CHLORHEXIDINE: The Must-Have in Disinfection and Antisepsis
Medichem S.A. is a privately owned company, based in Barcelona, founded in 1972

Our activities:
- 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

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%.

**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.
**NAME**
1,1'-hexamethylenebis[5-(p-chlorophenyl) biguanide]  
1,6-bis(N'-p-chlorophenyl-N5-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**

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

---

**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).
**NAME**
1,1’-hexamethylenebis[5-(p-chlorophenyl) biguanide] diacetate
1,6-bis(N’-p-chlorophenyl-N5-biguanido)hexane diacetate

**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

---

### SPECIFICATIONS AT RELEASE (EP)

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

---

### 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.

### 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.

### 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.

### 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.

### 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.

### 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.

---

**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 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.

**PRINCIPAL USES**

- **Dermal Use:** Antiseptic and disinfectant, used in hand sanitizers, surgical scrubs, and wound dressings.
- **Oral Use:** Antiseptic mouthwash, used to prevent gum disease and bad breath.

---

**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).
**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**

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

**PACKING**

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

**TRANSPORT REGULATIONS**

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

**SPECSIFICATIONS AT RELEASE (EP)**

<table>
<thead>
<tr>
<th>TEST</th>
<th>LIMIT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description:</strong></td>
<td>Almost colourless or pale-yellowish liquid</td>
</tr>
<tr>
<td><strong>Identification Test A:</strong></td>
<td>The IR spectrum complies with Chlorhexidine CRS spectrum</td>
</tr>
<tr>
<td><strong>Identification Test B:</strong></td>
<td>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</td>
</tr>
<tr>
<td><strong>pH:</strong></td>
<td>5.5 to 7.0</td>
</tr>
<tr>
<td><strong>Relative density:</strong></td>
<td>1.06-1.07g/ml</td>
</tr>
</tbody>
</table>

**TEST**

**LIMIT**

- Related Substances:
  - Impurity A: NMT 0.4%
  - Impurity B: NMT 0.2%
  - Impurity F: NMT 0.2%
  - Impurity G: NMT 0.3%
  - 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 (regularly NMT 10 ppm at release)
- Assay: 19.0 to 21.0 % (w/v)
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.

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

**MOLECULAR FORMULA**
C_{22}H_{30}Cl_{2}N_{10}·2HCl

**CAS NUMBER**
[3697-42-5]

**MOLECULAR WEIGHT**
578.4 g/mol

**REGULATORY STATUS:**
- US DMF
- EDMF

**SPECIFICATIONS AT RELEASE (EP)**

<table>
<thead>
<tr>
<th>TEST</th>
<th>LIMIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>White or almost white crystalline powder</td>
</tr>
</tbody>
</table>
| 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 (NMT 200 ppm at release) |
| 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)             |

**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.

**PACKING**
30 Kg HDPE drums. Other sizes available upon request.

**APPLICATIONS**
Chlorhexidine Dihydrochloride has been preregistered according to REACH requirements.

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

**PICTOGRAM**
- Chemical symbol
- Flame
- Water
- Exclamation mark

**PARTICLE SIZE (LASER DIFFRACTION)**
- STANDARD GRADE MATERIAL: D(v,0.9): NMT 15 µm
- MICRONISED GRADE MATERIAL: D(v,0.9): NMT 10 µm
**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*

**MIDDLE EAST**
- Armenia
- Iran
- Israel
- Jordan
- Kazakhstan
- Lebanon
- Saudi Arabia
- Turkey
- Yemen

**NORTH AMERICA**
- Canada*
- USA*

**CENTRAL AMERICA**
- Costa Rica
- El Salvador
- Guatemala
- Honduras
- Mexico
- Rep Panama

**SOUTH AMERICA**
- Argentina
- Bolivia
- Brazil
- Chile
- Colombia
- Venezuela

**THAILAND**
- Vietnam

**AFRICA**
- Algeria
- Egypt
- Ivory Coast
- Morocco
- South Africa*
- Tunisia

**ASIA**
- Bangladesh
- China
- India
- Indonesia
- Japan*
- Kazakhstan
- Malaysia*
- Pakistan
- Philippines
- Singapore*
- South Korea*
- Sri Lanka
- Taiwan

**OCEANIA**
- Australia*
- New Zealand*

---

*LOCAL INVENTORY

Combino Pharm was founded in 1996, with headquarters in Barcelona (Spain). It is the 1st Spanish generic company devoted to the Hospital market. Active in the Hospital Market (own brand in Spain and Portugal) and Retail markets. The company's portfolio includes over 35 active ingredients sold in 90 different dosage forms (85% own developments). The current pipeline consists of 20 products (in-house developments). Licenses and distributes products in more than 70 countries. An in-house selection development of finished dosage forms is also a focus. Combino is 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 is provided. Combino Pharm’s Manufacturing site in Malta offers “patent free” contract-manufacturing opportunities and EU GMP release services.


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%.
- The US Center of Disease Control and Prevention (CDC) recommends Chlorhexidine 2% for cleansing the site of insertion of vascular catheters.

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.

2% Aqueous Chlorhexidine Transparent

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.
- 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

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.

2% Alcoholic Chlorhexidine Coloured
