

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; **Canad.:** Antiseptic Skin Cream; **Chile:** Germosept; **Cz.:** Pharmatex; **Fr.:** Humex; Pharmatex; Sparaplaie; **Ger.:** Baktonium; Killavon; Laudamonium; Lysolform Killavon; **Hong Kong:** Pharmatex; **Hung.:** Pharmatex; **Ir.:** Dettol Fresh; **Israel:** Pharmatex; **Ital.:** Alfa C; Amuclean; Benalcon; Bergayn; Bluesteril; Citrosil; Citrosteril Ambiente; Citrosteril Deterfermi; Detergil; Dimarin R; Dimil; Disepit; Disigen; Disintyl; Display; Distasil; Distenil; Eso Deterfermi; Eso Fern; Essoson Casa; Essoson 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; P.M.C.; Iren-Quat; Video-Light; **Mex.:** Derman Talco; Lubrinal; Merthiolate; **NZ:** Dettol; Dettol Fresh; Virasolve; **Port.:** Pharmatex; **Rus.:** Pharmatex (Фарматек); Spermatek (Сперматек); **Spain:** Armil; Crema Contracepti Lanzas; Mini Ovulo Lanzas; **Switz.:** Benzaltek; **Thai.:** Pose-Bac; **Turk.:** Zefan; Zefiran; Zefol; Zefort; Zefosol; Zefektol; Zentani; **UK:** Bradosol; Dermax Therapeutic Shampoo; Dettol Antiseptic Wash; Dettol Fresh; **USA:** Bacti-Cleanse; Benza; Mycoicide NS; Ony-Clear; Zephiran; **Venez.:** Decomed.

Multi-ingredient Arg.: Antiseptic Plus; Crema de Ordene; Eurocoal; Hexil Antiseptic; Merthiolate NF; Muelita; Neo Colitort; Oilalfo; 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.:** Belagin; Cetrilan; Colpatrin; Colpist; Colpatrin; Dermofol; Dinil; Donnagel; Drapolene; Ginestatin; Higicler; Nasolin; Oxizinc; Pomada Minicora; Rinotil; Tricomax; Vagi Bi-otic; Visolon; **Canad.:** 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; Mercrylsols; Pharmatex; Rhinoflinomucil; **Ger.:** Bacacalin; Baciloidol 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.:** Conotrane; **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; Citrotil Alcolico Azzuro; Citrotil Alcolico Bruno; Citrotil Alcolico Incolore; Citrotil Nubesan; Citrosteril Impronite; Citrosteril Pronto; Citrosteril Strumenti; Collyria; Eso Fern Alcolico; Eso Fern Alcolico Plus; Eso S 80; Esoalcolico Incolore; Esoform 92; Esoform Alcolico; Essoson Pronto; Germozero Dermo; Germozero Plus; Hamamilla; Herbe; Incidin Special; Incidur Spray; Indulfan; Ipragocce; Lin-ea F; Lycia Limunique; Mediplus; Neo Emocicatrol; Neomedil; Norica; Ondong; Pupilla Light; Rexichlor; Sangen Casa; SaniSteril Strumenti Alcolico; Sekusept Extra Nj; Sicura3 Medical; Simp; Simpotantacique; Sterosan; Tirs; Zincometil; **Malaysia:** Drapolene; Oilatum Plus Antibacterial; QV Flare Up; **Mex.:** Dermacod; Glossiderm; Novagone; Sutint; **NZ:** Oilatum Plus; **Philipp.:** Drapolene; Oilatum Plus; **Pol.:** Coldrex; Oilatum Plus; Septolete; **Rus.:** Drapolene (Драполен); Septogal (Септогал); Septolete (Септолете); **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; Gyracon; Napilene; Nystin; Oilatum Plus; Sanaco; **Turk.:** Drapolene; Kortos; **UK:** Beechams Max Strength Sore Throat Relief; Beechams Throat-Plus; Cetanorm; Conotrane; 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)ethylammonium chloride.

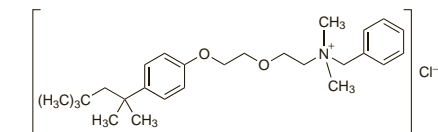
Бензетония Хлорид

$C_{27}H_{42}ClNO_2 = 448.1$.

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)

Canad.: 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; **Canad.:** 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; Eupnil; 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

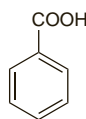
Benzoatos.

Benzoic Acid

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

$C_6H_5.CO_2H = 122.1$.

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.

$C_6H_5.CO_2Na = 144.1$.

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.
- Settipane GA. Aspirin and allergic diseases: a review. *Am J Med* 1983; **74** (suppl): 102–9.
- Michaëlsson G, Juhlin L. Urticaria induced by preservatives and dye additives in food and drugs. *Br J Dermatol* 1973; **88**: 525–32.
- Warin RP, Smith RJ. Challenge test battery in chronic urticaria. *Br J Dermatol* 1976; **94**: 401–6.
- Wüthrich B, Fabro L. Acetylsalicylsäure- und lebensmitteladditiv-intoleranz bei urtikaria, asthma bronchiale und chronischer rhinopathie. *Schweiz Med Wochenschr* 1981; **III**: 1445–50.
- Nethercott JR, et al. Airborne contact urticaria due to sodium benzoate in a pharmaceutical manufacturing plant. *J Occup Med* 1984; **26**: 734–6.
- Lahti A, Hannuksela M. Is Benzoic acid really harmful in cases of atopy and urticaria? *Lancet* 1981; **ii**: 1055.
- Nettis E, et al. Sodium benzoate-induced repeated episodes of acute urticaria/angio-oedema: randomized controlled trial. *Br J Dermatol* 2004; **151**: 898–902.
- Moneret-Vautrin DA, et al. Anaphylactoid reaction to general anaesthesia: a case of intolerance to sodium benzoate. *Anaesth Intensive Care* 1982; **10**: 156–7.
- Michils A, et al. Anaphylaxis with sodium benzoate. *Lancet* 1991; **337**: 1424–5.
- Lewis MAO, et al. Recurrent erythema multiforme: a possible role of foodstuffs. *Br Dent J* 1989; **166**: 371–3.

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.

- Edwards RC, Voegeli CJ. Inadvisability of using caffeine and sodium benzoate in neonates. *Am J Hosp Pharm* 1984; **41**: 658.
- Schiff D, et al. Fixed drug combinations and the displacement of bilirubin from albumin. *Pediatrics* 1971; **48**: 139–41.
- Praphanphoj V, et al. Three cases of intravenous sodium benzoate and sodium phenylacetate toxicity occurring in the treatment of acute hyperammonaemia. *J Inher Metab Dis* 2000; **23**: 129–36.

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.

- Green TP, et al. Disposition of sodium benzoate in newborn infants with hyperammonemia. *J Pediatr* 1983; **102**: 785–90.