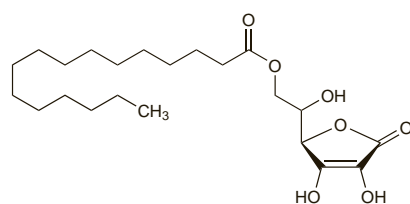


Fr.: Strepsils; Strepsils Lidocaine; Strepsils Miel-Citron; Strepsils Vitamine C; Strepsilspray Lidocaine; **Ger.:** Dobendan Synergie; Neo-Angin; **Gr.:** Strepsils; **Hong Kong:** Strepsils; Strepsils Dual Action; **Hung.:** Neo-Angin; Strepsils; Strepsils Menthil and Eucalyptus; Strepsils Plus; Strepsils Vitamin C; **India:** Cof Q; Cofslit; **Ir.:** Strepsils; Strepsils +Plus Anaesthetic; Strepsils Dual Action; Strepsils Vitamin C; **Israel:** Strepsils; Strepsils Plus; Strepsils with Menthil and Eucalyptus; Strepsils with Vitamin C; **Ital.:** Benagol; Benagol Mentolo-Eucalyptol; Benagol Vitamina C; **Malaysia:** Chericof; Strepsils; Strepsils Dual Action; **Neth.:** Strepsils; Strepsils Menthil en Eucalyptus; Strepsils Sinaasappel en Vitamine C; **NZ:** Strepsils; Strepsils Plus Anaesthetic; Strepsils with Vitamin C; **Philipp.:** Strepsils; **Pol.:** Neo-Angin; Strepsils; **Rus.:** Astrasept (Астрасепт); Coldact Loripils (Колдакт Лорпилс); Rinza Lorsept (Ринза Лорсепт); Strepsils (Стрепсилс); Strepsils Plus (Стрепсилс Плюс); Suprima-Lor (Суприма-Лор); **S.Afr.:** Strepsils; Strepsils Eucalyptus Menthil; Strepsils Orange-C; Strepsils Plus; Strepsils Soothing Honey & Lemon; **Singapore:** Strepsils; Strepsils Dual Action; **Spain:** Strepsils; Strepsils con Vitamina C; Strepsils Lidocaina; **Swed.:** Strepsils; **Switz.:** Neo-Angin au miel et citron; Neo-Angin avec vitamin C sans sucre; Neo-Angin sans sucre; **Thai.:** Strepsils Butter Menthil Capsicum; Strepsils Plus Anaesthetic; Strepsils Plus Vit C; Strepsils Sugar Free; Throatil; **Turk.:** Strepsils; Strepsils C; Strepsils Mentollu; **UK:** Strepsils; Strepsils with Vitamin C.

Ascorbyl Palmitate

Ascorbilo, palmitato de; Ascorbyle, palmitate d'; Ascorbylil palmitas; Ascorbilo palmitatas; Askorbylpalmitat; Askorbylpalmitát; Askorbylu palmitynian; Askorbylilpalmitaatti; Aszkorbilpalmitát; Vitamin C Palmitate. L-Ascorbic acid 6-hexadecanoate; L-Ascorbic acid 6-palmitate; 3-Oxo-L-gulofuranolactone 6-palmitate.

$C_{22}H_{38}O_7 = 414.5$.
CAS — 137-66-6.



NOTE. The code E304 is used for fatty acid esters of ascorbic acid, which include ascorbyl palmitate.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF*.

Ph. Eur. 6.2 (Ascorbyl Palmitate). A white or yellowish-white powder. Practically insoluble in water; freely soluble in alcohol and in methyl alcohol; practically insoluble in dichloromethane and in fatty oils. Store in airtight containers. Protect from light.

USNF 26 (Ascorbyl Palmitate). A white to yellowish-white powder with a characteristic odour. Very slightly soluble in water, in chloroform, in ether, and in vegetable oils; soluble 1 in 125 of alcohol. Store at 8° to 15° in airtight containers.

Profile

Ascorbyl palmitate is an antioxidant used as a preservative in pharmaceutical products and foods. It is often used with alpha tocopherol (p.1992), and this combination shows marked synergy. As it is a fat-soluble derivative of vitamin C (ascorbic acid, p.1983), ascorbyl palmitate is sometimes used as a source of vitamin C in nutritional supplements.

Preparations

Proprietary Preparations (details are given in Part 3)

Chile: Neolucid-C.

Multi-ingredient: **Hong Kong:** Proflavanol†; **Malaysia:** Proflavanol; **Port.:** Thiospot; **Singapore:** Proflavanol.

Benzalkonium Chloride (BAN, rINN)

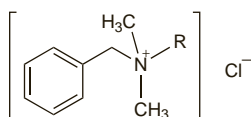
Benzalkoniumklorid; Bentsalkoniumkloridi; Benzalconio Cloruro; Benzalkonii chloridum; Benzalkonio chloridas; Benzalkoniowy chlorek; Benzalkonium Chloratum; Benzalkonium, chlorure de; Benzalkonium-chlorid; Benzalkónium-klorid; Benzalkonyum Klor-ür; Cloreto de Benzalconio; Cloruro de benzalconio.

Бензалкония Хлорид

CAS — 8001-54-5.

ATC — D08AJ01; D09AA11; R02AA16.

ATC Vet — QD08AJ01; QD09AA11; QR02AA16.



R = C₈H₁₇ to C₁₈H₃₇

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *Jpn.* Also in *USNF*. Some pharmacopoeias also have a monograph for a solution.

Chin. also includes benzalkonium bromide.

Ph. Eur. 6.2 (Benzalkonium Chloride). A mixture of alkylbenzyltrimethylammonium chlorides, the alkyl groups having chain lengths of C₈ to C₁₈. It contains not less than 95% and not more than 104% of alkylbenzyltrimethylammonium chlorides, calculated as C₂₂H₄₀ClN with reference to the anhydrous substance. A white or yellowish-white powder, or gelatinous yellowish-white pieces, hygroscopic and soapy to the touch. It forms a clear molten mass on heating. It contains not more than 10% of water. Very soluble in water and in alcohol. An aqueous solution froths copiously when shaken.

USNF 26 (Benzalkonium Chloride). A mixture of alkylbenzyltrimethylammonium chlorides of the general formula [C₆H₅.CH₂.N(CH₃)₃.R]Cl, in which R represents a mixture of the alkyls having chain lengths from C₈ to C₁₆. It contains not less than 40% of the C₁₂H₂₅ compound, calculated on the anhydrous substance, not less than 20% of the C₁₄H₂₉ compound, and not less than 70% of the 2 compounds together.

A white or yellowish-white, thick gel, or gelatinous pieces with a mild aromatic odour. It contains not more than 15% of water. Very soluble in water and in alcohol; the anhydrous form is soluble 1 in 100 of ether and 1 in 6 of benzene. A solution in water is usually slightly alkaline and foams strongly when shaken. Store in airtight containers.

Incompatibility. Benzalkonium chloride is incompatible with soaps and other anionic surfactants, citrates, iodides, nitrates, permanganates, salicylates, silver salts, tartrates, and zinc oxide and sulfate. Incompatibilities have been demonstrated with ingredients of some commercial rubber mixes or plastics. Incompatibilities have also been reported with other substances including aluminium, cotton dressings, fluorescein sodium, hydrogen peroxide, hypromellose, kaolin, hydrous wool fat, and some sulfonamides.

Adverse Effects, Treatment, and Precautions

As for Cetrimide, p.1634. Because some rubbers are incompatible with benzalkonium chloride silicone rubber teats should be used on eye drop containers unless the suitability has been established.

Catheters and cannulas. For reference to benzalkonium chloride used in the manufacturing process of heparin-bonded catheters interfering with determination of serum concentrations of sodium and potassium, see under Precautions for Heparin, p.1303.

Effects on the eyes. Benzalkonium chloride is one of the most disruptive ophthalmic additives to the stability of the lipid film and to corneal epithelial membranes; toxicity studies have tended to be carried out using relatively high concentrations of benzalkonium chloride² but damage to the tear film and corneal conjunctival surface have been noted in patients receiving regular long-term treatment for glaucoma with eye drops preserved with benzalkonium chloride in usual concentrations.^{3,4}

Corneal toxicity has also been reported in patients inadvertently exposed to benzalkonium chloride as a preservative in viscoelastic material during cataract surgery.⁵ The use of preservatives in eye drops should generally be avoided and the formulation of such preparations in single-dose containers is desirable.^{1,2} Benzalkonium chloride is not suitable for use in solutions for storing and washing hydrophilic soft contact lenses, as it can bind to the lenses and may later produce ocular toxicity when the lenses are worn.⁶ Similarly, benzalkonium chloride use in anaesthetic eye drops is discouraged, as the anaesthetic component reduces the blink reflex and increases the contact time with the eye drops which may consequently result in increased toxicity due to the preservative. Patients with dry eye syndrome are also at increased risk of toxicity as the corneal epithelium is exposed to the full strength of the eye drops, in addition to which these patients do not produce enough tears to dilute the preservative in the eye drops.

1. Burstein NL. The effects of topical drugs and preservatives on the tears and corneal epithelium in dry eye. *Trans Ophthalmol Soc U K* 1985; **104**: 402-9.

2. Burstein NL. Corneal cytotoxicity of topically applied drugs, vehicles and preservatives. *Surv Ophthalmol* 1980; **25**: 15-30.

3. Herrerias JM, *et al.* Ocular surface alteration after long-term treatment with an antiglaucomatous drug. *Ophthalmology* 1992; **99**: 1082-8.

4. Kuppens EVMJ, *et al.* Effect of timolol with and without preservative on the basal tear turnover in glaucoma. *Br J Ophthalmol* 1995; **79**: 339-42.

5. Eleftheriadis H, *et al.* Corneal toxicity secondary to inadvertent use of benzalkonium chloride preserved viscoelastic material in cataract surgery. *Br J Ophthalmol* 2002; **86**: 299-305.

6. Gasset AR. Benzalkonium chloride toxicity to the human cornea. *Am J Ophthalmol* 1977; **84**: 169-71.

Effects on the respiratory tract. Hypersensitivity to benzalkonium chloride, used as a preservative in nasal drops, was confirmed in a patient by a challenge that produced nasal congestion

and irritation of the eyes and throat lasting 48 hours.¹ A review² of 18 studies (14 *in vivo*, 4 *in vitro*) where benzalkonium chloride was used as the preservative in multidose nasal products found that 8 studies (all *in vivo*) found no toxic effects, while 10 reported degenerative changes to the nasal epithelia or exacerbation of rhinitis medicamentosa. However, in only 2 of these 10 studies were the differences between benzalkonium chloride and control groups found to be significant, and both of these included the use of oxymetazoline, which is known to cause rhinitis medicamentosa.

Benzalkonium chloride used as a preservative in nebulised solutions of anti-asthma drugs has been reported to cause dose-related bronchoconstriction especially in asthmatic patients,³ and has been associated with the precipitation of respiratory arrest.⁴

- Hillerdal G. Adverse reaction to locally applied preservatives in nose drops. *ORL J Otorhinolaryngol Relat Spec* 1985; **47**: 278-9.
- Marple B, *et al.* Safety review of benzalkonium chloride used as a preservative in intranasal solutions: an overview of conflicting data and opinions. *Otolaryngol Head Neck Surg* 2004; **130**: 131-41.
- Committee on Drugs, American Academy of Pediatrics. "Inactive" ingredients in pharmaceutical products: update. *Pediatrics* 1997; **99**: 268-78.
- Boucher M, *et al.* Possible association of benzalkonium chloride in nebulizer solutions with respiratory arrest. *Ann Pharmacother* 1992; **26**: 772-4.

Interactions

Benzalkonium chloride is not suitable for use in eye drops containing local anaesthetics (see Effects on the Eyes, above).

Uses and Administration

Benzalkonium chloride is a quaternary ammonium antiseptic and disinfectant with actions and uses similar to those of the other cationic surfactants (see Cetrimide, p.1634). It is also used as an antimicrobial preservative for pharmaceutical products. Benzalkonium bromide and benzalkonium saccharinate have also been used.

Solutions of benzalkonium chloride 0.01 to 0.1% are used for cleansing skin, mucous membranes, and wounds. More dilute solutions of 0.005% are suitable for irrigation of deep wounds. A 0.02 to 0.05% solution has been used as a vaginal douche. An aqueous solution containing 0.005 to 0.02% has been used for irrigation of the bladder and urethra and a 0.0025 to 0.005% solution for retention lavage of the bladder.

Creams containing benzalkonium chloride are used in the treatment of napkin rash and other dermatoses.

A 0.2 to 0.5% solution has been used as a shampoo in seborrhoeic dermatitis.

Lozenges containing benzalkonium chloride are used for the treatment of superficial infections of the mouth and throat.

Benzalkonium chloride is used as a preservative in ophthalmic solutions at a concentration of 0.01 to 0.02%, and in nasal and otic solutions at a concentration of 0.002 to 0.02%. Benzalkonium chloride is used for disinfecting rigid contact lenses (p.1622) but is unsuitable as a preservative in solutions for washing and storing hydrophilic soft contact lenses (see also Effects on the Eyes, above).

Benzalkonium chloride is also used as a spermicide.

Solutions of 0.13% are used for disinfection and storage of surgical instruments, sometimes with the addition of sodium nitrite to inhibit rust.

Action. The antibacterial effect of benzalkonium chloride 0.003% was enhanced by 0.175% of benzyl alcohol, phenylpropanol, or phenethyl alcohol.¹ For the use of phenethyl alcohol with benzalkonium chloride as a preservative for ophthalmic solutions, see Antimicrobial Action, under Phenethyl Alcohol, p.1655.

1. Richards RME, McBride RJ. Enhancement of benzalkonium chloride and chlorhexidine acetate activity against *Pseudomonas aeruginosa* by aromatic alcohols. *J Pharm Sci* 1973; **62**: 2035-7.

Catheter-related sepsis. Benzalkonium chloride has been investigated^{1,2} for incorporation into catheters to reduce catheter-related sepsis (p.1624).

- Tebbs SE, Elliott TSJ. A novel, antimicrobial central venous catheter impregnated with benzalkonium chloride. *J Antimicrob Chemother* 1993; **31**: 261-71.
- Moss HA, *et al.* A central venous catheter coated with benzalkonium chloride for the prevention of catheter-related microbial colonization. *Eur J Anaesthesiol* 2000; **17**: 680-7.

Preparations

USNF 26: Benzalkonium Chloride Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Benzalcream; Hidratant; Pharmatex; Unicon; **Austral:** Bepanthen; Dettol Fresh; **Belg.:** Cedium; **Braz.:** Bacterian; Fluimucil Solucao Nasal; **Canada:** Antiseptic Skin Cream; **Chile:** Germosept; **Cz.:** Pharmatex; **Fr.:** Humex; Pharmatex; Sparaplaie; **Ger.:** Baktonium; Killavon; Laudamonium; Lysosform Killavon; **Hong Kong:** Pharmatex; **Hung:** Pharmatex; **Ir.:** Dettol Fresh; **Israel:** Pharmatex; **Ital.:** Alfa C; Amuclean; Benalcon; Bergayin; Bluesteril; Citrosil; Citrosteryl Ambiente; Citrosteryl Deterfermi; Detergil; Dimarin R; Dimil; Disepil; Disigen; Disintyl; Display; Distasil; Distenil; Eso Deterfermi; Eso Fern; Essan Casa; Essan Soap; Germicidin; Germozero Clean; Helis; Hygienist; Pavimeriti e Plastrelle; Iridina Light; Lacinbase; Loziona; Maxitenil; Neo-Desogen; Norica; Polisan; Sanaform; Sangen; SaniSteril Deterfermi; Saquat; Sguardi; Singen; Steraminil; Steramina G; Stilla Delicata; Streptosil L; PMC; Ten-Quat; Video-Light; **Mex.:** Derman Talco; Lubrinal; Merthiolate; **NZ:** Dettol; Dettol Fresh; Virasolve; **Port.:** Pharmatex; **Rus.:** Pharmatex (Фарматек); Spermatek (Сперматек); **Spain:** Amil; Crema Contracepti Lanzas; Mini Ovulo Lanzas; **Switz.:** Benzaltek; **Thai.:** Pose-Bac; **Turk.:** Zefan; Zefiran; Zefol; Zefort; Zefosol; Zentefektol; Zentani; **UK:** Bradosol; Dermax Therapeutic Shampoo; Dettol Antiseptic Wash; Dettol Fresh; **USA:** Bacti-Cleanse; Benza; Mycocide NS; Ony-Clear; Zephiran; **Venez.:** Decomed.

Multi-ingredient Arg.: Antiseptic Plus; Crema de Ordene; Eurocoal; Hexil Antiseptic; Merthiolate NF; Muelita; Neo Coliort; Oilallo; Polviderm NF; Soquette; **Austral:** Animine; Clean Skin Face Wash; Gum-Ese; Mycil Healthy Feet; Oilatum Plus; Paxyl; Solypol; TAGG; Virasolve; **Austria:** Aleot; Dequonal; Dermaspray; Dorithricin; Limex; Tyrothricin comp; **Belg.:** Akispray; Dermaspray; **Braz.:** Bactelan; Cetralin; Colpatrin; Colpistat; Colpistatin; Dermofit; Dinil; Donnagel; Drapolene; Ginestatin; Higicler; Nasolin; Oxizinc; Pomada Minicora; Rinotil; Tricomax; Vagi Bi-otic; Visolon; **Canada:** Bactine; Family Medic First Aid Treatment; Medi-Dan; Protectaid; Tanac; **Chile:** Dermobarina; Dexagin; Medisept; Orajel Compustop; **Cz.:** Coldrex Laryplus; Dr. Rentschler Halstabletten; Oilatum Plus; Septolete; **Fr.:** Acarid; Biseptine; Dermasprad Antiseptique; Dermobacter; Humex; Kenalcol; Mercryl; Mercrylsolins; Pharmatex; Rhinoflinomucil; **Ger.:** Bacacalin; Baciloidil rasant; Cutasept; Dequonal; Dorithricin Original; Dynehan Mundgel; Freka-Derm; Freka-Sept 80; Gingicain D; Hexaqua L; Hexaqua S; Incidin; Incidin extra N; Incidin Extra; Incidin perfect; Incidur Spray; Inova; Kohsolin FF; Korsolex Extra; Korsolex FF; Lysotel Med; Mikrobac; Qatohex; Sekusept Extra N; Sekusept forte; Septolit; Skinman Soft; Ultrasol-F; **Gr.:** Beta Ophthol; Cutasept; Olantex; **Hong Kong:** Dermobacter; Dermojela; Drapolene; Mycil; Oilatum Plus; Protectaid; Virasolve; **Hung:** Coldrex Laryplus; Dorithricin; **India:** Rashfree; **Indon.:** Mexochrom; Oilatum Plus; **Ir.:** Conotranep; **Israel:** Emulsiderm; Mycil; Oilatum Junior Flare-Up; Oilatum Plus; Torbetol; **Israel:** Aptagone; Apta-X; Emulsiderm; Garonsept; **Ital.:** Agipul; AZ 15; Barrycidal; Bernalcol; Cerostenil; Cerox; Citromed 80 and 85; Citromed Chirurgico; Citromedics Pronto; Citrosil Alcolico Azzuro; Citrosil Alcolico Bruno; Citrosil Alcolico Incolore; Citrosil Nubesan; Citrosteryl Impronite; Citrosteryl Pronto; Citrosteryl Strumenti; Collyria; Eso Fern Alcolico; Eso Fern Alcolico Plus; Eso S 80; Esoalcolico Incolore; Esoform 92; Esoform Alcolico; Essan Pronto; Germozero Dermo; Germozero Plus; Hamamilla; Herbe; Incidin Special; Incidur Spray; Indulan; Ipragocce; Lin-ea F; Lycia Limunique; Mediplus; Neo Emocicatrol; Neomedil; Norica; Ondong; Pupilla Light; Rexichlor; Sangen Casa; SaniSteril Strumenti Alcolico; Sekusept Extra N; Sicura3 Medical; Simp; Simpotantacique; Sterosan; Tirs; Zincometil; **Malaysia:** Drapolene; Oilatum Plus Antibacterial; QV Flare Up; **Mex.:** Dermacid; Glossderm; Novagone; Sutint; **NZ:** Oilatum Plus; **Philipp.:** Drapolene; Oilatum Plus; **Pol.:** Coldrex; Oilatum Plus; Septolete; **Rus.:** Drapolene (Драполен); Septogal (Септогал); Septolete (Септолет); **S.Afr.:** Oilatum Plus; **Singapore:** Dorithricin; Drapolene; Napitol; Oilatum Plus; QV Flare Up; **Spain:** Aviajuventus; Alcohol Benzalcolico; Alcohol CL Benz; Alcohol Potenciado; Avli; Curine; Dermo Halibut; Desinav; Egarone; Ginejuvent; Gradin Del D Andreu; Lindemil; Mercryl Plus; Odamida; Otogen Calmante; Pental Forte; Phonal; Pomada Heridas; Resorborina; Sebulsol; Tulgrasum Cicatrizzante; Vaselatum; **Switz.:** Cutasept; Dequonal; Frekaderm; Leucen; Parapic; **Thai.:** Drapolene; Gynecon; Gynecon-T; Gynoco; Gynova; Gyracron; Napilene; Nystin; Oilatum Plus; Sanaco; **Turk.:** Drapolene; Kortos; **UK:** Beechams Max Strength Sore Throat Relief; Beechams Throat-Plus; Cetanorm; Conotran; Dermol; Dettol; Drapolene; Emulsiderm; Germolene; Germoloids; Mycil; Neo Baby Cream; Oilatum Junior Flare-Up; Oilatum Plus; Protectaid; **USA:** Bactine Antiseptic; Bactine Pain Relieving Cleansing; Cetylclide II; Cortic ND; Medi-Quik; Mediotic-HC; Orajel Mouth Aid; Oxzyl; Pedi-Pro; Tanac; Tanac Dual Core; Vagi-Gard Medicated Cream; Vi Rid-Rעד; Zonite; **Venez.:** Gynovit; Pedi-Lotion.

Benzethonium Chloride (BAN, rINN)

Benzetoniumklorid; Bentsetoniumklorid; Benzethonii chloridum; Benzéthonium, chlorure de; benzethonium-chlorid; Benzetonium chloridas; Benzetoniowy chlorek; Benzetónium-klorid; Cloruro de benzetonio; Diisobutylphenoxyethoxyethylmethylbenzylammonium chloride. Benzylidimethyl-(2-[2-[(4-(1,1,3,3-tetramethylbutyl)phenoxy]ethoxy)ethyl]ammonium chloride.

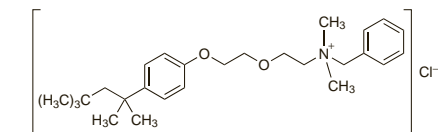
Бензетония Хлорид

C₂₇H₄₂ClNO₃ = 448.1.

CAS — 121-54-0.

ATC — R02AA09.

ATC Vet — QR02AA09.



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

Ph. Eur. 6.2 (Benzethonium Chloride). A white or yellowish-white powder. Very soluble in water and in alcohol; freely soluble in dichloromethane. An aqueous solution froths copiously when shaken. Protect from light.

USP 31 (Benzethonium Chloride). White crystals with a mild odour. Soluble 1 in less than 1 of water, of alcohol, and of chloroform, and 1 in 6000 of ether. A 1% solution in water is slightly alkaline to litmus. Store in airtight containers. Protect from light.

Incompatibility. Benzethonium chloride is incompatible with soaps and other anionic surfactants.

Profile

Benzethonium chloride is a quaternary ammonium antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, p.1634). It is used as a preservative in pharmaceutical and cosmetic products. It has also been used as a vaginal spermicide.

◇ Benzethonium chloride, which produced mild skin irritation at a concentration of 5% but not lower, was not considered to be a sensitizer, and was considered to be safe at a concentration of 0.5% in cosmetics applied to the skin and at a maximum concentration of 0.02% in cosmetics used in the eye area.¹

1. The Expert Panel of the American College of Toxicology. Final report on the safety assessment of benzethonium chloride and methylbenzethonium chloride. *J Am Coll Toxicol* 1985; **4**: 65–106.

Preparations

USP 31: Benzethonium Chloride Concentrate; Benzethonium Chloride Tincture; Benzethonium Chloride Topical Solution.

Proprietary Preparations (details are given in Part 3)

Canada: Clearskin Antibacterial; Neutrogena Antiseptic Cleanser; Skin Cleanser & Deodorizer; **S.Afr.:** Johnson's Antiseptic Powder; **USA:** Antiseptic Wound & Skin Cleaner.

Multi-ingredient Arg.: Butimerin; Solumerin; **Austral:** Summers Eve Feminine; **Belg.:** Neo-Golaseptine; **Braz.:** Andolba; Hipodex; Solemil; Spray Anti-Septico; **Canada:** Antiseptic Skin Cream; Lipsorex Plus; Lipsorex; MRX; Protecto; VoSol HC; **Chile:** Aucusil; Dermaglos Plus; Lefimil; Molca; **Cz.:** Cemaquin; **Ger.:** Brand-u. VVundgel-Medice N; **Hong Kong:** Cemaquin; **Ital.:** Barrycidal; Sangen Casa; **NZ:** VoSol; **S.Afr.:** Dry & Clear Medicated Skin Cleanser; **Spain:** Alcohol Poten; Eupnol; Halibut; Halibut Hidrocortisona; Isdinex; **Switz.:** Angidine; Cemaquin; Rhinocure; Rhinocure simplex; Tyrocombine; Tyrothricine + Gramicidine; **Thai.:** Iwazin; Sigatrin; **USA:** Acetasol; Acetasol HC; Aerocaine; Americaine First Aid; Dermoplast Antibacterial; Skin Shield; Vagisil; VoSol HC; VoSol+.

Benzoates

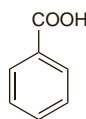
Benzoatos.

Benzoic Acid

Acide benzoïque; Acidum benzoicum; Bensoesyra; Bentsoehap-po; Benzoessäure; Benzoësav; Benzoico, ácido; Benzoïnē rūgštis; Dracylic Acid; E210; Kwas benzoesowy; Kyselina benzoová.

C₆H₅.CO₂H = 122.1.

CAS — 65-85-0.



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

Ph. Eur. 6.2 (Benzoic Acid). A white or almost white, crystalline powder or colourless crystals, odourless or with a very slight characteristic odour. Slightly soluble in water; soluble in boiling water; freely soluble in alcohol and in fatty oils. M.p. 121° to 128°.

USP 31 (Benzoic Acid). White crystals, scales, or needles, with a slight characteristic odour. Soluble 1 in 300 of water, 1 in 3 of alcohol, 1 in 5 of chloroform, and 1 in 3 of ether; freely volatile in steam. Congealing range 121° to 123°.

Incompatibility. The incompatibilities of benzoic acid are described under Sodium Benzoate, below.

Sodium Benzoate

Benzoan sodný; Benzoato sódico; E211; Natrii benzoas; Natrio benzoatas; Natrium Benzoicum; Natriumbenzoat; Natriumbent-soatit; Natrium-benzoat; Sodii Benzoas; Sodium, benzoate de; Soda benzoësan; Sodium Benzoat.

C₆H₅.CO₂Na = 144.1.

CAS — 532-32-1.

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

Ph. Eur. 6.2 (Sodium Benzoate). A white or almost white, slightly hygroscopic, crystalline or granular powder or flakes. Freely soluble in water; sparingly soluble in alcohol (90% v/v).

USNF 26 (Sodium Benzoate). A white, odourless or practically odourless, granular or crystalline powder. Soluble 1 in 2 of water, 1 in 75 of alcohol, and 1 in 50 of alcohol 90%.

Incompatibility. Benzoic acid and its salts are incompatible with quaternary compounds, calcium salts, ferric salts, and salts of heavy metals. Their activity is also diminished by nonionic surfactants or due to absorption by kaolin. They are relatively inactive above a pH of about 5.

Adverse Effects and Precautions

The benzoates can cause hypersensitivity reactions, but there have also been reports of non-immunological contact urticaria. The acid can be irritant to skin, eyes, and mucous membranes.

Infants given large doses of sodium benzoate have suffered vomiting. Symptoms of overdosage reported in this group have included vomiting, irritability and, in more severe cases, renal tubular dysfunction, hypokalaemia, hypocalcaemia, and metabolic acidosis.

Premature infants have been reported to be at risk of metabolic acidosis and kernicterus.

Hypersensitivity. Respiratory reactions to benzoates may occur, especially in patients susceptible to aspirin-induced asthma.^{1,2} Urticarial reactions have also been associated with these compounds,^{3,4} though at a lower incidence⁵ and they can be non-immunological.⁶ However, these reports have to be balanced against a controlled study⁷ that showed no difference in the incidence of urticaria or atopic symptoms between patients given benzoic acid and those given lactose placebo. A retrospective study⁸ of 47 patients who had previously shown a hypersensitivity reaction after ingesting food or products containing benzoate sodium found that the incidence of a repeat episode of acute urticaria or angioedema on re-challenge was very low (2%).

Anaphylactoid reactions have been reported in 2 patients.^{9,10}

Erythema multiforme has been observed in several patients.¹¹

- Rosenhall L. Evaluation of intolerance to analgesics, preservatives and food colorants with challenge tests. *Eur J Respir Dis* 1982; **63**: 410–19.
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Neonates. Serious metabolic disturbances in premature neonates given intravenous fluids with benzyl alcohol as a preservative have been attributed to the accumulation of benzoic acid, a metabolite of benzyl alcohol (see p.1632). This risk led to the recommendation that Caffeine and Sodium Benzoate Injection (USP), which has been given as a respiratory stimulant, should not be used in neonates.¹

Sodium benzoate has been tried in the treatment of some neonatal metabolic disorders (see Uses and Administration, below). However, benzoates can also displace bound bilirubin from albumin putting neonates at risk of kernicterus.² Three cases of toxicity have been reported after accidental high doses of intravenous sodium benzoate and sodium phenylacetate were given to children with hyperammonaemia.³ All the children initially became agitated and confused, had Kussmaul respiration (rapid, deep breathing) and developed a partial metabolic acidosis with an increased anion gap. Two patients subsequently developed cerebral oedema and hypotension and died while the third survived after haemodialysis.

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Pharmacokinetics

The benzoates are absorbed from the gastrointestinal tract and conjugated with glycine in the liver to form hippuric acid, which is rapidly excreted in the urine.

Neonates. References.

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