylates. It is a fine, odourless, white to off-white microcrystalline powder. Practically insoluble in water, in alcohol, and in ether. It reacts with alkalis and mineral acids. Store in airtight containers. Protect from light.

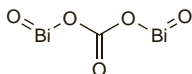
Bismuth Subcarbonate (USAN)

Basic Bismuth Carbonate; Basisches Wismutkarbonat; Bázisos bizmutkarbonát; Bism. Carb.; Bismuth Carbonate; Bismuth Oxy-carbonate; Bismuth, sous-carbonate de; Bismuthi subcarbonas; Bismuto subcarbonatas; Bismutylum Carbonicum; Carbonato de Bismutita; Subcarbonato de bismuto; Uhlíčitán bismutitű zásaditű; Vismutsubkarbonat; Vismutisubkarbonaatti.

Основный Углекислый Висмут

$CBi_2O_5 = 510.0$.

CAS — 5892-10-4 (anhydrous bismuth subcarbonate); 5798-45-8 (bismuth subcarbonate hemihydrate).



(anhydrous bismuth subcarbonate)

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

Ph. Eur. 6.2 (Bismuth Subcarbonate). A white or almost white powder. Practically insoluble in water and in alcohol. It dissolves in mineral acids with effervescence. Protect from light.

USP 31 (Bismuth Subcarbonate). A white or almost white powder. Practically insoluble in water, in alcohol, and in ether; dissolves in dilute acids with effervescence. Protect from light.

Bismuth Subcitrate Potassium (USAN)

1001277; Biscalcitrate potassium; Bismuth Biscalcitrate; Bismuth biscalcitrate. Bismuth pentapotassium dihydroxide bis(2-hydroxypropene-1,2,3-tricarboxylate hydrate).

Основный Калиевый Цитрат Висмута

$C_{12}H_{14}BiK_5O_{17} = 834.7$.

CAS — 880149-29-1.

NOTE. Do not confuse with bismuth citrate (p.1710) or tripotassium dicitratobismuthate (colloidal bismuth subcitrate, p.1711).

Bismuth Subgallate (USAN)

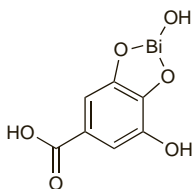
Basic Bismuth Gallate; Basisches Wismutgallat; Bázisos bizmutgallát; Bism. Subgall.; Bismuth Oxygallate; Bismuth, sous-gallate de; Bismuthi subgallas; Bismuto subgalatas; Bismut Subgallat; Bismutu galusan zasadowy; Gallan bismutitű zásaditű; Subgalato de bismuto; Vismutsubgallat; Vismutisubgallaatti.

Основный Галловокислый Висмут

$C_7H_5BiO_6 = 394.1$.

CAS — 99-26-3.

The symbol † denotes a preparation no longer actively marketed



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

Ph. Eur. 6.2 (Bismuth Subgallate). A complex of bismuth and gallic acid. It contains not less than 48% and not more than 51% of Bi, calculated with reference to the dried substance. A yellow powder. Practically insoluble in water and in alcohol; dissolves in mineral acids with decomposition and in alkali hydroxides, producing a reddish-brown liquid. Protect from light.

USP 31 (Bismuth Subgallate). A basic salt containing 52 to 57% of Bi_2O_3 when dried at 105° for 3 hours. It is an odourless amorphous bright yellow powder. Practically insoluble in water, in alcohol, in chloroform, and in ether; insoluble in very dilute mineral acids; dissolves readily with decomposition in warm, moderately dilute hydrochloric, nitric, or sulfuric acids; readily dissolves in solutions of alkali hydroxides to form a clear yellow liquid which rapidly becomes deep red. Store in airtight containers. Protect from light.

Bismuth Subnitrate

Basic Bismuth Nitrate; Basisches Wismutnitrat; Bázisos bizmut-nitrát; Bism. Subnit.; Bismuth Hydroxide Nitrate Oxide; Bismuth Nitrate, Heavy; Bismuth Oxy-nitrate; Bismuth, sous-nitrate de; Bismuth (Sous-Nitrate de) Lourd; Bismuthi subnitrás; Bismuthyl Nitrate; Bismuto subnitratas; Bismuto subnitratas sunkusis; Bismut Subnitrat; Bismutu azotan zasadowy; Bismutu(III) azotan zasadowy; Magistery of Bismuth; Nitrate de Bismutito; Subazotato de Bismuto; Subnitrate de bismuto; Vismutsubnitrat; Vismutisubnitrat; White Bismuth.

Основный Азотнокислый Висмут

$Bi_5O(OH)_9(NO_3)_4 = 1462.0$.

CAS — 1304-85-4.

ATC — A02BX12.

ATC Vet — QA02BX12.

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

Fr. also includes Bismuth (Sous-Nitrate de) Léger (Bismuthi Subnitrás Levis) which is described as a variable mixture of bismuth hydroxide, carbonate, and subnitrate.

Ph. Eur. 6.2 (Bismuth Subnitrate, Heavy). It contains not less than 71% and not more than 74% of Bi, calculated with reference to the dried substance. A white or almost white powder. Practically insoluble in water and in alcohol; dissolves in mineral acids with decomposition.

USP 31 (Bismuth Subnitrate). A basic salt containing not less than 79% of Bi_2O_3 calculated on the dried basis. It is a white, slightly hygroscopic powder. Practically insoluble in water and in alcohol; readily dissolves in nitric and hydrochloric acids.

Tripotassium Dicitratobismuthate

Bismut Subsitrat; Colloidal Bismuth Subcitrate; Dicitratobismutata tripotásico; Tripotasyum Dicitratobismutat.

Висмут Трикалия Дицитрат

CAS — 57644-54-9.

ATC — A02BX05.

ATC Vet — QA02BX05.

NOTE. Do not confuse with bismuth citrate (p.1710) or bismuth subcitrate potassium (p.1711).

Adverse Effects, Treatment, and Precautions

The bismuth compounds listed above are insoluble or very poorly soluble, and bismuth toxicity does not appear to be common if they are used for limited periods. However, excessive or prolonged dosage may produce symptoms of bismuth poisoning, and for this reason long-term systemic therapy is not recommended. Reversible encephalopathy (see below) was once a problem in some countries, notably France and Australia; bone and joint toxicity had also occurred, sometimes associated with the encephalopathy. This led to restrictions on the use of bismuth salts and a virtual disappearance of these toxic effects.

Nausea and vomiting have been reported. Darkening or blackening of the faeces and tongue may occur due to conversion to bismuth sulfide in the gastrointestinal tract.

The effects of *acute bismuth intoxication* include gastrointestinal disturbances, skin reactions, stomatitis, and discoloration of mucous membranes; a characteristic blue line may appear on the gums. There may be renal failure and liver damage.

Other adverse effects may not be related to the bismuth content. With bismuth subnitrate given orally there is a risk of the nitrate being reduced in the intestines to nitrite and the development of methaemoglobinemia. Absorption of salicylate occurs from oral bismuth salicylate and therefore the adverse effects, treatment of adverse effects, and precautions of aspirin (p.20) should be considered.

Gastric lavage should be considered in overdose; activated charcoal by mouth and the use of a chelating agent such as dimercaprol, succimer, or unithiol have been recommended (see also Overdose, below). Renal function should be monitored for 10 days after acute overdose.

Bismuth compounds should not be given to patients with moderate to severe renal impairment.

Encephalopathy. Reviews^{1,2} and reports³⁻¹¹ of bismuth encephalopathy. Many of the original reports implicated bismuth subgallate or subnitrate, in most but not all cases at high doses or for prolonged periods; toxicity has also occurred with other salts.⁶⁻⁹ Patients receiving the subcitrate (480 mg daily) or the subnitrate (1.8 g daily) for 8 weeks in the treatment of *Helicobacter pylori* infection, showed no evidence of neurological changes compared with a control group.¹²

- Winship KA. Toxicity of bismuth salts. *Adverse Drug React Acute Poisoning Rev* 1983; **2**: 103-21.
- Slikkerveer A, de Wolff FA. Pharmacokinetics and toxicity of bismuth compounds. *Med Toxicol Adverse Drug Exp* 1989; **4**: 303-23.
- Morrow AW. Request for reports: adverse reactions with bismuth subgallate. *Med J Aust* 1973; **1**: 912.
- Martin-Bouyer G. Intoxications par les sels de bismuth administrés par voie orale: enquête épidémiologique. *Thérapie* 1976; **31**: 683-702.
- Stahl JP, et al. Encéphalites au sel insoluble de bismuth: toujours d'actualité. *Nouv Presse Med* 1982; **11**: 3856.
- Hasking GJ, Duggan JM. Encephalopathy from bismuth subsalicylate. *Med J Aust* 1982; **2**: 167.
- Weller MPI. Neuropsychiatric symptoms following bismuth intoxication. *Postgrad Med J* 1988; **64**: 308-10.
- Mendelowitz PC, et al. Bismuth absorption and myoclonic encephalopathy during bismuth subsalicylate therapy. *Ann Intern Med* 1990; **112**: 140-1.
- Playford RJ, et al. Bismuth induced encephalopathy caused by tri potassium dicitrate bismuthate in a patient with chronic renal failure. *Gut* 1990; **31**: 359-60.
- Von Bose MJ, Zaudig M. Encephalopathy resembling Creutzfeldt-Jakob disease following oral, prescribed doses of bismuth nitrate. *Br J Psychiatry* 1991; **158**: 278-80.
- Teepker M, et al. Myoclonic encephalopathy caused by chronic bismuth abuse. *Epileptic Disord* 2002; **4**: 229-33.
- Noach LA, et al. Bismuth salts and neurotoxicity: a randomised, single-blind and controlled study. *Hum Exp Toxicol* 1995; **14**: 349-55.

TOPICAL APPLICATION. Encephalopathy has been associated with the use of bismuth iodoform paraffin paste (BIPP) for the packing of wound cavities after surgery to the head and neck, although there is some debate as to whether the bismuth or the iodoform component is responsible—see p.1650.

Overdose. Bismuth salicylate or tripotassium dicitratobismuthate in recommended doses are rarely associated with serious adverse effects but there are reports of renal failure,¹⁻⁶ encephalopathy,⁷⁻⁹ and neurotoxicity¹ in acute^{1-6,8} or chronic^{7,9} overdose. Bismuth has been detected in the blood, urine, stools, and kidneys of these patients; a blood concentration of 1.6 micrograms/mL was found² 4 hours after an oral dose of 9.6 g.

The optimal treatment of bismuth overdose is unknown. Gastric lavage, purgation, and hydration should be considered, even if the patient presents late, as bismuth may be absorbed from the colon.^{1,2} Chelating agents may be effective; unithiol has been reported to increase the renal clearance of bismuth with a reduction in the blood concentration.⁷ Haemodialysis may be necessary¹⁻³ but whether this hastens tissue clearance is uncertain. Haemodialysis plus unithiol treatment has been reported to successfully eliminate bismuth.⁶ Peritoneal dialysis has also been effectively used in a paediatric patient.⁵

Prolonged ingestion of bismuth salicylate in excessive doses by an elderly diabetic was associated with hearing disturbances, vertigo, acid-base abnormalities and mild clotting disturbances.¹⁰ The toxicity was thought to be due to the salicylate component.

- Hudson M, Mowat NAG. Reversible toxicity in poisoning with colloidal bismuth subcitrate. *BMJ* 1989; **299**: 159.
- Taylor EG, Klennerman P. Acute renal failure after colloidal bismuth subcitrate overdose. *Lancet* 1990; **335**: 670-1.
- Huwez F, et al. Acute renal failure after overdose of colloidal bismuth subcitrate. *Lancet* 1992; **340**: 1298.