Uses and Administration

Benzoates have antibacterial and antifungal properties. Their antimicrobial activity is due to the undissociated benzoic acid and is therefore pH-dependent. They are relatively inactive above a pH of about 5.

Benzoates are used as preservatives in pharmaceutical formulations including oral preparations; benzoic acid and sodium benzoate are typically used in concentrations of up to 0.2% and 0.5%, respectively. They are used as preservatives in foods, (and are also present naturally in some foods), and at similar concentrations in cosmetics.

Benzoic acid 6% with salicylic acid 3%, as Compound Benzoic Acid Ointment (BP 2008) (Whitfield's Ointment) has a long history of use as an antifungal (see Skin Infections, p.521). Benzoic acid has also been used in desloughing preparations and has been given as a urinary antiseptic.

An injection of caffeine and sodium benzoate has been used as a CNS stimulant, but see Neonates, under Adverse Effects and Precautions, above for a caution against its use in neonates.

Sodium benzoate is used as part of the treatment of hyperammonaemia that occurs in inborn errors of the urea cycle. It has also been reported to be effective in reducing plasma-glycine concentrations in nonketotic hyperglycinaemia (p.2393), although it may not be effective in preventing mental retardation.

Sodium benzoate is a common ingredient of cough preparations.

Hyperammonaemia. Sodium benzoate is used for treatment of hyperammonaemia (p.1929).[1-3] It is given with sodium phenylacetate (see p.2390 for doses) and a combined preparation is available in some countries.

1. Maestri NE, *et al*. Long-term survival of patients with argininosuccinate synthetase deficiency. *J Pediatr* 1995; **127:** 929–35.
2. Maestri NE, *et al*. Long-term treatment of girls with ornithine transcarbamylase deficiency. *N Engl J Med* 1996; **335:** 855–9.
3. Zammarchi E, *et al*. Neonatal onset of hyperornithinemia-hyperammonemia-homocitrullinuria syndrome with favorable outcome. *J Pediatr* 1997; **131:** 440–3.

Preparations

BP 2008: Benzoic Acid Solution; Compound Benzoic Acid Ointment; Toluflavour Solution;
USP 31: Benzoic and Salicylic Acids Ointment; Caffeine and Sodium Benzoate Injection.

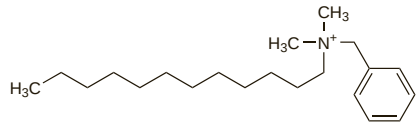
Proprietary Preparations (details are given in Part 3)
Indon.: Topix; Yodsaben; ***Mex.:*** Colufase†.

Multi-ingredient: ***Arg.:*** Expectosan Hierbas y Miel; Fungicida†; Ixana; No-Tos Adultos; No-Tos Infantil; Pectobron; Refenax Jarabe; Solvex Liquido Fungicida†; Torfan H†; ***Austral.:*** Whitfields (Benzoic Acid Compound) Ointment; ***Austria:*** Acerbine; Mycopol; ***Belg.:*** Colimax†; Kamfeine†; Pholco-Mereprine; Toplexil; Tux†; ***Braz.:*** ABC Solucao†; Antimicon†; Benzomel†; Bronquidex; Bronquiogem; Cessatosse†; Dermicon; Dermycose†; Eaca Balsamico; Egotussano†; Expec; Expectobron†; Frenotosse; Fungolab; Gotas Nican†; Iodesin; Iodeto de Potassio†; Iodopulmin†; Iol†; Ipecol†; KI-Expectorante; Limao Bravo†; Micotiazol; Micotox†; Micoz†; Peitoral Angico Pelotense†; Penetro; Po Antisseptico; Pulmoforte†; Pulmoverina†; Rhum Creosotado; Tiratosse†; Toplexil; Tossanil†; Tussodina†; Tussol†; Tussucalman†; Xarope de Caraguata†; Xarope Peitoral de Ameixa Composto†; Xarope Sao Joao†; Xpe SPC†; ***Canad.:*** Bronco Asmol; MRX†; Plax; ***Chile:*** Broncodeina; Caristop; Gotas Nican†; Gruben; Listerine; Pectoral Pasteur; Pectoserum†; Pulmagol; Summer's Eve Hierbas†; Summer's Eve Vinagre y Agua†; ***Denm.:*** Pectyl; ***Fr.:*** Broncalene; Broncalene Nourisson; Codotussyl Maux de Gorge; Dermacide; Dimetane Expectorant Enfant†; Dinacode avec codeine†; Dinacode†; Ephydion; Fluocaril blancheur; Germose†; Listerine; Neo-Codion; Ozothine; Paregorique; Passedyl; Pulmofluide Simple; Quintopan†; Rhinamide; Silomat†; ***Ger.:*** Sagrosept†; ***Hong Kong:*** Fungifax†; Gly Thymol; Listerine; Listerine Tartar Control; Listerine Teeth and Gum Defence; ***Hung.:*** Glycosept; ***India:*** Keralin; Mycoderm; Pragmatar; Zoderm; ***Indon.:*** Kalpanax; Kopamex; Listerine Coolmint; Mikorex; Sapona; ***Israel:*** Oxacatin; Pertussol; Phytoderm Compositum; Pitrisan; Shiulon; Spirit Whitfield; Toplexil; Tussophedrine New Formula; ***Ital.:*** Borocaina; Dentinale; Neo Borocillina; Paracodina; Sedocalcio; Tiocosol; Tionamil†; ***Malaysia:*** Nixoderm; ***Mex.:*** Pulmovital; ***NZ:*** Egomycol†; Listerine; Listerine Tartar Control; ***Philipp.:*** Dermalin; Listerine Coolmint; Listerine Freshburst; Listerine Original; Listerine Teeth & Gum Defense; United Home Whitfield's Ointment; ***Port.:*** Broncodiazina; Bronquiasmol†; Calmarum†; Codol; Drenoflux; Micaveen; ***Rus.:*** Neo-Codion Babies (Нео-Кодион Для Младенцев); ***S.Afr.:*** Aserbine; Dry & Clear Medicated Skin Cleanser; ***Singapore:*** Listerine; Listerine Cool Mint; Listerine Fresh Burst; Listerine Tartar Control; Whitfield†; ***Spain:*** Acerbiol; Broncoformo Muco Dexa; Broncovital†; Bronquidiazina CR; Bronquimar; Etermol Antitusivo; Neumopectolina†; Pastillas Pectoral Kely; Pazbronquial; Pulmo Menal†; Pulmofasa; Tos Mai; ***Switz.:*** Acerbine†; Dinacode N†; Foral†; Gem; Nasobol†; Neo-DP†; Nican; Onguent aux herbes Keller; Phol-Tussil; Phol-Tux; Saintbois; Toplexil; ***Turk.:*** Artu; Gayabeksin; Latusin; Nesgarin; ***UK:*** Aserbine†; Eczema Ointment; Hemocane; Potters Gees Linctus; Sanderson's Throat Specific; Toepedo; ***USA:*** Ammonul; Atrosept; Bensal HP; Cystex; Dolsed†; MHP-A; Prosed/DS; Trac Tabs 2X†; UAA; Ucephan; Uridon Modified†; Urised; Uriseptic; Uritact; ***Venez.:*** Acetoben; Amodion; Boramint†; Corsaben†; Dromil Sauco; Fedratal†; Isacol†; Kantol†; Metilfedrin†; Niosilin; Photoderm AKN; Pi-Fedrin; Tabonuco; Yerba Santa; Yodalmina†.

Benzododecinium Bromide

Benzododecinio, bromuro de. Benzyldodecyldimethylammonium bromide.

$C_{21}H_{38}BrN$ = 384.4.
CAS — 10328-35-5 (benzododecinium); 7281-04-1 (benzododecinium bromide).
ATC — D09AA05.
ATC Vet — QD09AA05.



(benzododecinium)

Pharmacopoeias. In *Fr.*

Benzododecinium Chloride *(rINN)*

Benzododecinii Chloridum; Benzododécinium, Chlorure de; Cloruro de benzododecinio; Lauralkonium Chloride. Benzyldodecyldimethylammonium chloride.

Бензододециния Хлорид
$C_{21}H_{38}ClN$ = 340.0.
CAS — 139-07-1.
ATC — D09AA05.
ATC Vet — QD09AA05.

NOTE. The name Lauralkonium Chloride is also a *rINN* for another quaternary ammonium compound ($C_{29}H_{44}ClNO_2$; CAS – 19486-61-4).

Profile

Benzododecinium bromide is a quaternary ammonium antiseptic with properties similar to those of other cationic surfactants (see Cetrimide, p.1634). It is used in mouthwashes, eye preparations, and nasal sprays and solutions for the treatment of minor infections. It has also been used as a spermicide. Benzododecinium chloride has also been used.

Preparations

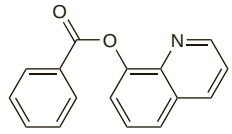
Proprietary Preparations (details are given in Part 3)
Cz.: Ajatin; ***Fr.:*** Rhinedrine.

Multi-ingredient: ***Cz.:*** Ophtal; ***Fr.:*** Prorhinel; Sedacollyre; ***Switz.:*** Kemerhinose; Prorhinel.

Benzoxiquine *(USAN, rINN)*

Benzoxiquina; Benzoxiquinum; NSC-3951. 8-Quinolinol benzoate (ester).

Бензоксихин
$C_{16}H_{11}NO_2$ = 249.3.
CAS — 86-75-9.



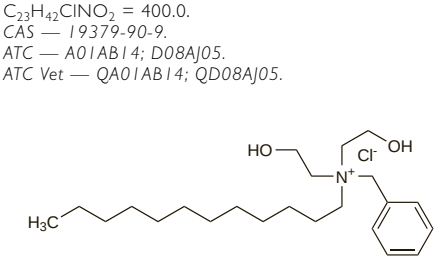
Profile

Benzoxiquine is an antiseptic that has been included in cosmetic products and multi-ingredient preparations used topically for the treatment of fungal infections. The salicylate has also been used.

Benzoxonium Chloride *(rINN)*

Benzoxonii Chloridum; Benzoxonium, Chlorure de; Cloruro de benzoxonio. Benzyldodecylbis(2-hydroxyethyl)ammonium chloride.

Бензоксония Хлорид
$C_{23}H_{42}ClNO_2$ = 400.0.
CAS — 19379-90-9.
ATC — A01AB14; D08AJ05.
ATC Vet — QA01AB14; QD08AJ05.



Profile

Benzoxonium chloride is a quaternary ammonium antiseptic used for disinfection of the skin and mucous membranes. It is also used for instrument disinfection. Allergic contact dermatitis from benzoxonium chloride has been reported.

Preparations

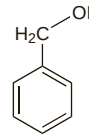
Proprietary Preparations (details are given in Part 3)
Belg.: Orofar; ***Chile:*** Bialcol; ***Gr.:*** Orocil; ***Ital.:*** Bactofen; Bialcol.

Multi-ingredient: ***Belg.:*** Orofar Lidocaine; ***Chile:*** Alcolex; ***Cz.:*** Orofar; ***Ger.:*** Loscon†; ***Gr.:*** Orocil Lido; ***Hung.:*** Mebucain; Vita-Merfen†; ***Israel:*** Merfen; Vita-Merfen NF; ***Philipp.:*** Orofar-L; ***Pol.:*** Orofar; ***Port.:*** Orofar†; ***Rus.:*** Theraflu Lar (Терафлю Лар); ***Switz.:*** Mebucalets f; Merfen; Orofar; Vita-Merfen.

Benzyl Alcohol *(rINN)*

Alcohol bencílico; Alcohol benzylicus; Alcoholum Benzylicum; Alcool Benzylique; Alkohol benzylowy; Bensylalkohol; Bentsyylialkoholi; Benzenemethanol; Benzil-alkohol; Benzilo alkoholis; Benzylalkohol; Benzylique, alcool; Fenilmetanol; Phenylcarbinol; Phenylmethanol.

Бензиловый Спирт
$C_6H_5.CH_2OH$ = 108.1.
CAS — 100-51-6.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *Jpn*. Also in *USNF*.

Ph. Eur. 6.2 (Benzyl Alcohol). A clear colourless, oily liquid. Soluble in water; miscible with alcohol, and with fatty and essential oils. Store under nitrogen in airtight containers at a temperature of 2° to 8°. Protect from light.

USNF 26 (Benzyl Alcohol). A clear, colourless, oily liquid. Sparingly soluble in water; freely soluble in alcohol (50%); miscible with alcohol, with chloroform, and with ether. It is neutral to litmus.

Incompatibility. Benzyl alcohol is incompatible with oxidising agents and strong acids. The antimicrobial activity may be reduced by nonionic surfactants and benzyl alcohol may be lost from solutions stored in polyethylene containers.

Stability. Benzyl alcohol oxidises to produce benzaldehyde and benzoic acid and oxidation may take place slowly on exposure to air. Benzaldehyde may also be produced on autoclaving.

Adverse Effects and Precautions

There have been a few reports of hypersensitivity reactions to benzyl alcohol when used as a preservative.

The pure alcohol is irritant and requires handling with care; ingestion or inhalation can cause nausea, vomiting, diarrhoea, headache, and vertigo. Overexposure results in respiratory failure and CNS depression. However, concentrations of benzyl alcohol normally used for preservation are not associated with such effects.

There have been some instances of neurotoxic effects in patients given intrathecal injections that contained benzyl alcohol.

A fatal toxic syndrome in premature infants was attributed to benzyl alcohol present as a preservative in solutions used to flush intravenous catheters. This has led to restriction on the use of benzyl alcohol in neonates and young children, (see below).

Effects on the lungs. Severe bronchitis and haemoptysis was reported in a patient with obstructive pulmonary disease who, over a period of 2 years, had inhaled salbutamol nebuliser solution diluted with a bacteriostatic sodium chloride solution containing benzyl alcohol.[1]

1. Reynolds RD. Nebulizer bronchitis induced by bacteriostatic saline. *JAMA* 1990; **264**: 35.

Effects on the nervous system. Rapid development of flaccid areflexic paraplegia, total anaesthesia below the groin, and radicular abdominal pain occurred in a 64-year-old man after a lumbar intrathecal injection of cytarabine that contained 1.5% benzyl alcohol.[1] The patient recovered fully after 100 mL of CSF was replaced with sodium chloride 0.9% and 40 mg of methylprednisolone. Intrathecal injections of cytarabine dissolved in sterile distilled water before and after the episode of paraplegia caused no neurologic symptoms. On reviewing 20 other cases of paraparesis associated with methotrexate or cytarabine intrathecal injections, benzyl alcohol had been used as a preservative in

7. Of these, 4 developed neurotoxicity immediately; in the other 3 it did not develop for between 6 and 48 hours. The duration varied. One patient did not improve, one made a partial recovery, a third took 6 weeks to recover, another took 5 days; yet 2 patients recovered within 1′ to 2′ hours while the final patient experienced only transient effects.

1. Hahn AF, *et al.* Paraparesis following intrathecal chemotherapy. *Neurology* 1983; **33:** 1032–8.

Hypersensitivity. Hypersensitivity reactions to benzyl alcohol have been reported.[1-3]

1. Grant JA, *et al.* Unsuspected benzyl alcohol hypersensitivity. *N Engl J Med* 1982; **306:** 108.
2. Shmunes E. Allergic dermatitis to benzyl alcohol in an injectable solution. *Arch Dermatol* 1984; **120:** 1200–1.
3. Wilson JP, *et al.* Parenteral benzyl alcohol-induced hypersensitivity reaction. *Drug Intell Clin Pharm* 1986; **20:** 689–91.

Neonates. During 1981 and 1982 reports were published from 2 centres in the USA[1-3] of 20 deaths in low-birth-weight neonates attributed to the use of benzyl alcohol as a preservative in solutions used to flush their umbilical catheters and in some cases also to dilute their medication. The neonates suffered a toxic syndrome whose features included metabolic acidosis, symptoms of progressive encephalopathy, intracranial haemorrhage, and respiratory depression with gasping.

These deaths prompted the FDA[4] to recommend that benzyl alcohol should not be used in such flushing solutions; sodium chloride injection 0.9% without preservative should be used instead. The FDA had also advised against the use of benzyl alcohol or any preservative in fluids being used for the dilution or reconstitution of medicines for the newborn.

Those reporting the deaths[2,3] considered that the toxic syndrome could have been caused by the accumulation of the benzoic acid metabolite of benzyl alcohol, which could not be handled effectively by the immature liver; given the very low weight of the neonates they would have been receiving a comparatively high dose of benzyl alcohol. In commenting on the problem, the American Academy of Pediatrics[5] agreed that the FDA's warning was warranted, but pointed out that there was no evidence from controlled studies to confirm that benzyl alcohol was responsible.

1. Gershanik JJ, *et al.* The gasping syndrome: benzyl alcohol (BA) poisoning? *Clin Res* 1981; **29:** 895A.
2. Brown WJ, *et al.* Fatal benzyl alcohol poisoning in a neonatal intensive care unit. *Lancet* 1982; **i:** 1250.
3. Gershanik J, *et al.* The gasping syndrome and benzyl alcohol poisoning. *N Engl J Med* 1982; **307:** 1384–8.
4. Anonymous. Benzyl alcohol may be toxic to newborns. *FDA Drug Bull* 1982; **12:** 10–11.
5. American Academy of Pediatrics. Benzyl alcohol: toxic agent in neonatal use. *Pediatrics* 1983; **72:** 356–7.

Pharmacokinetics

Benzyl alcohol is metabolised to benzoic acid. This is conjugated with glycine in the liver to form hippuric acid which is excreted in the urine. Benzaldehyde and benzoic acid are degradation products *in vitro*.

Uses

Benzyl alcohol is used as an antimicrobial preservative. It is bacteriostatic mainly against Gram-positive organisms and some fungi. It is used in a range of pharmaceutical preparations in concentrations up to 2%. Concentrations of 5% or more are employed when it is used as a solubiliser. Benzyl alcohol is used as a preservative in foods and cosmetics. It is also used as a disinfectant at a concentration of 10%.

In addition to its antiseptic properties, concentrations of benzyl alcohol of up to 10% possess weak local anaesthetic and antipruritic activity.

Preparations

Proprietary Preparations (details are given in Part 3)
Canad.: Babys Own Teething Gel†; Zilactin Cold Sore Gel; ***USA:*** Zilactin.

Multi-ingredient: ***Arg.:*** Standard XXI; ***Austral.:*** Coso; Soothe'n Heal; ***Austria:*** Dermaspray; ***Belg.:*** Dermaspray†; Purigel Crisp; Purigel NF; ***Chile:*** Aucusik; Medikem†; Medisept†; ***Denm.:*** Doloproct Comp; ***Fr.:*** Biseptine; Codotussyl Maux de Gorge; Dermaspraid Antiseptique; Pastilles Medicinales Vicks; ***Ger.:*** Autoderm Extra; Gelipur; Spitacid; ***India:*** Dicloran MS; ***Israel:*** Otomycin; ***Ital.:*** Borocaina; Foille Scottature; Foille Sole; Pitiren; Prurex; Skab 2; ***Singapore:*** Saak†; ***Spain:*** Acerbiol; Pastillas Antisep Garg M; ***UK:*** Sudocrem; ***USA:*** Itch-X; MouthKote O/R; Oragesic; Super Ivy Dry; Topic; Tucks.

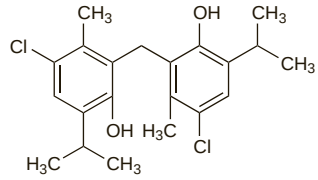
Used as an adjunct in: ***Jpn:*** Panpurol†.

Biclotymol *(rINN)*

Biclotimol; Biclotymolum. 2,2′-Methylenebis(6-chlorothymole).

Биклотимол

$C_{21}H_{26}Cl_2O_2$ = 381.3.
CAS — 15686-33-6.



Profile

Biclotymol is a phenolic antiseptic that is used in lozenges and sprays for mouth and throat infections. It is also an ingredient of cough preparations.

Preparations

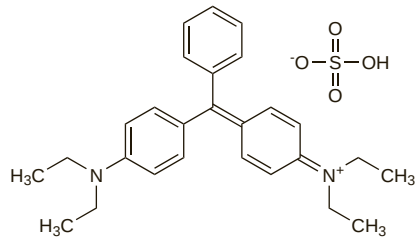
Proprietary Preparations (details are given in Part 3)
Cz.: Hexaspray†; ***Fr.:*** Hexaspray; Humex; Rhinathiol maux de gorge†; Sagadreps†; Sagaspray; Solutricine Maux de Gorge; ***Hong Kong:*** Hexaspray; ***Port.:*** Hexaspray; ***Rus.:*** Hexaspray (Гексаспрей).

Multi-ingredient: ***Fr.:*** Hexalyse; Hexapneumine; Hexarhume; ***Hong Kong:*** Hexalyse; Hexapneumine; ***Rus.:*** Hexalyse (Гексализ).

Brilliant Green

CI Basic Green 1; Colour Index No. 42040; Diamond Green G; Emerald Green; Ethyl Green; Malachite Green G; Solid Green; Verde brillante; Viride Nitens. 4-(4-Diethylaminobenzhydrylidene)cyclohexa-2,5-dien-1-ylidenediethylammonium hydrogen sulphate.

$C_{27}H_{34}N_2O_4S$ = 482.6.
CAS — 633-03-4.



NOTE. The name Emerald Green has also been used for copper acetoarsenite.

Profile

Brilliant green is a triphenylmethane antiseptic dye with actions similar to those of methylrosanilinium chloride (p.1653). Its activity is greatly reduced in the presence of serum.

A gel containing brilliant green 0.5% with lactic acid was formerly used in the treatment of skin ulcers.

An alcoholic solution of brilliant green 0.5% and methylrosanilinium chloride 0.5% (Bonney's Blue) was formerly used for disinfecting the skin, but concern over evidence of *animal* carcinogenicity with methylrosanilinium chloride has led to a decline in its use. A solution of the two disinfectants has been used for marking incisions before surgery.

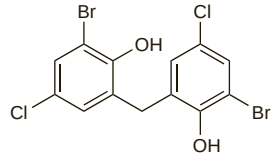
There have been occasional reports of sensitivity to brilliant green.

Adverse effects. For a report of necrotic skin reactions after application of a 1% solution of brilliant green to stripped skin, see under the Adverse Effects of Methylrosanilinium Chloride, p.1653.

Bromchlorophen

Bromchlorophene; Bromochlorophane; Bromoclorofeno. 2,2′-Methylenebis[6-bromo-4-chlorophenol].

$C_{13}H_8Br_2Cl_2O_2$ = 426.9.
CAS — 15435-29-7.



Profile

Bromchlorophen is a halogenated bisphenol antiseptic more active against Gram-positive than Gram-negative bacteria. It is used for disinfection of the hands and skin. It has also been used in deodorants and toothpastes.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Ger.:*** Dibromol.

Bromsalans

Bromosalicilanilidas.
CAS — 55830-61-0.

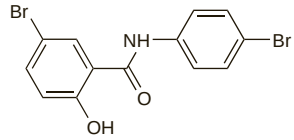
Description. Bromsalans are a series of brominated salicylanilides that possess antimicrobial activity.

Dibromsalan *(USAN, pINN)*

Dibromsalán; Dibromsalanum; NSC-20527. 4′,5-Dibromosalicylanilide; 5-Bromo-*N*-(4-bromophenyl)-2-hydroxybenzamide.

Дибромсалан

$C_{13}H_9Br_2NO_2$ = 371.0.
CAS — 87-12-7.

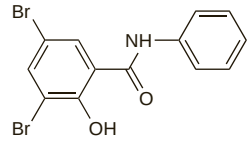


Metabromsalan *(USAN, pINN)*

Métabromsalan; Metabromsalán; Metabromsalanum; NSC-526280. 3,5-Dibromosalicylanilide; 3,5-Dibromo-2-hydroxy-*N*-phenylbenzamide.

Метабромсалан

$C_{13}H_9Br_2NO_2$ = 371.0.
CAS — 2577-72-2.

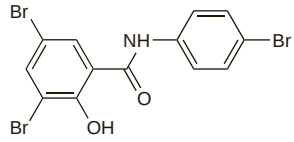


Tribromsalan *(BAN, USAN, rINN)*

ET-394; NSC-20526; TBS; Tribromsalán; Tribromsalanum. 3,4′,5-Tribromosalicylanilide; 3,5-Dibromo-*N*-(4-bromophenyl)-2-hydroxybenzamide.

Трибромсалан

$C_{13}H_8Br_3NO_2$ = 449.9.
CAS — 87-10-5.



Profile

Bromsalans have antibacterial and antifungal activity and have been used in medicated soaps, but there have been many reports of photosensitivity arising from this use.

Preparations

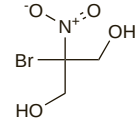
Proprietary Preparations (details are given in Part 3)
Ital.: Bergamon Sapone.

Bronopol *(BAN, rINN)*

Bronopolum. 2-Bromo-2-nitropropane-1,3-diol.

Бронопол

$C_3H_6BrNO_4$ = 200.0.
CAS — 52-51-7.
ATC Vet — QD01AE91.



Pharmacopoeias. In *Br.* and *Pol.*
BP 2008 (Bronopol). White or almost white crystals or crystalline powder, odourless or almost odourless. Freely soluble in