

CHLORHEXIDINE
BASE & SALTS

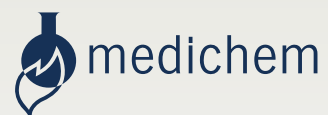


CHLORHEXIDINE:

The Must-Have

in Disinfection and Antisepsis





Medichem in a flash

- Medichem S.A. is a privately owned company, based in Barcelona, founded in 1972
- Our activities:
 - Active Pharmaceutical Ingredients
 - Chlorhexidine, world leaders
 - Contract Manufacturing
- Process development and manufacture of non-infringing, cGMP Active Pharmaceutical Ingredients (APIs)
- FDA inspected since 1985 - Both Celrà and Malta plants are no "Form 483"
- ISO 9001 & ISO 14001 certified
- Manufacturing sites: Girona (25,000 m²) and Malta (8,800 m²)
- Medichem Manufacturing (Malta) Ltd. founded in 2005
- Nanjing Medichem Biopharmaceutical Development Co. Ltd. (NRC) founded in 2012
- Team of over 250 highly professional, committed and devoted people
- Full respect for the environment at all our sites



General Properties

- Chlorhexidine salts have a **very wide range of antimicrobial activity**, being effective either against gram-positive or gram-negative organisms. They also have **fungicidal and sporicidal effect** (the latter one at higher temperatures).
- Chlorhexidine has a **strong basic character with cationic properties**. It is available in both freebase and stable salts forms. Chlorhexidine is **slightly soluble in water and most organic solvents** and because of this poor solubility. It is mainly used in salt form.

Due to the cationic character of Chlorhexidine salts, they are **chemically compatible with other cationic and non-ionic substances**, but are **chemically incompatible with anionic compounds** (sulphates, phosphates, carbonates, ...).
- Medichem manufactures **4 Chlorhexidine compounds**:
 - Chlorhexidine Base
 - Chlorhexidine Digluconate 20% solution
 - Chlorhexidine Diacetate
 - Chlorhexidine Dihydrochloride
- The main features of Chlorhexidine salts manufactured by Medichem are the **very low content of impurities** specially *p*-Chloroaniline and the consistent quality. This can only be achieved by a **very careful and advanced process**, carried out according to Good Manufacturing Practices and to a Quality Management System, certified according to ISO 9001 guidelines in our FDA inspected factory. Since July 2001 Medichem is also certified according to ISO 14001 Environmental Management System.
- It is Medichem's purpose, to **excel and provide the highest quality**, going beyond the Pharmacopoeias. Medichem has **contributed to the development of the new EP and USP monographs** for all Chlorhexidine salts. These new monographs represent an enhanced and up to date standard with limits for individual impurities according to ICH guidances.

Chlorhexidine is used in Disinfectants, Cosmetics and Pharmaceutical products. It is also used in more than 60 different pharmaceutical products and medical devices.



HAND AND SKIN DISINFECTANTS

- The primary requirement for healthcare washing is the ability to **remove debris and transient microorganisms**.
- Chlorhexidine products meet the demanding requirements of **surgery, skin preparation, healthcare and procedural handwash to reduce hospital required diseases**.
- **Chlorhexidine Digluconate 20% sol.** is the salt used for these applications, being the typical range of concentration most commonly used 0.5 to 4%.



ORAL CARE

- Clinical studies have shown the short-term effectiveness of Chlorhexidine in **plaque control and gingivitis associated to plaque**, healing **after periodontal and oral surgery, before periodontal surgery** to prevent post-surgery bacteremia, treatment of **mouth ulcers**, treatment of **proteic stomatitis and oral infections**.
- **Chlorhexidine Digluconate 20% sol.** is the salt most commonly used to manufacture products such as mouthwashes, toothpastes, oral rinses, gels and sprays.
- The typical range of concentration for these applications is **0.12 - 0.20%**.
- Chlorhexidine Diacetate and Chlorhexidine Dihydrochloride are also used in some special cases.



COSMETIC FIELD

- In the cosmetic field, Chlorhexidine is **used as a preservative**, not as a disinfectant.
- Chlorhexidine Dihydrochloride also has applications especially in the cosmetic field for **ointments, creams and shampoos**.



VETERINARY

- Chlorhexidine is mainly used for the treatment of **mastitis in cows**. The Chlorhexidine-based products are suitable to **destroy a wide range of microorganisms**, including the pathogenic bacteria, which cause mastitis (i.e. *Streptococcus Agalactiae*, *E. Coli*, *Staphylococcus Aureus*).
- Chlorhexidine is also available in many pet products such as **shampoos and pet treats**. It is also used as a **disinfectant to sterilize** surgical equipment.
- Typical products manufactured using Chlorhexidine are **teat creams, dips and wipes**. Other applications of Chlorhexidine in dairy hygiene are the **healing of superficial cuts, abrasions or insect stings**, and the **general dairy hygiene**.
- The typical products manufactured using **Chlorhexidine Digluconate 20% sol.** are aqueous solutions ready to use or concentrated solutions. Chlorhexidine Digluconate 20% sol. is the most commonly used salt of Chlorhexidine for all these applications. However, Chlorhexidine Diacetate is widely used for this application in certain geographical areas.

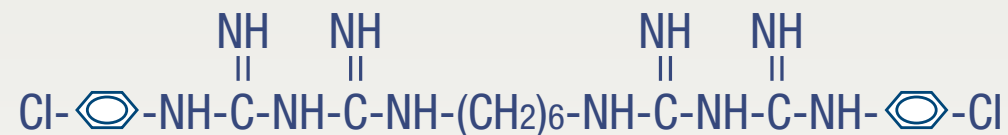


OTHER APPLICATIONS

- Chlorhexidine products are used in a large number of other applications such as **treatment of wounds and burns, gynaecology and obstetrics, sterilization and cleaning of surfaces and equipment**.
- These products contain typically **Chlorhexidine Digluconate 20% solution**.
- Chlorhexidine Dihydrochloride is also used to manufacture **soar throat tablets**.
- Chlorhexidine Diacetate is used for **general disinfection** (equipment, surfaces and textiles) and to **manufacture antacid tablets**.



Chlorhexidine Base



NAME

1,1'-hexamethylenebis[5-(*p*-chlorophenyl) biguanide]

1,6-bis(*N'*-*p*-chlorophenyl-*N*⁵-biguanido)hexane

MOLECULAR FORMULA

C₂₂ H₃₀ Cl₂ N₁₀

CAS NUMBER

[55-56-1]

MOLECULAR WEIGHT

505.5 g/mol

REGULATORY STATUS:

 US DMF

SPECIFICATIONS AT RELEASE

TEST	LIMIT
Description:	White or almost white powder
Identification:	The IR Spectrum matches with the standard
Solubility:	Clear and colourless or almost colourless solution
Chloroaniline:	Not more than 500 ppm
Loss on drying:	Not more than 1.0%
Sulphated Ash:	Not more than 0.1%
Assay:	97.5 - 101.0% (on dry)

Chlorhexidine Base

PACKING

25 Kg net HDPE drums. Other sizes available upon request.

STABILITY

Medichem performs ongoing stability studies on Chlorhexidine Base to ensure continuous quality throughout its shelf life. Stability data generated during more than 30 years of Chlorhexidine Base production have been used to set a shelf life of 5 years. Shelf life can only be guaranteed if the product is stored as indicated below.

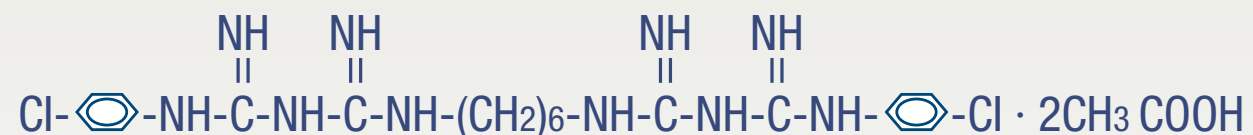
STORAGE CONDITIONS

- Store at controlled room temperature (15-30°C).
- Keep in the original drums tightly closed.
- Keep the drums away from direct sunlight.

TRANSPORT REGULATIONS

Classified as hazardous substance according to transport regulations (class 9, UN 3077).

Chlorhexidine Diacetate



NAME

1,1'-hexamethylenebis[5-(*p*-chlorophenyl) biguanide] diacetate
1,6-bis(*N'*-*p*-chlorophenyl-*N*⁵-biguanido)hexane diacetate

SPECIFICATIONS AT RELEASE (EP)

MOLECULAR FORMULA

C₂₂ H₃₀ Cl₂ N₁₀ · 2C₂ H₄ O₂

CAS NUMBER

[56-95-1]

MOLECULAR WEIGHT

625.6 g/mol

REGULATORY STATUS:

-  US DMF
-  EDMF
-  CANADIAN DMF

TEST	LIMIT
Description:	White or almost white microcrystalline powder
Identification:	Test A: The IR spectrum matches with the IR spectrum of the Eur.Ph. reference standard of <i>Chlorhexidine Diacetate CRS</i>
Chloroaniline:	Not more than 500 ppm (<i>regularly NMT 200 ppm at release</i>)
Loss on drying:	NMT 3.5%
Related Substances:	Total impurities: NMT 2.5%
Sulphated Ash:	NMT 0.15%
Assay:	98.0%-101.0% (on dried substance)

Chlorhexidine Diacetate

PARTICLE SIZE (LASER DIFFRACTION)

STANDARD GRADE MATERIAL:

D(v,0.9): NMT 150 µm

MICRONISED GRADE MATERIAL:

D(v,0.9): NMT 10 µm

APPLICATIONS



REACH Regulation (EC) No. 1907/2006

The substance Chlorhexidine Diacetate has been pre-registered according to REACH requirements. No registration number is given for this pre-registered substance since the transition period for its registration according to Article 23 of REACH has not expired yet.

PACKING

25 Kg or 50 Kg net HDPE drums.
Other sizes available upon request.

STABILITY

Medichem performs ongoing stability studies on Chlorhexidine salts to ensure continuous quality throughout its shelf life. Stability data generated during more than 30 years of Chlorhexidine salts production have been used to set a shelf life of 5 years. Shelf life can only be guaranteed if the product is stored as indicated above.

STORAGE

- Store at controlled room temperature (15-30°C).
- Keep in the original container tightly closed.
- Keep the drums away from direct sunlight.

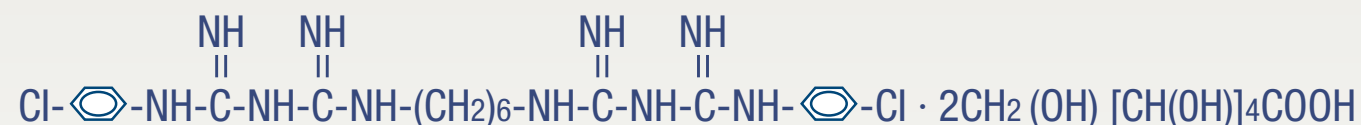
TRANSPORT REGULATIONS

Classified as hazardous substance according to transport regulations (class 9, UN 3077).



Chlorhexidine Digluconate

20% w/v solution



NAME

1,1'-hexamethylenebis[5-(*p*-chlorophenyl) biguanide] digluconate
1,6-bis(N'-*p*-chlorophenyl-N⁵-biguanido)hexane digluconate

MOLECULAR FORMULA

C₂₂ H₃₀ Cl₂ N₁₀ · 2C₆ H₁₂ O₇

CAS NUMBER

[18472-51-0]

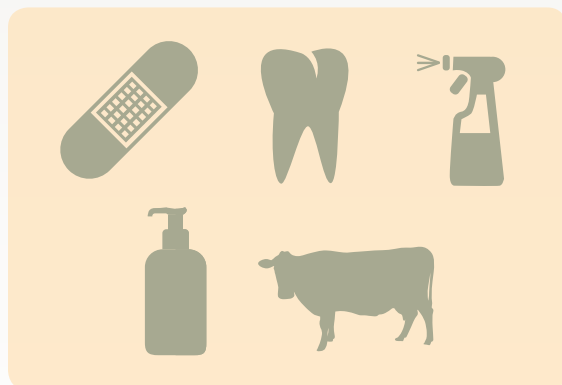
MOLECULAR WEIGHT

898 g/mol

REGULATORY STATUS:

- US DMF
- CEP
- CANADIAN DMF
- TAIWANESE DMF

APPLICATIONS



TRANSPORT REGULATIONS

Classified as hazardous substance according to transport regulations (class 9, UN 3082).

PACKING

1000 Kg IBC Containers.
50 Kg and 200 Kg HDPE drums.

Chlorhexidine Digluconate

20% w/v solution

SPECIFICATIONS AT RELEASE (EP)

TEST	LIMIT	TEST	LIMIT
Description:	Almost colourless or pale-yellowish liquid	Related Substances:	Impurity A: NMT 0.4%
Identification Test A:	The IR spectrum complies with <i>Chlorhexidine CRS spectrum</i>		Impurity B: NMT 0.2%
Identification Test B:	The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution		Impurity F: NMT 0.2%
pH:	5.5 to 7.0		Impurity G: NMT 0.3%
Relative density:	1.06-1.07g/ml		Impurity H: NMT 0.5%
			Impurities I + O: NMT 0.4%
			Impurity J: NMT 0.4%
		Impurity K: NMT 0.4%	
		Impurity L: NMT 0.2%	
		Impurity N: NMT 1.0%	
		Impurity Q: NMT 0.2%	
		Any unspecified impurity: NMT 0.10%	
		Total impurities: NMT 3.0%	
		Impurity P (chloroaniline):	Not more than 500 ppm (<i>regularly NMT 10 ppm at release</i>)
		Assay:	19.0 to 21.0 % (w/v)

Chlorhexidine Digluconate

20% w/v solution

BIOCIDAL PRODUCTS DIRECTIVE (BPD) - DIRECTIVE 98/8/EC

- In 2007 Medichem, S.A. notified Chlorhexidine Digluconate (CAS No. 18472-51-0, EC No. 242-354-0) according to BPD for its use as an active substance in the following product types:
 - **PT1:** human hygiene biocidal products
 - **PT2:** private area and public health area disinfectants and other biocidal products
 - **PT3:** veterinary hygiene biocidal products
- This dossier is under evaluation by the Representative member state (Portugal). Once the dossier is approved, Chlorhexidine Digluconate will be included in Annex I of the BPD.

Meanwhile, we provide our clients any assistance required for their national submissions. In October 2013, ECHA published the list of active substance suppliers, the provisional list which will form the basis of the list ECHA will publish under art 95 of the BPR (Biocidal Products Regulation, 528/2012). Chlorhexidine Digluconate, manufactured by Medichem, S.A. has been included in the list.

- According to the BPR, from 1st September 2015, a biocidal product cannot be placed on the EU market if the manufacturer or importer of the active substance contained in the biocidal product, or where relevant, the importer of the biocidal product, is not included in the art 95 list.

Chlorhexidine Digluconate

20% w/v solution

REACH

Medichem has also registered Chlorhexidine Digluconate in 2013 according to the requirements and timeframes of REACH regulation. Registration number: 01-2119946568-22-0001.

STABILITY:

Medichem performs ongoing stability studies on Chlorhexidine Digluconate to ensure continuous quality throughout their retest period. Retest period can only be guaranteed if the product is stored as indicated below.

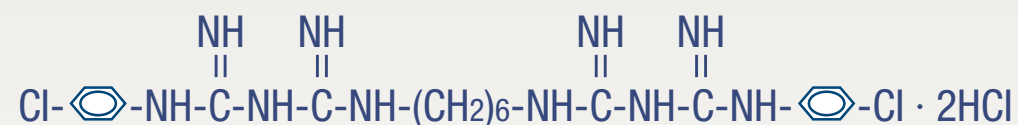
STORAGE

- Store preferably below 25° C. Do not allow the product to freeze. If this happens, it can be rehomogenized maintaining the same properties.
- Keep in the original drums tightly closed.
- Keep the drums away from direct sunlight.



Chlorhexidine

Dihydrochloride



NAME

1,1'-hexamethylenebis[5-(*p*-chlorophenyl) biguanide] dihydrochloride
1,6-bis(*N'*-*p*-chlorophenyl-*N*⁵-biguanido)hexane dihydrochloride

SPECIFICATIONS AT RELEASE (EP)

MOLECULAR FORMULA

C₂₂ H₃₀ Cl₂ N₁₀ · 2HCl

CAS NUMBER

[3697-42-5]

MOLECULAR WEIGHT

578.4 g/mol

REGULATORY STATUS:



EDMF



TEST

LIMIT

Description:	White or almost white crystalline powder
Identification:	A. The I.R. spectrum matches with the reference spectrum of Chlorhexidine dihydrochloride. D. It complies with the reaction (a) of chlorides
Chloroaniline:	Not more than 500 ppm (<i>NMT 200 ppm at release</i>)
Related Substances:	Not more than 2.5% (total impurities)
Loss on drying:	Not more than 1.0%
Sulphated Ash:	Not more than 0.1%
Assay:	98.0%-101.0% (dried substance)

Chlorhexidine

Dihydrochloride

PARTICLE SIZE (LASER DIFFRACTION)

STANDARD GRADE MATERIAL:

D(v,0.9): NMT 15 µm

MICRONISED GRADE MATERIAL:

D(v,0.9): NMT 10 µm

PACKING

30 Kg HDPE drums.
Other sizes available upon request.

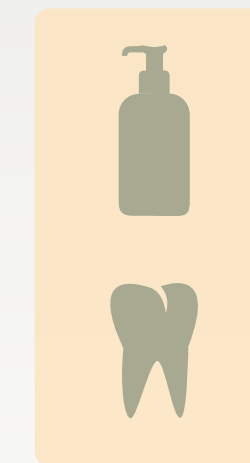
STABILITY

Medichem performs ongoing stability studies on Chlorhexidine salts to ensure continuous quality throughout their shelf life. Stability data generated during more than 30 years of Chlorhexidine salts production have been used to set a shelf life of 5 years. Shelf life can only be guaranteed if the product is stored as indicated above.

STORAGE

- Store at controlled room temperature (15-30° C).
- Keep in the original drums tightly closed.
- Keep the drums away from direct sunlight.

APPLICATIONS



REACH

Chlorhexidine Dihydrochloride has been preregistered according to REACH requirements.

No registration number is given for this preregistered substance since the transition period for its registration according to Article 23 of REACH has not expired yet.

TRANSPORT REGULATIONS

Classified as hazardous substance according to transport regulations (class 9, UN 3077).



Distribution

around the world

EUROPE

Austria
Belarus
Belgium
Bosnia-Herzegovina
Bulgaria
Croatia
Cyprus
Czech Republic
Denmark
Finland
France*
Germany*
Greece
Ireland
Italy*
Latvia
Netherlands
Norway
Poland
Portugal
Romania
Russia*
Serbia
Spain*

Sweden
Switzerland*
Ukraine
United Kingdom*

NORTH AMERICA

Canada*
USA*

CENTRAL AMERICA

Costa Rica
El Salvador
Guatemala
Honduras
Mexico
Rep Panama

SOUTH AMERICA

Argentina
Bolivia
Brazil
Chile
Colombia
Venezuela

MIDDLE EAST

Armenia
Iran
Israel
Jordan
Kazakhstan
Lebanon
Saudi Arabia
Turkey
Yemen

ASIA

Bangladesh
China
India
Indonesia
Japan*
Kazakhstan
Malaysia*
Pakistan
Phillippines
Singapore*
South Korea*
Sri Lanka
Taiwan

Thailand*
Vietnam

AFRICA

Algeria
Egypt
Ivory Coast
Morocco
South Africa*
Tunisia

OCEANIA

Australia*
New Zealand*

* LOCAL INVENTORY



Combino

at a glance

- Founded in 1996. Headquarters in Barcelona (Spain)
- 1st Spanish generic company devoted to the Hospital market
- Active in the Hospital Market (own brand in Spain and Portugal) and Retail markets.
- Portfolio of over 35 active ingredients sold in 90 different dosage forms (85% own developments)
- Current pipeline of 20 products (in-house developments)
- Licenses and distributes products in more than 70 countries
- In-house selection development of finished dosage forms
- Vertically integrated (API Medichem, FDF Combino Pharm. Both manufactured in our own facilities)- supply of FDF and/or API
- Full regulatory and intellectual property support
- Combino Pharm's Manufacturing site in Malta offers "patent free" contract-manufacturing opportunities and EU GMP release services



2% Aqueous

Chlorhexidine Transparent

THERAPEUTIC INDICATION

Antiseptic for preventing infections on intact skin before injections or insertion of catheters.

HIGHLIGHTS

- 2% Chlorhexidine-aqueous reduces by 49% the risk of vascular catheter-related bloodstream infection in comparison with povidone-iodine 10%. (1)
- The US Center of Disease Control and Prevention (CDC) recommends Chlorhexidine 2% for cleansing the site of insertion of vascular catheters. (2)

REGULATORY DETAILS

- API supplier: Medichem
- FDF manufacturer: EU



PRESENTATION

- Unidose ampoules 10 ml
- Bottles 60 ml

REGULATORY STRATEGY

- Dossier ready for licensing.
- Already commercialised in Spain and Portugal.

1. Chaiyakunapruk N, Veenstra DL, Lipsky BA, Saint S. Chlorhexidine compared with povidone-iodine solution for vascular catheter-site care: a meta-analysis. *Ann Intern Med* 2002; 136:792-801. 2. O'Grady NP, Alexander M, Dellinger ET, et al. Guidelines for the prevention of intravascular catheter-related infections. *Infect Control Hosp Epidemiol* 2002;23: 759-69. *Intern Med* 2002; 136:792-801.



2% Alcoholic

Chlorhexidine Coloured

THERAPEUTIC INDICATION

Preoperative antiseptic. Disinfection of the skin before minor or major surgery. It contains a tint to colour the skin, therefore it is appropriate for marking the surgical site.

HIGHLIGHTS

- According to the new clinical trial published in the *New England Journal of Medicine* (January 2010), Chlorhexidine-alcohol 2% reduces by 41% the surgical-site infections in comparison with povidone-iodine 10% aqueous solution. (1)
- It is a unique ready to use Chlorhexidine that can actually colour the skin perfectly for marking the surgical site.

REGULATORY DETAILS

- API supplier: Medichem
- FDF manufacturer: EU

1. Darouiche, et al. Chlorhexidine-Alcohol versus Povidone-Iodine for surgical-site antiseptics. *N Engl J Med* 362; 18-26.



PRESENTATION

- Bottles 250 ml
- Bottles 125 ml

PATENT STATUS

Formulation covered by our own patent application.

REGULATORY STRATEGY

- Dossier ready for licensing.
- Already commercialised in Spain and Portugal.



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Active Ingredients

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Finished Dosage Forms

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