Chlorhexidine

1 Nonproprietary Names

BP: Chlorhexidine acetate
Chlorhexidine gluconate solution
Chlorhexidine hydrochloride

JP: Chlorhexidine gluconate solution
Chlorhexidine hydrochloride

PhEur: Chlorhexidini diacetas
Chlorhexidini digluconatis solutio
Chlorhexidini dihydrochloridum

Chlorhexidine is usually encountered as the acetate, gluconate, or hydrochloride salt, and a number of pharmacopeias contain monographs for such materials. *See* Sections 9 and 17.

2 Synonyms

1,6-bis[*N*′-(*p*-Chlorophenyl)-N^5-biguanido]hexane; *N*,*N*″-bis (4-chlorophenyl)-3,12-diimino-2,4,11,13-tetraazatetradecanediimidamide; 1,6-di(4′-chlorophenyldiguanido)hexane.

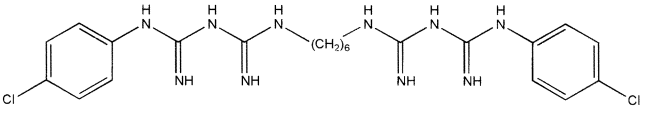
3 Chemical Name and CAS Registry Number

1,1′-Hexamethylenebis[5-(4-chlorophenyl)biguanide] [55-56-1]

4 Empirical Formula and Molecular Weight

$C_{22}H_{30}Cl_2N_{10}$ 505.48

5 Structural Formula



6 Functional Category

Antimicrobial preservative; antiseptic.

7 Applications in Pharmaceutical Formulation or Technology

Chlorhexidine salts are widely used in pharmaceutical formulations in Europe and Japan for their antimicrobial properties. Although mainly used as disinfectants, chlorhexidine salts are also used as antimicrobial preservatives.

As excipients, chlorhexidine salts are mainly used for the preservation of eye-drops at a concentration of 0.01% w/v; generally the acetate or gluconate salt is used for this purpose. Solutions containing between 0.002% and 0.006% w/v chlorhexidine gluconate have also been used for the disinfection of hydrophilic contact lenses.

For skin disinfection, chlorhexidine has been formulated as a 0.5% w/v solution in 70% v/v ethanol and, in conjunction with detergents, as a 4% w/v surgical scrub. Chlorhexidine salts may also be used in topical antiseptic creams, mouthwashes, and dental gels, and in urology for catheter sterilization and bladder irrigation.[1,2]

Chlorhexidine salts have additionally been used as constituents of medicated dressings, dusting powders, sprays, and creams.

8 Description

Chlorhexidine occurs as an odorless, bitter tasting, white crystalline powder. *See* Section 17 for information on chlorhexidine salts.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for chlorhexidine.

Test	JP 2001	PhEur 2002
Identification	+	+
Acidity or alkalinity		
Chlorhexidine gluconate solution	5.5–7.0	5.5–7.0
Relative density		
Chlorhexidine gluconate solution	1.06–1.07	1.06–1.07
4-Chloroaniline		
Chlorhexidine acetate	—	⩽500 ppm
Chlorhexidine gluconate solution	+	⩽0.25%
Chlrohexidine hydrochloride	+	⩽500 ppm
Related substances	—	+
Loss on drying		
Chlorhexidine acetate	—	⩽3.5%
Chlorhexidine hydrochloride	⩽2.0%	⩽1.0%
Sulfated ash		
Chlorhexidine acetate	—	⩽0.15%
Chlorhexidine gluconate solution	⩽0.1%	—
Chlorhexidine hydrochloride	⩽0.1%	⩽0.1%
Heavy metals	⩽10 ppm	—
Arsenic	⩽2 ppm	—
Chlorhexidine acetate	⩽2ppm	—
Chlorhexidine gluconate	—	—
Chlorhexidine hydrochloride	⩽2ppm	—
Assay		
Chlorhexidine acetate	—	98.0–101.0%
Chlorhexidine gluconate solution	19.0–21.0%	19.0–21.0%
Chlorhexidine hydrochloride	⩾98.0%	98.0–101.0%

See also Section 17.

10 Typical Properties

Antimicrobial activity: chlorhexidine and its salts exhibit antimicrobial activity against Gram-positive and Gram-negative microorganisms.[3] At the low concentrations normally used for preservation and antisepsis, chlorhexidine salts are rapidly bactericidal. However, species of *Proteus* and *Pseudomonas* are less susceptible to chlorhexidine, which is also inactive against acid-fast bacilli,

bacterial spores, and some fungi. Chlorhexidine salts are effective against some lipophilic viruses such as adenovirus, herpes virus, and influenza virus. Optimum antimicrobial activity occurs at pH 5–7. Above pH 8, the chlorhexidine base may precipitate from aqueous solutions.

Bacteria (Gram-positive): chlorhexidine salts are active against most species; the minimum inhibitory concentration (MIC) is normally in the range 1–10 μg/mL, although much higher concentrations are necessary for *Streptococcus faecalis*. Typical MIC values are shown in Table II.

Table II: Typical minimum inhibitory concentrations (MIC) of chlorhexidine against Gram-positive bacteria.

Microorganism	MIC (μg/mL)
Bacillus spp.	1.0–3.0
Clostridium spp.	1.8–70.0
Corynebacterium spp.	5.0–10.0
Staphylococcus spp.	0.5–6.0
Streptococcus faecalis	2000–5000
Streptococcus spp.	0.1–7.0

Bacteria (Gram-negative): chlorhexidine salts are less active against Gram-negative species than against Gram-positive species. Typical MICs are 1–15 μg/mL, but pseudomonads, particularly *Pseudomonas aeruginosa*, may be more resistant. *Serratia marcescens* may also be resistant. Combinations of chlorhexidine acetate with the following substances have shown enhanced or more than additive activity towards *Pseudomonas aeruginosa*: benzalkonium chloride; benzyl alcohol; bronopol; edetic acid; phenylethanol, and phenylpropanol.[4,5] Typical MIC values are shown in Table III.

Table III: Typical MIC values of chlorhexidine against Gram-negative bacteria.

Microorganism	MIC (μg/mL)
Escherichia coli	2.5–7.5
Klebsiella spp.	1.5–12.5
Proteus spp.	3–100
Pseudomonas spp.	3–60
Serratia marcescens	3–75
Salmonella spp.	1.6–15

Fungi: chlorhexidine salts are slowly active against molds and yeasts, although they are generally less potent in their inhibitory activity against fungi than against bacteria. Typical MIC values are shown in Table IV

Table IV: Typical MIC values of chlorhexidine against fungi.

Microorganism	MIC (μg/mL)
Aspergillus spp.	75.0–500.0
Candida albicans	7.0–15.0
Microsporum spp.	12.0–18.0
Penicillium spp.	150.0–200.0
Saccharomyces spp.	50.0–125.0
Trichophyton spp.	2.5–14.0

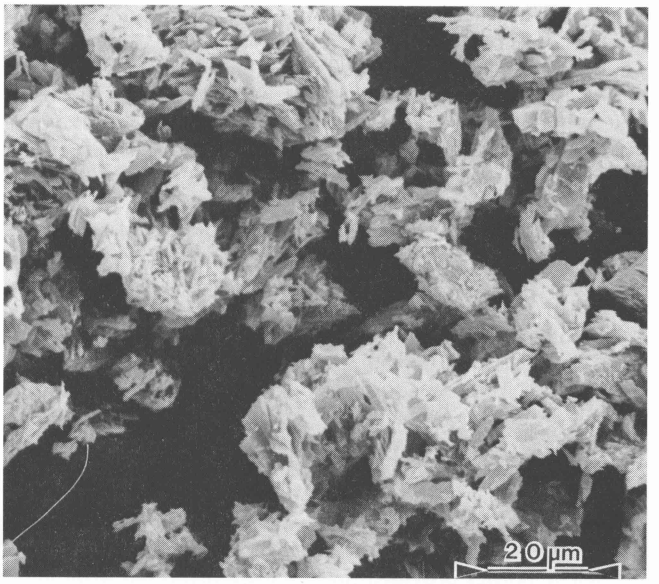
Spores: chlorhexidine salts are inactive against spores at normal room temperature.[6] At 98–100°C there is some activity against mesophilic spores.

Critical micelle concentration: ≈0.6% w/v (depends on other ions in solution).[7]

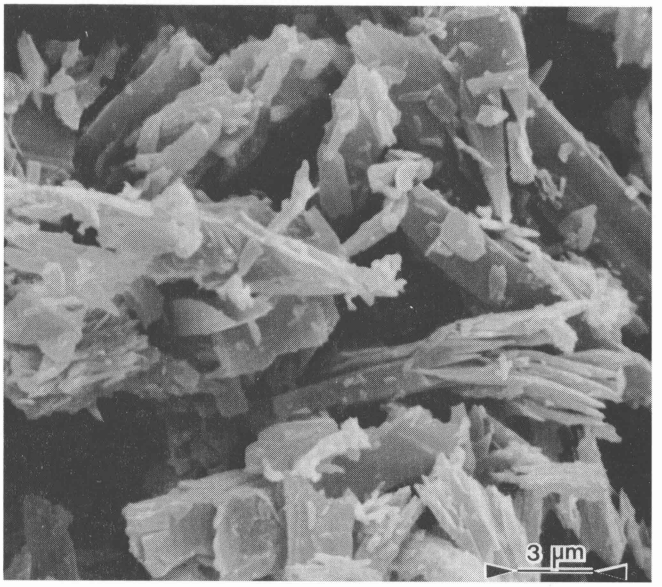
Melting point: 132–134°C

See also Section 17 for additional information.

SEM: 1
Excipient: Chlorhexidine
Manufacturer: SST Corp.
Magnification: 600×



SEM: 2
Excipient: Chlorhexidine
Manufacturer: SST Corp.
Magnification: 2400×



11 Stability and Storage Conditions

Chlorhexidine and its salts are stable at normal storage temperatures when in the powdered form. However, chlorhexidine hydrochloride is hygroscopic, absorbing significant amounts of moisture at temperatures up to 37°C and relative humidities up to 80%.

Heating to 150°C causes decomposition of chlorhexidine and its salts, yielding trace amounts of 4-chloroaniline. However, chlorhexidine hydrochloride is more thermostable than the acetate and can be heated at 115°C for 1 hour without appreciable formation of 4-chloroaniline.

In aqueous solution, chlorhexidine salts may undergo hydrolysis to form 4-chloroaniline. Following autoclaving of a 0.02% w/v chlorhexidine gluconate solution at pH 9 for 30 minutes at 120°C, it was found that 1.56% w/w of the original chlorhexidine content had been converted into 4-chloroaniline; for solutions at pH 6.3 and 4.7 the 4-chloroaniline content was 0.27% w/w and 0.13% w/w, respectively, of the original gluconate content.[8] In buffered 0.05% w/v chlorhexidine acetate solutions, maximum stability occurs at pH 5.6.

When chlorhexidine solutions were autoclaved at various time and temperature combinations, the rate of hydrolysis increased markedly above 100°C and as pH increased or decreased from pH 5.6. At a given pH, chlorhexidine gluconate produced more 4-chloroaniline than did the acetate.

It was predicted that in an autoclaved solution containing 0.01% w/v chlorhexidine, the amount of 4-chloroaniline formed would be about 0.000 03%. At these low concentrations there would be little likelihood of any toxic hazard as a result of the increase in 4-chloroaniline content in the autoclaved solution.

Chlorhexidine solutions and aqueous-based products may be packaged in glass and high-density polyethylene or polypropylene bottles provided that they are protected from light. If not protected from light, chlorhexidine solutions containing 4-chloroaniline discolor owing to polymerization of the 4-chloroaniline.[9–11]

Cork-based closures or liners should not be used in packaging in contact with chlorhexidine solutions.

As a precaution against contamination with *Pseudomonas* species resistant to chlorhexidine, stock solutions may be protected by the inclusion of 7% w/v ethanol or 4% w/v propan-2-ol.

Chlorhexidine salts, and their solutions, should be stored in well-closed containers, protected from light, in a cool, dry place.

12 Incompatibilities

Chlorhexidine salts are cationic in solution and are therefore incompatible with soaps and other anionic materials. Chlorhexidine salts are compatible with most cationic and nonionic surfactants, but in high concentrations of surfactant, chlorhexidine activity can be substantially reduced owing to micellar binding.

Chlorhexidine salts of low aqueous solubility are formed and may precipitate from chlorhexidine solutions of concentration greater than 0.05% w/v, when in the presence of inorganic acids, certain organic acids, and salts, e.g., benzoates, bicarbonates, borates, carbonates, chlorides, citrates, iodides, nitrates, phosphates, and sulfates.[12] At chlorhexidine concentrations below 0.01% w/v, precipitation is less likely to occur.

In hard water, insoluble salts may form owing to interaction with calcium and magnesium cations. Solubility may be enhanced by the inclusion of surfactants such as cetrimide.

Other substances incompatible with chlorhexidine salts include viscous materials such as acacia, sodium alginate, sodium carboxymethylcellulose, starch, and tragacanth.[13,14] Also incompatible are brilliant green, chloramphenicol, copper sulfate, fluorescein sodium, formaldehyde, silver nitrate, and zinc sulfate.

Interaction has been reported between chlorhexidine gluconate and the hydrogel poly(2-hydroxyethyl methacrylate), which is a component of some hydrophilic contact lenses.[15,16]

13 Method of Manufacture

Chlorhexidine may be prepared either by condensation of polymethylene bisdicyandiamide with 4-chloroaniline hydrochloride or by condensation of 4-chlorophenyl dicyandiamine with hexamethylenediamine dihydrochloride. Chlorhexidine may also be synthesized from a series of biguanides.[17]

14 Safety

Chlorhexidine and its salts are used widely, primarily as topical disinfectants. As excipients, chlorhexidine salts are mainly used as antimicrobial preservatives in ophthalmic formulations.

Animal studies suggest that the acute oral toxicity of chlorhexidine is low, with little or no absorption from the gastrointestinal tract. However, although humans have consumed up to 2 g of chlorhexidine daily, for 1 week, without untoward symptoms, chlorhexidine is not generally used as an excipient in orally ingested formulations.

Reports have suggested that there may be some systemic effects in humans following oral consumption of chlorhexidine.[18–20] Similarly, the topical application of chlorhexidine or its salts produced evidence of very slight percutaneous absorption of chlorhexidine, although the concentrations absorbed were insufficient to produce systemic adverse effects.[21]

Severe hypersensitivity reactions, including anaphylactic shock, have been reported following the topical administration of chlorhexidine,[22–26] although such instances are rare given the extensive use of chlorhexidine and it salts.

In ophthalmic preparations, irritation of the conjunctiva occurs with chlorhexidine solutions of concentration stronger than 0.1% w/v. Accidental eye contact with 4% w/v chlorhexidine gluconate solution may result in corneal damage.[27]

The aqueous concentration of chlorhexidine normally recommended for contact with mucous surfaces is 0.05% w/v. At this concentration, there is no irritant effect on soft tissues, nor is healing delayed. The gluconate salt (1% w/v) is frequently used in creams, lotions, and disinfectant solutions.

Direct instillation of chlorhexidine into the middle ear can result in ototoxicity;[28] when used in dental preparations, staining of teeth and oral lesions may occur.[29,30]

Use of chlorhexidine on the brain or meninges is extremely dangerous.

LD_{50} (mouse, IP): 0.04 g/kg[31]
LD_{50} (mouse, oral): 2.52 g/kg
LD_{50} (rat, IP): 0.06 g/kg
LD_{50} (rat, IV): 0.02 g/kg
LD_{50} (rat, oral): 9.2 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. The dust of chlorhexidine and its salts may be irritant to the skin, eyes, and respiratory tract. Gloves, eye protection, and a respirator are recommended.

16 Regulatory Status

Chlorhexidine salts are included in nonparenteral and parenteral medicines licensed in the UK.

17 Related Substances

Chlorhexidine acetate; chlorhexidine gluconate; chlorhexidine hydrochloride.

Chlorhexidine acetate

Empirical formula: $C_{22}H_{30}Cl_2N_{10}\cdot 2C_2H_4O_2$
Molecular weight: 625.64
CAS number: [56-95-1]
Synonyms: chlorhexidini acetas; chlorhexidine diacetate; 1,1′-hexamethylenebis[5-(4-chlorophenyl)biguanide] diacetate; *Hibitane diacetate*.
Appearance: a white or almost white, microcrystalline powder.
Melting point: 154°C
Moisture content: chlorhexidine acetate is hygroscopic, absorbing significant amounts of moisture at relative humidities up to about 80% and temperatures up to 37°C.
Partition coefficients:
Mineral oil : water = 0.075
Peanut oil : water = 0.04
Solubility: soluble 1 in 15 of ethanol (95%), 1 in 55 of water; slightly soluble in glycerin and propylene glycol.
Safety:
LD_{50} (mouse, IP): 0.04 g/kg[31]
LD_{50} (mouse, IV): 0.03 g/kg
LD_{50} (mouse, oral): 2 g/kg
LD_{50} (mouse, SC): 0.33 g/kg
Comments: aqueous solutions may be sterilized by autoclaving; the solutions should not be alkaline or contain other ingredients that affect the stability of chlorhexidine. *See* Sections 11 and 12.
The EINECS number for chlorhexidine acetate is 200-302-4.

Chlorhexidine gluconate

Empirical formula: $C_{22}H_{30}Cl_2N_{10}\cdot 2C_6H_{12}O_7$
Molecular weight: 897.88
CAS number: [18472-51-0]
Synonyms: chlorhexidine digluconate; chlorhexidini digluconatis; 1,1′-hexamethylenebis[5-(4-chlorophenyl)biguanide] digluconate; *Hibiclens*; *Hibiscrub*; *Hibitane*; *Unisept*.
Appearance: chlorhexidine gluconate is usually used as an almost colorless or pale yellow-colored aqueous solution.
Acidity/alkalinity: pH = 5.5–7.0 for a 5% w/v aqueous dilution.
Solubility: miscible with water; soluble in acetone and ethanol (95%).
Safety:
LD_{50} (mouse, IV): 0.02 g/kg[31]
LD_{50} (mouse, oral): 1.8 g/kg
LD_{50} (mouse, SC): 1.14 g/kg
LD_{50} (rat, IV): 0.02 g/kg
LD_{50} (rat, oral): 2 g/kg
LD_{50} (rat, SC): 3.32 g/kg
Comments: the commercially available 5% w/v chlorhexidine gluconate solution contains a nonionic surfactant to prevent precipitation and is not suitable for use in body cavities or for the disinfection of surgical instruments containing cemented glass components. Aqueous dilutions of commercially available chlorhexidine gluconate solutions may be sterilized by autoclaving. *See* Sections 11 and 12.
The EINECS number for chlorhexidine gluconate is 242-354-0.

Chlorhexidine hydrochloride

Empirical formula: $C_{22}H_{30}Cl_2N_{10}\cdot 2HCl$
Molecular weight: 578.44
CAS number: [3697-42-5]
Synonyms: chlorhexidine dihydrochloride; chlorhexidini hydrochloridum; 1,1′-hexamethylenebis[5-(4-chlorophenyl)biguanide]dihydrochloride.
Appearance: a white or almost white, crystalline powder.
Melting point: 261°C, with decomposition.
Solubility: sparingly soluble in water; very slightly soluble in ethanol (95%); soluble 1 in 50 of propylene glycol.
Safety: LD_{50} (mouse, SC): >5 g/kg[31]
Comments: chlorhexidine hydrochloride may be sterilized by dry heat. *See* Sections 11 and 12.
The EINECS number for chlorhexidine hydrochloride is 223-026-6.

18 Comments

The EINECS number for chlorhexidine is 200-238-7.

19 Specific References

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22 Date of Revision

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